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# Chitosan Formulations: Chemistry, Characteristics and Contextual Adsorption in Unambiguous Modernization of S&T

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## Abstract

Since long scientists explored natural/bio-polymers to explicit their innate features to develop certain novel utilities in modernization of prevalent Science & Technology. Consequently biotope derived polysaccharide embrace huge prospective desired functions. Amid, chitosan, the second most ubiquitous polymer after cellulose exists as a  $\beta$ -(1–4)-linked d-glucosamine/N-acetyl-d-glucosamine randomly distributed linear polycationic yield from partial deacetylation of chitin polysaccharide. Chitin's complexity limits its extraction/insolubility in aqueous solution, thus less studied/research until 1980s. As major polysaccharides are either neutral/negatively charged in an acidic environment, instead chitosan is cationic, eventually forms electrostatic complexes/multilayer structures/composites with anionic synthetic dopants/natural polymers. Chitosan own biocompatibility, non-toxicity, low allergy and biodegradability allow utility as in water treatment, wound-healing, pharmaceutical excipient/drug carrier, obesity treatment and scaffold for tissue engineering. It is reflected in the increasing number of related publications throughout in biomedical, environmental and industrials applications. Feeble chitosan solubility limits their applications, yet benign synthetic techniques viz.; sol-gel, encapsulation, chemical grafting are employed to yield composites/hydrogels/films/granules which generates new functionality, besides enhanced bio-compatibility and biodegradability. This chapter presents the R&D, trends and the latest prospects involved in advance synthesis of chitosan supported composites/hydrogels/films/granules/sheets with special highlighted pharmaceutical/biomedical and environmental applications.

**Keywords:** chitin, chitosan, pharmaceuticals, biomedical, environment, sol-gel, composite, hydrogel, formulations

## 1. Introduction

Bio-polymers yield via flora and fauna; plants, fungi and many other natural origins constantly attentive the worldwide researchers by virtue of endurance for atmosphere and our life [1]. Among bio-molecules polysaccharide like chitin/

chitosan which carried skeletal architecture in many animals besides feedstock used in rational designing of smart materials consequently [1, 2]. S&T vitally explored chitin/chitosan for comprehensive growth and economic progression in assorted fields including clinical, medical, pharmaceuticals and environment along with fulfilling sophisticated nanotechnology requirements [3]. Today scientific modernism and industry inventively carry out R&D in pharmaceuticals, environment, and bio-technology which fortify livelihood and offers accessible facilities via copious trustworthy merchandise [1–4]. For this purpose, chitin/chitosan matrix is fore-mostly investigated to derive innovative formulations owing innate exclusive, multi-functional and particular variable characteristics devoid in customary stuff and counter parts [1–6].

Chitin own  $\beta$ -[1,4]-2-acetamido-2-deoxy-D-glucose/N-acetylglucosamine monomeric unit as linked via glycosidic bonds which occurs as the second copious natural polymers after cellulose to cater numerous remarkable prospective needs in prevalent modernization [1]. Chitin is regularly produced all over the world with capacity of 1500 tons/annum. Chitin/chitosan is frequently utilized in biochemistry, microbiology, chemistry, polymer engineering, pharmacy, medicines and material sciences [4]. Flexible raw chitin undergoes alkaline deacetylation to derive chitosan matrix own further facile molding via assorted biological/physicochemical amendments to yield better capable composites, hybrids and blends exceeded over counterpart cellulose. Chitin/chitosan owe elite characters viz.; highly flexible, bio-compatible, bio-degradable and non-toxic. Nano-technology signified chitin chemistry in S&T via preparation of various innovative, creative and widely usable matrix formulations from lithe chitosan [7, 8]. Model chitin/chitosan matrix can be improved which offers requisite beneficial applications in recent modernization [1–9]. Thus, chitosan is extraordinarily impressive to derive easy formulations accredited to innate proactive  $\text{—NH}_2/\text{—OH}$  functionalities as executed via varied physic-chemical chemical alterations viz.;  $\text{—NH}_2/\text{—OH}$  acylation or alkylation and primary amine N-quaternization besides C-6 carboxylation [1]. Extensive adaptations in chitosan imparts inclusive cationic characters due to protonation of primary  $\text{—NH}_2$  to ammonium ion  $\text{—NH}_3^+$  which resulted acid to alkaline pH dependency and extra solubility [2–9]. Liberal breakthrough are offered in many fields including nanoscience, biotechnology, pharmaceuticals and tissue engineering scaffolds procured via chitin/chitosan outstanding character viz.; biodegradable, biocompatible, non-toxic and antifungal/microbial immunogenic profiles [9]. Some chitosan derived superior formulated materials in nanoscience/biotechnology along with case study of fluoride mitigation from water are summarized in this chapter.

