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"CHITOSAN" THE JACK OF ALL TRADE FOR SUSTAINED RELEASE: AN OVERVIEW

Prashant Kumar Sharma*, Ritesh Kumar Tiwari and Lalit Singh

Department of Pharmaceutics, Shri Ram Murti Smarak College of Engg. & Technology, (Pharmacy), Bareilly, India.

***Corresponding Author: Prashant Kumar Sharma**
Department of Pharmaceutics, Shri Ram Murti Smarak College of Engg. & Technology, (Pharmacy), Bareilly, India.

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ABSTRACT
Over the past few decades, tendency toward innovative drug delivery systems has majorly increased attempts to ensure efficacy, safety and patient acceptability. As discovery and development of new chemical agents is a complex, expensive and time-consuming process, so recent trends are shifting toward designing and developing innovative drug delivery systems for existing drugs. In those type of delivery polymer is needed for the stain drug deliver Chitosan the second most abundant next to cellulose, naturally occurring amino polysaccharide, derived as a deacetylated form of chitin. It isnon-toxic, biocompatible, antibacterial and biodegradable properties. As the chitosan is used as the polymer in the dosage form for the stain release of the drug in the systematic circulation. This review discusses the various forms of chitosan materials such as beads, films, microspheres, nanoparticles, nanofibers, hydrogels, etc. as drug delivery and the vast literature available on chitosan-based materials in drug delivery applications.

KEYWORDS: Chitosan, Chitosan Beads, Chitosan Buccal Films, Chitosan Microspheres, Chitosan Nanoparticles, Chitosan Nanofibers, Chitosan Hydrogels.

INTRODUCTION

Chitosan

Chitin (β-(1–4)-poly-N-acetyl-D-glucosamine) is widely distributed in nature and is the second most abundant polysaccharide after cellulose. Chitosan is a polysaccharide obtained by deacetylation chitin, which is the major constituent of the exoskeleton of cretaceous water animals. This biopolymer was traditionally used in the orient for the treatment of abrasions and in America for the healing of machesgashes. a recent analysis of the varnish on one of Antonius Stradivarius violins showed the presence of a chitinous material. Chitosan was reportedly first discovered by Rouget in 1859, when he boiled chitin in a concentrated potassium hydroxide solution. This resulted in the deacetylation of chitin, fundamental research on chitosan did not start in earnest until about a century later. In 1934, two patents, one for producing chitosan from chitin and the other for making film and fibers from chitosan.[1]

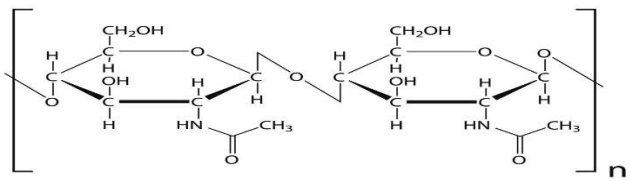


Fig 1: Structure of chitin.

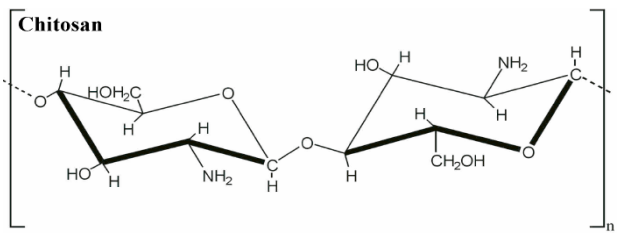


Fig 2: Structure of Chitosan.

The main driving force in the development of the new application for chitosan lies in the fact that the polysaccharide is not only naturally abundant, but it is also non-toxic and biodegradable. Unlike oil and coal, chitosan is a naturally regenerating resource (e.g., crab and shrimp shells) that can be a further enhanced by artificial culturing. It was reported that chitosan and chitin are contained in the cell walls of fungi. Chitin, however, is more widely distributed in the nature than chitosan and can be found in mushrooms, yeasts, and the hard outer shells of insects and crustaceans. It was reported, for example, that about 50-80% of the organic compounds in the crustacean and the cuticles of insects consists of chitin. At present, most chitosan in practical and commercial use comes from the production of deacetylated chitin with the shells of crab, shrimp, and krill (the major waste by-product of the shellfish-processing industry) being the most available sources of chitosan.[2]

One of the most useful properties of chitosan is for chelation.