## **2. Chitin-chitosan chemistry**

### **2.1 Mucoadhesiveness**

Chitosan is mucoadhesive due to inherent cationic nature and hydrophobic interactions that found weaker than anionic polymeric carbomer. Sustainable mucoadhesive character offers high cohesive/adhesive bonds within polymeric matrix as comparatively weak mucus gel layers. The rational chemical, biological or physical treatments on raw chitosan framework gets improved via complexation with multivalent anionic excipients like inorganic/organic ionic drug components. Some strategic alterations in its skeletal are partial due to cationic substructures imparting ionic interactive mucoadhesion. Oral bioavailability involving with such mucoadhesive chitosan particularly not gets achieved if mixed with polyanionic carbomer. However cationic character and ultimately mucoadhesive properties can

be enhanced up to 3/4-fold by trimethylation at  $\text{NH}_2$  functionality via PEGylated derivatization or immobilization of thiol groups. Chitosan forms disulfide bonding with mucus gel layer glycoproteins yields most mucoadhesiveness [10]. Gelling material: Macromolecular polymer gel called hydrogel can be constructed through the cross-linked polymeric network using hydrophilic monomers by chain/step growth, besides a purposeful cross-linker employed to endorse net-like structure owing void imperfections. Such hydrogel absorbs water via hydrogen bonding, resulted self-healing alike to expand typical firmness hitherto mechanical elasticity. Self-healing spontaneously forms new bonds within a hydrogel matrix during reconstructive covalent dangling surface chaining or via non-covalent hydrogen bonding. Inherently flexible chitosan skeleton have motivated the R&D of self-healing hydrogels are invoked as reconstructive tissue engineering scaffolds besides in passive and preventive utility.

Chitosan hydrogels are resulted for *in-situ* gelling which is properly altered via pH-dependent hydrostability [1–4]. In-situ gelling delivery system derived from chitosan and polyacrylic acid blend yields liquid state formulation at moderate acidic pH which gets transformed into viscous gel at pH 7.5. Chitosan's  $\text{—OH/NH}_2$  functionality undergoes cross-linking via disulfide treatment/thiolation found to impart additional *in situ* gelling due to significant viscosity use to access oxygen on nasal/ocular mucus surfaces. Chitosan–thioglycolic acid conjugate cross-linked hydrogels are rationally designed owing 16,500-fold instant viscosity to be utilized for advanced clinical uses [11]. Gene expression material: Chitosan skeleton gets modified to impart gene expression characteristics. Strategic self-branching of chitosans improved its basic gene transfer properties without conciliation its innate safety domain [12]. Trisaccharide moiety with molecular mass of 11–71 kDa are facile to get self-branched onto chitosan framework showed elevated transfection efficiency for gene expression two to five times than that of own linear counterparts. Chitosan/plasmid NP matrix have shown enhanced gene expression levels due to strategic self-branching which found to result in higher stability properties toward nucleases [13]. Reducing conditions of cytoplasm, plasmid gets released in target cells due to framed disulfide bondings which are cleaved *in-situ* and release at the target site. Transfection rate of thiolated chitosan-plasmid NP matrix is fivefold superior to unmodified chitosan/pDNA-NP complex [14]. Advanced gene expression materials owing enhanced cationic characteristics to work as tools for DNA-based drug delivery are developed through assorted physicochemical treatments onto raw chitosan skeleton viz.: trimethylation at primary amino function, cyclodextrin derivatization, and PEG-alkylation [15]. Chitosan based stable complexes of poly-anionic drugs own interfering RNAs/DNAs can perform its controlled/sustainable release. Chitosan being less toxic its higher ratio gets utilized than other cationic counterpart like poly-arginine and poly-lysine, to yield stable complexes with anionic drug moiety. These chitosan complexes protects degradation by DNases and ultimately imparts high stability and resultant NPs smaller than 100 nm have shown effective positive zeta potential as vital for endocytosis and best for non-viral gene carrier [16].