- Chitosan can selectively bind desired materials such as cholesterol, fats, metal ions, proteins, and tumor cells.
- Chelation has been applied to areas of food preparation, health care, water improvements, and pharmaceutics.
- Chitosan has also shown affinity for proteins, such as wheat germ agglutinin and trypsin.
- Other properties that make chitosan very useful include inhibition of tumor cell, antifungal effects, acceleration of wound healing, stimulation of the immune system, and acceleration of plant germination

Chitosan is a good cationic polymer for member formation. In early research, it was shown that membranes formed from the polymer could be exploited for water clarification, filtrated, fruit coating, surgical dressing, and controlled release. In 1978, for example, Hirano showed that n-acetyl chitosan membranes were ideal for controlled agrochemical release. Later, he found that a semi-permeable membrane with a molecular weight cutoff ranging from 2900 to 13000 could be formed from chitosan capsules for cell encapsulation. the chitosan-alginate capsules had a liquid alginate core. Since then, several other studies have been reported on the use of chitosan copolymers for immobilization of hybridoma cells and plants cell. However, the apparent poor biocompatibility of chitosan with hybridoma and insects cells was indicated by Smith and McKnight. Structurally it is composed of (copolymer) N-acetyl-D-glucosamine and D-glucosamine units with one amino (NH^2) group and two hydroxyl (OH) groups in each repeating glycosidic units.[3]

Chitosan Properties

Polymer are nature exiting the nature like cellulose, dextrin, pectin, alginic acid and agar are naturally acidic in nature, whereas chitosan is an example of highly basic polysaccharide. Chitosan properties like solubility, viscosity, polyelectrolyte behavior ability to form films.

Physicochemical properties

The physic-chemical properties of chitosan are as follows

- Chitosan is a colorless, off-white, hard, inelastic, nitrogenous polysaccharide.
- The chitin molecular weight average range from 1.03×106 to 2.5×105 Daltons.
- Formed chitosan by deacetylation reduces it to 1×105 to 5×105 Daltons.
- Chitin can easily process into gels, powders, membranes, fibers, colloids films, and beads.
- Chitosan is a linear polymer
- Chitosan having Reactive amino groups and hydroxyl groups they are easily substituted by other groups.
- Because it is a polysaccharide it chelate with many transitional metal ions.

Biological properties

- Biocompatible- They have no antigenic property thus the compatible with animal and plant tissues.
- Natural obtained polymer
- Biodegradable to normal body temperature
- Safe and non-toxic
- Binds to mammalian and microbial cells
- Regenerative effect on connective gum tissue
- It acts as a Haemostatic 3, hypocholesterolemic, radical scavenging activity, anticoagulant property.[4]

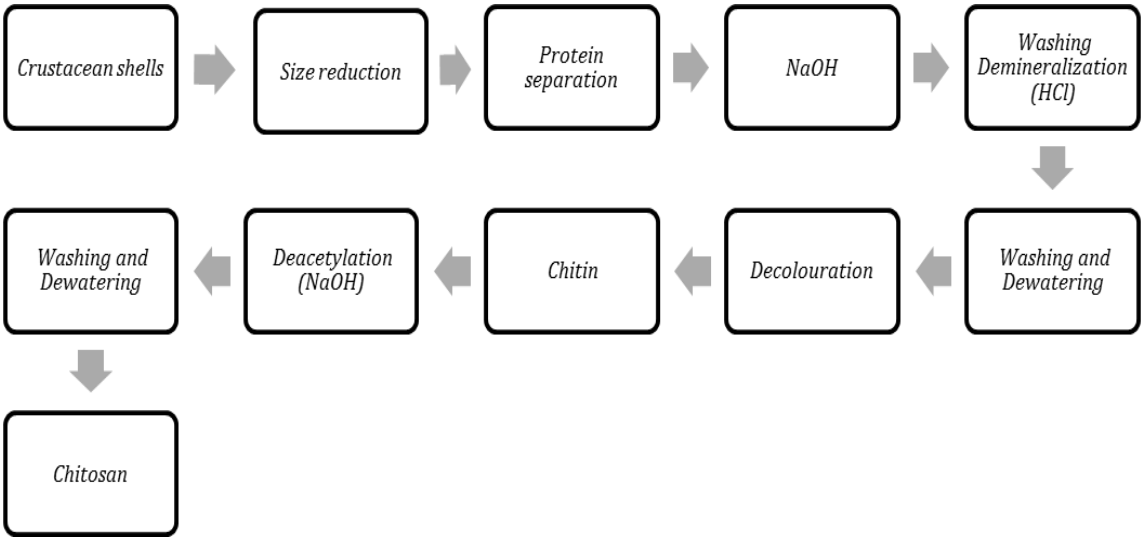
Manufacturing Process of the Chitosan

Chitin can be isolated from crustacean shells by chemical process. It involves some processing Steps as follows

a) Demineralization: It involves acid treatment (HCl) which expels the inorganic matter mainly calcium carbonate.

b) Deproteinization: In includes the extraction of protein matter in alkaline medium (NaOH).

C) Decoloration: It involves bleaching of the product by chemical reagents to achieve colorless product.[5]



- **Chitosan in drug delivery**

Chitosan offer exceptional biological properties due to which it has gained enormous importance in biomaterials formulation and has been remained under extensive exploration in drug delivery system. Chitosan is having the excellent biocompatibility and biodegradation. Some other properties of the chitosan are

· Haemostatics
· Bacteriostatic
· Anticholesteremic
· Anticarcinogenic and
· Fungistatic

The chitosan can be used for the various formulations of chitosan materials in drug delivery system and other biomedical applications along with their method of preparations. Several factors must be taken into account of the bioagents, particle sizes, residual toxicity of the final products, release kinetic profiles and finally the type of delivery system.[6]

- **Chitosan microspheres**

The practice of microsphere-based delivery system allows control over drug release profile and specific target site by carefully tailoring the formulation of various polymer-drug combinations. This type delivery system provides increased lifespan, controlled release rate and moreover target-specific drug. Different methods for the formulation of microspheres includes interaction with counterions like (sulfate, phosphates, hydroxides), cross-linking, solvent evaporation, ionic gelation, spray drying, emulsion polymerization, and precipitation/ coacervation etc.

S.NO	AUTHOR NAME	POLYMER/METHOD/DRUG	CONCLUSION	REFERENCE NO.
1	**Jameela *et.al***	Chitosan / Microspheres / Mitoxantrone	He has found that release rate depends on extends of crosslink His drug was release for 36 days. The preparation of the microspheres was prepared by precipitationmethod using sodium sulfate as precipitant, as well as precipitation controller.	[7]
2	**Guo Jingjing *et.al***	Chitosan/ microspheres/ linked antigenic peptides vaccine	He has prepared the microsphere of chitosan to deliver the antigenic peptides vaccine. The result was that chitosan microsphere used as an effective system the disease was targeted was T. gondii	[8]
3	**Zhuoyue Song *et.al.***	Chitosan/ Magnetic Chitosan Microspheres/ Oyster	He has prepared the microemulsion of magnetic chitosan microspheres. MCM had smooth surface with particle diameter of 2-6um. MCM would be used as promising adsorbents for the deproteinization of polysaccharides.	[9]

- **Chitosan Tablets**

The simple preparation procedure, low cost, and biocompatibility of gel-forming hydrophilic polymer was the main factor for their widely used as a matrix for oral extended release dosage.[10] The gel-forming capacity of the polymer giving three-dimensional networks is the controlling factor for drug release. Because of their biocompatibility and non-toxicity chitosan have been

using as a matrix for tablet preparation. The tablets methods are simple and it can be either by wet granulation or simply direct compression techniques.[11]

S.NO	AUTHOR NAME	POLYMER/METHOD/DRUG	CONCLUSION	REFERENCE NO.
1	**Liang Li *et.al.***	The Polymer Used Is The Chitosan/ Direct Compression Techniques	The *in-vitro* adhesion properties were found to be comparable to the commercially available tablets. The release rate found to be rapid which was controlled by changing the mixing ratio of chitosan and alginate. Increase in chitosan content along with viscosity grade of alginate decrease the release rate. Sublingually administered to rabbit gives bioavailability of drug to 69.6% as compared to 30.4% by orally.	[12]
2	**Yang Shao *et.al.***	Anionic Polymer of Chitosan	Investigated the effect of other anionic polymer combination to chitosan on the release rate. In vitro drug release in simulated gastric juice revealed combination of chitosan to anionic polymer further slowdown the release rate compared to the single polymer. The chitosan-xanthan gum was found as the best combination with extended-release rate up to 24 hours.	[13]
3	**Sahasathian *et.al.***	Chitosan/ Tablet/ Amoxicillin	The result showed that chitosan with the particle size less than 75 µm yieldedthe best-controlled release pattern and it was comparable tothat was obtained from the hydroxypropylmethylcellulose (HPMC) tablets. Moreover, the tablets containing chitosan with particle size less than 75 µm were able to provide a significantly improved sustained release profile of amoxicillin compared to the release profile of a commercial capsule.	[14]