## 2.2 Permeation characters

Chitosan own  $\text{—NH}_2/\text{—OH}$  functionality which own pronounced cationic characters and makes it facile for the permeation enhancement due to interactive structural reformation of tight junction-associated proteins [1]. Rationally designed degree of deacetylation and molecular mass of raw chitosan found to control permeation enhancement and toxicity besides fairly more epithelial permeability to the greater extent [1–5]. Chitosan is facile to blend with assorted permeation enhancer doping agents can lead synergistic effective phenomenon resulted 4-fold improved



activity. Chitosan-cyclodextrin derived nanoparticles exhibit more permeation enhancement for small peptides as a carrier, nevertheless 30-fold additional permeation enhancement is achieved on certain mucosal membranes via thiol formation/derivatization of chitosan [6]. Many chitosan blends/composites are employed for effective drug delivery of assorted biomaterial/drugs in the treatment of cancer [1], optical [2], and colon diseases [4] as shown in **Table 1**. Based on inherent chitosan’s molecular weight of low, medium and higher the *N*-trimethylated with polyethylene glycol (PEG) derivatives are formulated as hydrogel and used in nasal drug delivery [1]. The high/moderate molecular weight chitosan with *N*-trimethylation after blending PEG found to have shorter sol-gel transition span at physiological temperatures and good hydrophilic property besides strong mucoadhesiveness. Such hydrogel formulations of chitosan showed advantageous features like good pharmacokinetic, rheological and mucoadhesiveness, slow/control/sustainable improved drug delivery, fair compatibility encourage stability, more efficacies and low toxicity along with fast sol-gel transition at ambient temperatures [1].

Chitosan-nanostructured frameworks involved rationally designed biological/physicochemical cross-linking within its matrix via alteration at hydroxyl/primary amino functionalities. Cross-link skeleton are reframed as stable droplets via emulsion followed by high-speed stirring random collisions, while precipitation is elicited by coalescence of chitosan droplets with alkali solutions. Ultrafine chitosan NPs

Chitosan formulations	Utility	Applications
Chitosan derived nanogels	For optical pH-sensing analysis	Responsive hybrid nanogels derived from chitosan shown nonreversible pH-sensitivity. Highly stable chitosan-nanogel quantum dots are also used.
Zinc-pectin-chitosan hybrid	Resveratrol drug delivery in colon	1% chitosan formulation with pectin/drug 3:1 ratio at pH 1.5 exhibited best performance of drug release at colon.
Chitosan-zidovudine composite	Stops Zidovudine loss in human plasma, with long life	Extended retention time (shelf life) for composite that gathers in kidney than heart, liver, spleen, lung and brain.
Sodium alginate-chitosan composite	For vaginal delivery of drug	Chitosan-sodium (ratio 1:4, w/w) alginate composite shown controlled release of chlorhexidine digluconate drug.
Cyclosporin A-chitosan hybrid	Extraocular administration	Enhanced therapeutic index of challenge drugs used in extraocular diseases.
Chitosan-based polyelectrolyte coats	Drug delivery on skin	Films/coats viable for notable drug release/permeation through skin.
Chitosan nanospheres loaded by 5-fluorouracil	Delivery of 5-fluorouracil for cancer treatment	These stable nanosized chitosan particles can entrap and deliver drugs in tumor cells.
Chitosan-tripolyphosphate composite own drug	Insulin delivery for diabetic disease	Chitosan improve bio-availability besides intestinal sorption resulted low blood glucose.
Chitosan-DNA nanostructures	Entrapped plasma DNA carrier	Chitosan-nanostructures guard entrapped plasma DNA from nuclease filth.
Chitosan conjugated complex	Encapsulated conjugate delivery	Highly targets tumor cells.
Chitosan doped drugs	Fluorescein drug gets effectively delivery	Potent drug delivery on epithelial cells of ocular mucosa.