- **Chitosan Nanoparticles**

The uses of nanoparticles in pharmaceutical industries are expanding step by step. The small size of nanoparticles makes them equipped for traveling through various biological barriers (like brain barrier) bringing drugs to the target site enhancing its efficacy.[15] Chitosan nanoparticles (cSNPs) are acting as an excellent drug carrier because of some intrinsic beneficial properties such as biocompatibility, biodegradability, non-toxicity, bioactive and relatively to some extent target specific triggered by its cationic character. Several methods have been reported for the preparation of chitosan nanoparticle, such as emulsion, coacervation or precipitation, ionic gelation, reverse micellar method, sieving method and Nano precipitation etc.[16,17] The nanoparticles prevent the enzymatic degradation of labile drugs in the gastrointestinal tract.[18] Several review articles have been published on chitosan nanoparticle-based drug delivery systems.[19,20] In which the author highlighted the advantages and advanced properties of nano-sized chitosan in drug delivery applications.[21]

S.NO	AUTHOR NAME	POLYMER/METHOD/DRUG	CONCLUSION	REFERENCE NO.
1	**Mitra *et.al.***	Chitosan/ Hydrogel Nanoparticles/ Dextran-Doxorubicin	Dextran minimize its side effect and encapsulation of this conjugate in chitosan hydrogel nanoparticle increase drug efficacy	[22]
2	**Sarmento *et al.***	Chitosan-Alginate/ Nanoparticles/ Insulin	Confocal microscopic examinations of FITC-labelled insulin Nanoparticles showed clear adhesion to rat intestinal epithelium and internalization of insulin within the intestinal mucosa.	[23]
3	**Fernandez-Urrusuno *et.al.***	Chitosan/ Nanoparticles/ Insulin	Nanoparticles enhanced the nasal absorption of insulin to a greater extent than anaqueous solution of chitosan. The amount and molecular weight of chitosan. The amount and molecular weight of chitosan did not have a significant effect on insulin response.	[24]

- **Chitosan Nanofibers**

Electrospinning of polymers into ultrafine fibers of nano size is another basic and novel method. Nanofibers were shown great promises in drug delivery provided that it's processing variables during fabrication can control precisely.[25,26] These nanofibers find potential application in biomedical and drug delivery fields pertaining to their integrally high surface to volume ratio and porosity, resulted in enhanced drug loading capacity, mass transfer properties and cell attachment.[27,28] Surface functionalization of nanofibers further advances their potential in drug and gene delivery applications.[29,30] Electrospinning of chitosan into nanofibrous materials was reported by many researchers.[31,32]

S.NO	AUTHOR NAME	POLYMER/METHOD/DRUG	CONCLUSION	REFERENCE NO.
1	**Bhattarai *et.al.***	Chitosan/ Nanofibrous/ Polyethyethene Oxide	This nanofibers exhibited biocompatibility with chondrocytes and endorsed the attachment of human osteoblasts and chondrocytes without changing the cell morphology and viability. The high surface area and short diffusion path length resulted from superior release rate to nanofiber drug system as compared to bulk material.	[33]
2	**L.Cremar *et.al.***	Chitosan/ nanofiber/ wound healing dressing application	The results of this study indicate that produced chitosan/ composite membranes can serve as potential wound dressing materials given its antimicrobial activity and similarity to the extracellular matrix which promotes cell adhesion/growth.	[34]
3	**Xue-Hui Chu *et.al***	Chitosan/ Nanofiber/Hepatocyte Adhesion	The successful integration of such nanofiber scaffold with BAL, through the introduction of nanometer materials into liver tissue engineering, may provide effective means to overcome the current problem of large-scale cultivation of hepatocytes in bioreactor	[35]

- **Chitosan Beads**

Chitosan can be modified in different forms to control the release rate and efficiency of the bioactive agent in delivery systems. Crosslinked chitosan beads are another important form of chitosan investigated by many researchers in delivery systems.[36,37] Chitosan a cationic polysaccharide forms gels bead with counter ions mostly polyphosphate has been used. However other counter ions were also reported like molybdate and other multivalent ions acting as coagulating agent.[38]

S.NO	AUTHOR NAME	POLYMER/METHOD/DRUG	CONCLUSION	REFERENCE NO.
1	**Kulkarni *et.al.***	Chitosan/ Chitosan Beads/ Diclofenac Sodium	Prepared and investigated the controlled release of diclofenac sodium; a drugused in the treatment of chronic inflammatory disease from glutaraldehyde crosslinked chitosan beads. The drug release was reported to effect by a number of physiochemical parameters such as temperature, beads characteristic, pH and stirring rate. Higher temperature affected beads release low drug as compared to lower temperature synthesized ones.	[39]
2	**Amit Kumar Nayak *et.al.***	Chitosan-Alginate/Beads/ Metformin HCl	Metformin HCl-loaded TSP-alginate beads were prepared by ionotropic-gelation technique and using CaCl2 as cross-linker. Proteins, enzymes, genomic materials, etc. can be encapsulated easily within these types of ionotropically gelled polymeric beads systems.	[40]
3	**My Linh Nguyen *et.al***	Phenol Using Crosslinked Chitosan Beads After Modification With Histidine And Saccharomyces Cerevisiae	Use of glutaraldehyde-crosslinked chitosan beads modified with histidine and Saccharomyces cerevisiae (SC-HIS- CCB) for improved phenol biosorption was investigated from equilibrium. The negative Gibbs free energy change confirmed the spontaneous nature of this biosorption process.	[41]

- **Chitosan Films**

Chitosan displays excellent film forming capability and finds many applications in drug delivery systems as a carrier for bioactive agents ranging from small molecule like antibiotic to macromolecules like nucleic acid and proteins.[42] Chitosan, due to its bacteriostatic property is known to enhance wound healing rate and also possess hemostaticproperties.[43] Thus chitosan films have been considered as wound dressing material. Generally, solution casting methods have been used to prepare chitosan films. The preparation of both simple chitosan and crosslinked chitosan films were reported by researchers for various applications. Crosslinking improves both physical and mechanical properties of chitosan like tensile strength, thermal stability, water-resistant property, color, and moisture retaining capacity etc.[44–48] Chitosan and crosslinked films have been investigated as drug delivery device in several fields like oral mucosal delivery[49,50,51], buccal delivery[52,53], transdermal delivery[54,55], sublingual delivery[56] and periodontal delivery.[57]

S.NO	AUTHOR NAME	POLYMER/METHOD/DRUG	CONCLUSION	REFERENCE NO.
1	**Varshoaz *et.al.***	Chitosan/ Buccal Film/ Lidocaine	Developed and studied the release behavior of Lidocaine a local anesthetic agent form crosslinked chitosan films for oral mucosal delivery. TripolyphosphatePenta sodium salt was used as crosslinker. The flux rate of Lidocaine was increased by high Mw and concentrated solution of chitosan.	[58]
2	**Sahar Salehi *et.al.***	Chitosan/ Buccal Film/ Rizatriptan Benzoate	*In-vitro* drug release profiles, disintegration and dissolution time, swelling properties, mechanical properties, and mucoadhesive characteristics of RB-loaded films were investigated.	[59]
3	**Leticia Mazzarino *et.al.***	Chitosan/ Mucoadhesive Films/ Curcumin	Mucoadhesive films containing curcumin-loaded nanoparticles were developed; Films were prepared by the casting method after incorporation of curcumin-loaded chitosan-coated polycaprolactone nanoparticles into plasticized chitosan solutions. These results indicate that the mucoadhesive films containing nanoparticles offer a promising approach for buccal delivery of curcumin	[60]

- **Chitosan Hydrogels**

Hydrogels are three dimensional crosslinked polymer systems which have the ability to retain large amounts of water through bonding without dissolving due to physical and chemical interactions between the polymer networks.[61] The gelation and biodegradation are two key components influencing the fate of cells.