**Table 1.**  
*Certain chitosan formulations/composites used for controlled drug delivery [1].*

owing narrow particle size 1 and 10 nm also achieved by means of reverse micellar medium to be used for effective drug delivery. Methodical encapsulation of other conjugates in chitosan matrix is viable to get prominent NPs using surfactant dissolved in an organic medium to yield reverse micelles with advanced R&D view to be utilized in macromolecule delivery. Fractional conjugation of PEG at alkaline conditions resulted self-aggregated amide linked soluble composites which ensnare insulin drug via electrostatic interactions with residual cell proteins. **Table 1** shows a selection of studies on the utilization of chitosan NP composites for drug delivery systems.

### 2.3 Safe chitosan composites

Advanced alterations in chitosan frameworks to yield assorted nanostructured matrix can proffer myriad biomedical/pharmaceutical applications. Chitosan is comparatively safe due to abundance in nature from renewable sources, biodegradable and biocompatible nature; yet unmodified chitosan usage is limited by virtue of huge hydrophobicity and high viscosity which tends facile coagulation with proteins at high pH. Despite many limitations still chitosan is vulnerably amazing matrix for drug delivery purpose. These nanocomposites derived from chitosan are prestigiously advantageous over conventional counterparts due to enormous surface area and supplementary features procured through blending/grafting/impregnation particularly for clinical utility. Chitosan matrix plays vital role in tissue engineering and fabricated composite of this bio-polymer acts as good bone implant materials. Research efficacy of chitosan derived hybrid/composite materials cater many challenges and own myriad functionality in S&T [17].

### 2.4 Sculptured formulations

Biological polysaccharides like chitin/chitosan proved the most excellent model toward the formulation with hydroxyapatites via tempted apatite nucleation which resulted HA crystal growth by virtue of super-active  $\text{—C=O}$ ,  $\text{—OH}$  and  $\text{—NH}_2$  functionalities. Quality and quantitative share of staples chitosan besides other vital factors like presence of inorganic ions, pH and temperature governs effective mineralization of hydroxyapatites.  $\alpha, \beta$ -Chitosan staple-HA crystals of chondroitin sulfate scaffolds are obtained as major bio-matrix hosting embed guests practicable for native physico-chemical and hierarchical controls anticipated in bio-mineralized tissue replacement materials. Chitosan has elevated empathy for charged octacalcium phosphate/OCP acting as a herald to enamel, dentine and bones compartmentally formulated crystals own orientated/alternated hydrated-apatite coating akin hydroxyapatite/HA. Nano-hydroxyapatite yields via chitosan-gelatin networking surface are facile to modulate under amicable conditions of adjustable charges, templates density; temperature [1, 17]. Chitosan is facile for intervening poly-anionic linear 1-4-R-D-galacturonosyl/methyl esters/1-2-R-L-rhamnopyranosyls impart apatite-formation due to innate carboxyl functionality which undergoes mineralization along with catalytic heterogeneous apatite nucleation. Skilled chitosan-apatite hydrogels with increased strength obtained via rationally designed egg-box skeleton with  $\text{Ca}^{2+}$  cations [18].

### 2.5 Step up chitosan matrix: to get rid native limiting traits for myriad utility

Ever growing scientific decisive exigent it needs stepping-up adoptable chitosan matrix to overcome native restraining traits and to avail its innumerable challenging applications. Prime barriers in chitosan utility imparted due to certain restrictive characters viz.; reduced mechanical stability/strength, weak crystallinity and low solubility in water as well as in organic solvents ultimately constrained practical

utility. Hence, raw chitosan seek vital formulations/modifications performed under doping, blending, grafting and impregnation methodologies which enhance limiting features establishing enough shelf-life for its advanced applications. Mechanical stability gets achieved by manipulating environmental factors and processing conditions viz.; temperature, chemical/ionic stabilizing agents in fabrication of chitosan based matrixes [19].