Hydrogels show the capability to transport small molecules like drugs. Completely swollen hydrogels possess some physical characteristic common to living tissues, comprising rubbery and soft consistency, low interfacial tension with water and biological fluids.[62,63] The physical properties of hydrogels are regulated by the Mw, degree of crosslinking, charges and association. Increase in the degree of crosslinking resulted increase of stiffness and moduli, both of which was important for the protection of encapsulated drug from physical deformation during transportation and migration of hydrogel. Another important property is the pore or mesh size of hydrogel and hydrodynamic size of drug, which controls the diffusion of encapsulated drug. Chitosan hydrogels as a drug delivery device has grabbed the attention of many scientists. With the development of chitosan hydrogels a new intelligent drug delivery device has recognized that release the drug under different environmental stimuli.[64,65]

S.NO	AUTHOR NAME	POLYMER/METHOD/DRUG	CONCLUSION	REFERENCE NO.
1	**Duan *et.al***	Chitosan/ Hydrogel/ Lithium Hydroxide, Potassium Hydroxide, Aqueous Urea	The hydrogel prepared by this method possess homogeneous structure and compression fracture stress nearly about 100 times more than the hydrogel prepared by conventional acid dissolving method. Furthermore, the hydrogels showed exceptional biocompatibility along with safety and smart controlled drug release behavior activated by acid.	[66]
2	**Azab *et.al.***	Chitosan/ Chitosan Hydrogels/ Radioisotope (131I-Norcholesterol)	The hydrogels were surgically implanted subcutaneously and intraperitoneal. Radioisotope (131I-norcholesterol) loading in the hydrogel causes necrosis and severe tissue responses, but upto a distance of few microns. Thus this hydrogels could act as a biodegradable and biocompatible carrier for radioisotope delivery in brachytherapy for cancer.	[67]
3	**Dai *et.al.***	Chitosan/ Alginate-Chitosan Hydrogel/ Nifedipine	Investigated the swelling behavior and delivery characteristic of pH-sensitive alginate-chitosan hydrogel beads loaded with 'nifedipine', a drug used to treat hypertension. The amount of nifedipine released from the hydrogel increases with increasing pH (42% at 1.5 pH and 99% at 6.8 pH).	[68]

- **Chitosan Conjugates**

Chitosan and chitosan nanoparticles in conjugation with different compounds like folic acid and glucose have being investigated as a target-specific delivery system, especially for tumor cells Folate receptor is known as a highly specific tumor marker, usually overexpressed in cancer tumors.[65] Thus the conjugates possess the bifunctional property of both the chitosan and its conjugated compounds. Chitosan act as a carrier with bio-friendly or biocompatibility property[66], while the conjugated compounds contribute towards target specificity.[67,68]

S.NO	AUTHOR NAME	POLYMER/METHOD/DRUG	CONCLUSION	REFERENCE NO.
1	**Huijuan *et.al.***	Chitosan/ Conjugated Nanoparticles/ Doxorubicin Hydrochloride	Prepared folate-chitosan conjugated nanoparticles to improve the tumor target specificity using Doxorubicin hydrochloride (DOX). The prepared conjugate does not express any cell toxicity and also improves the cell uptake capacity of the drug due to the folate-receptor-mediated endocytosis. Thus GCNPs resulted as a promising delivery system in cancer therapy showing specific interaction with cancer cells identifying between glucose and Gluts.	[69]
2	**Heebeom Koo *et.al.***	Chitosan/ Conjugates/ Paclitaxel	Enhanced drug-loading and therapeutic efficacies are highly essential properties for nanoparticles as tumor-targeting drug carriers. Herein, he developed the glycol chitosan nanoparticles with hydrotropic oligomers (HO-CNPs) as a new tumor-targeting drug delivery system. These overall results demonstrate its potential as a new nano-sized PTX carrier for cancer treatment.	[70]
3	**Krum Kafedjiiski *et.al.***	Chitosan–Glutathione Conjugate	The obtained conjugate displayed 265.5 mmol immobilized free thiol groups and 397.9 mmol disulfide bonds per gram polymer. Because of the formation of disulfide bonds within the polymer, the stability of matrix tablets could be strongly improved. Results from the rotating cylinder method showed more than 55-fold increase in the adhesion time of thiolated chitosan vs. unmodified chitosan	[71]

CONCLUSIONS

In the field of biomedical Controlled and targeted drug delivery system are interesting aspects as it is a demand of time with increasing availability of drug which is highly specific to side to avoid its side effect. Chitosan as a biocompatible and biodegradable polymer plays an important role for such application. The chitosan nanocomposites further convey better properties with tunable what's more, upgrade responsive framework for target explicit medications. Different formulations of chitosan and its composites with inorganic nanoparticles increase the solubility of insoluble drugs forming stable complex and their safe delivery to the specific site. Other application of chitosan nanocomposite includes wound dressing, tissue engineering, bioimaging, biosensor, packaging etc.

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