Multifunctional composites/hybrids/matrixes fabrication put global R&D inputs in modern S&T developments. Chitosan-based materials due to inherent biocompatibility, biodegradability and mucoadhesiveness are used in numerous biomedical applications, including prolong/control release of drugs/cell/genes, cartilage/bone-tissue scaffolds, wound dressings, blood anticoagulants, and space filling implants [20]. Crude chitosan as diverse semi-solid structure undergoes facile and assorted alterations/modifications in mild conditions like at lower pH (than  $pK_a$  6.3), yields non-Newtonian, shear-thinning fluid. Such formulations own good mucoadhesiveness due to cationic nature as imparted by free  $\text{—OH/—NH}_2$  interaction with mucin by hydrogen/electrostatic forces, thus acts as suitable excipient for buccal, nasal, ocular and vaginal dosage [1]. Chitosan formulations have shown penetrative enhanced and active transport via epithelium layer encloses tight junctions [1]. Chitosan show high susceptibility to environmental factors and processing conditions like heating and freezing thus impose stressful degradation of its skeleton.

Rather, variable molecular weight, polydispersity, controlled deacetylation degree, purity and % moisture determines degradation/splitting of  $\beta$ -1,4-glycosidic/depolymerization and *N*-acetyl/deacetylation link cleavages resulted decrease molecular weight and raised deacetylation degree. Strong intermolecular interactions of chitosan interchain crosslinking modify its skeleton, leads irreversible loss in physicochemical properties [20].

## 2.6 Factors affecting chitosans stability

### 2.6.1 Purity

Chitosan is available in many grades of purity depending on molecular weight, and deacetylation degree. Chitosan manufacturing methods greatly responsible for different qualities and properties with resulted corresponding deviations. Further specifications are frequently curtailed and mislead its utility features. While chitosan recovers from sources engross demineralization, deproteinization and decoloration which imparts certain impurities, like ashes, heavy metals, and protein causing complex dissolution and impede preparations. Chitosans purity affects biological immunogenicity/biodegradability also alters solvent solubility and mechanical strength/stability while, microbiological contamination enhances its enzymatic hydrolysis/degradations. So chitosan based material formulations seeks contaminants free and high quality extra [21].

### 2.6.2 Polydispersity

Assorted molecular weight distributions in preparation of chitosan matrix is viable for significant physicochemical and biological features like hydrophilicity, viscosity, water-uptake ability, biodegradability, and mucoadhesion. Based on original resources and corresponding preparation methodologies the commercial grade chitosan own average *molecular weight* of 10–100,000 kDa and estimated via, osmometry, light scattering, NMR, viscometer and chromatographic techniques. These measurements needs properly validation, since molecular weight of chitosan differs based on the applied technique. Degree of deacetylation can decrease

molecular weight, uniformity, polydispersity index (between 0.85 and 1.15 own good polymer homogeneity) and proper functionality of chitosan products. High molecular weight chitosan is comparatively more thermal stability than low MW stuffs. Moreover, numerous factors viz.; strong acids/alkali, high temperature, mechanical shear, irradiation found to influence the molecular weight of chitosan. High pressure homogenization, wide shearing, centrifugation often decrease  $M_w$  and responsible for the fluctuations in polydispersity index. The compression force drawn in tablet formation is accountable for heat generation so manipulates  $M_w$  distribution.

### 2.6.3 Prototype degree of deacetylation

The degree of deacetylation viably accounts ratio of glucosamine to *N*-acetylglucosamine units, whereas glucosamine and *N*-acetylglucosamine distribution all along its elongated chain illustrates its characteristics pattern of deacetylation. Chitosan's deacetylation degree is managed via adaptable time and temperature involved in de-*N*-acetylation according to specification parameter around 70–95%. Deacetylation conditions demonstrated characteristic  $P_A$  varies from block to random vital to accurately define its degree of de-*N*-acetylation and  $P_A$  which are crucial factors for attaining desired physicochemical/biological functions. Low DD induces sharp inflammatory response due to quick degradation rate, while high DD grounds minimal inflammation and *in-vitro* minor affinity to enzymes.  $P_A$  and DD found to manipulate biodegradability via homogeneously distributed acetylation yields inferior enzymatic degradation. Studies revealed alteration in DD found to influence hydrolytic and thermal capacity of chitosan derived materials as more de-*N*-acetylated slower acidic hydrolysis during storage. Highly deacetylated chitosan owe less porosity, lesser hydrophilic, and more photo-sensitive for degradation thus restricts degradation in acidic conditions.  $P_A$  significantly collies with charge density and affects chitosans solubility owing identical  $M_w$  and DD as block of acetylation/deacetylation which gets aggregated in acidic environment and hinders its dissolution process.

### 2.6.4 % Moisture

Basically chitosan is hygroscopic thus capably forms hydrogen bonding via inherent  $\text{—OH}$  and  $\text{—NH}_2$  functionalities which affects relative humidity i.e., moisture content depending on storage in surrounding temperature independent of DD or  $M_w$ . While water-uptake capacity/hydrophilicity of chitosan based materials found to decrease with enhancement of degree of de-acetylation as absorbed water plays critical role in solid formulations by affecting concern flow properties and compressible tensile strength. Fluctuated moisture level in chitosan derived material alters physicochemical and mechanical properties as dehydration decreases crushing strength besides augmented friable disintegration. Higher moisture content imparts faster pronounced damage via hydrolysis and limits chitosans applicability, thus it need to optimize/reformulate or moisture. Swelling index testing is used to investigate water-uptake ability changes upon long-term storage of chitosan materials for both semi-solid and solid formulations.

## 2.7 Chitosan stability affecting factors

### 2.7.1 Environmental conditions

The environmental factors are very crucial for sensitive chitosan and it can be stored in closed containers at temperatures of 2–8°C particularly in ascertaining



shelf-life. The extra stable chitosan materials provide reliable quality of chitosan. The crucial environmental parameters like humidity and temperature alters physicochemical properties and applications of chitosan [22].

### *2.7.2 Humidity*

Moisture i.e., ambient relative humidity of chitosan strongly controls transport followed Fickian process, as high humidity is viable for an anomalous diffusion kinetic. Humidity > 60% is responsible for water penetration more intensively via chitosan chains, thus % moisture increased significantly resulted plasticizing/swelling and prolong storage results hydrolytic damage besides alter physicochemical and biological characters. Ambient humidity 75% is viable for greater swelling of chitosan and liable for better and faster release of drug as a carrier. Overall, undue hydration at elevated humidity fades mucoadhesiveness of chitosan based drug carriers due to “dilution” of functionality accessible for mucin adhesive interactions. Suitable humidity conditions are important for storage of solid chitosan formulation products as rate of hydration found extensive at high RH. Also proper air-tight containers are advisable in order to protect hygroscopic products against interfering environmental humidity.

### *2.7.3 Heat/temperature*

Heat/temperature variably affects the water content in chitosan-based materials. Elevated temperature > 40°C can origins major moisture loss/dehydration that gives decreased hardness and mechanical strengths. Atmospheric temperature found to influence degradation and hydrolysis rate of chitosan matrix, mainly in liquid and semi-solid phases. However, chain hydrolysis is not observed in the chitosan storage at 5°C, thus verifies storage in a refrigerator at 2–8°C.

### *2.7.4 Acidic dissolution/processing*

Hydrolysis is problematic in pharmaceuticals due to its dissolution in diluted acids as scheduled in chitosan-based formulations. Acid catalyzes splitting of polymer chains/linkages depending upon acid type/concentration, treatment time, and temperature besides decreases its average molecular weight, viscosity and weaken mechanical strength. Chitosan hydrolysis is performed usually under specific organic acids like lactic, formic, lactic, and mineral acids hydrochloric. Faster chain damage observed if lower DD chitosan which own extra porosity and electrostatic repulsion between protonated  $\text{NH}_2$  which promotes penetration of acid inside its flexible skeleton. Chitosan gets decomposed in aqueous acetic acid at 5°C and intrinsic viscosity under specific solvent and temperature direct affects polymers average molecular weight. Mark-Houwink exponent explores alterations in chitosans specific conformation via amplified chain length indicated framework as  $\alpha = 0$  consign compact sphere and  $\alpha = 0.7$  refer random coil while  $\alpha = 2$  own rigid ceilings helpful in determining average molecular weights.

### *2.7.5 Sterilization*

Sterilization eliminate/remove/kill/deactivate all living forms and species present on, or chitosan matrix employed for drug administered owing high microbiological purity. Chitosan formulations/materials are usually sterilized either physically or chemically leading irreversible alteration in its structural features and function via many techniques like filter sterilization, steam sterilization, dry heat, ethylene oxide activated, and  $\gamma$ -radiation exposures. Sterilization of chitosan gels can be achieved

through saturated steam found to cause chain/linkage scission resulting about 50% decrease in viscosity and loss of molecular weight. Similarly, autoclaving sterilizes chitosan films and reduces inherent tensile strength via interchain crosslinking of amino groups which ultimately weaken polymeric solubility. There are no significant changes observed in structure of chitosan through autoclaving also its molecular weight is unaffected once steam sterilized prior to autoclave. Gamma/ $\gamma$ -irradiated sterilization cause significant chain scissions owing low water sorption capacity and decreases molecular weights depending on doses of irradiation and polymer chain rearrangements. Epoxide exposure causes minor changes in morphology and physicochemical features of chitosan restricted to surfaces. Ultraviolet light displayed degradation of chitosan via free radical formations that can destruct amino/hydroxy groups.

#### 2.7.6 Thermal heating

Heat is frequently employed in chitosan-based formulation which is responsible to change polymeric properties, like aqueous solubility, viscosity, and its appearance. Chitosan decompose/damage is on heating at rising temperature and span of heating. The first stage degradation occurs at 30–110°C due to evaporation of the residual water and second thermal damage in chitosan skeleton observed over temperature range 180–340°C. Differences in glass transition temperatures resulted diverse increasing molecular weight chitosan. Third stage degradation is viewed at 470°C due to subsequent weight loss of chitosan. Thus, chitosan matrix is advisable to heat up to temperatures below glass transition temperature with unaltered physicochemical features. Still the gentle heating is necessary to dissolve chitosan in acidic solution since overheating cause's polymer discoloration and depolymerization which eventually change rheological properties. The added/doped drugs, plasticizer or additives in chitosan matrix reduces its glass transition temperature. Thus excipients employed in chitosan formulations preparation are doped at the temperature 120 and 170°C. Thermal decomposition alters electrostatic charges resulting higher hydrolysis and accelerated aggregations.

#### 2.7.7 Lyophilization

Freeze-drying or lyophilization is established drying way in which chitosan is dried by sublimation of ice which is advantageous to prevent aggregations. *Lyophilization* of chitosan can feasibly improve physicochemical stability of colloidal microparticulate in formulated delivery products over extended time periods with better physicochemical stability. Yet, lyophilization impose stress on unmodified chitosan and damage its polymeric chains via weakening inter/intramolecular hydrogen bonding and hydrophobic interactions [23]. This brings negatively effect on viscosity, zeta potential, and water-uptake ability of chitosan formulations.

### 2.8 Strategic improvements in chitosan products

Chitosan polymer owes poor stability over time renders unsuitable/inapplicable in the pharmaceutical products. Thus, effortful researches are done to improve the stability of chitosan formulations without affecting its chain damage as shown in **Figure 1** [24].

#### 2.8.1 Stabilizing agents

Chitosan is very susceptible to physicochemical degradation upon storage thus it needs to apply proper excipients so as to improve stability of chitosan-based



**Figure 1.**

*Strategic upgrading for stability of chitosan matrix to improve their productivity.*

systems. Dry heat exposure/steam sterilization have own remarkable consequence on properties and performance chitosan formulations. Thus developed assorted stabilizing additives to protect chitosan during thermal processing and sterilization. Polyols like mannitol, sorbitol, and glycerol as *the stabilizing agents* in chitosan formulations prior to autoclave protects hydration layer around its skeletal surface through interchain hydrogen bonds which markedly slow down its degradation besides protects viscosity and thermogelling properties. Chitosan microparticles obtained via ionotropic gelation followed by tripolyphosphate sodium crosslinking in polyethylene glycol shown stabilized zeta potential and prevent aggregation over long span. Added stabilizer reduces the particles electrostatic charge and led to aggregation after long storage.

Stabilizing polyols like disaccharides act as water replacement agents and interact via hydrogen bonding replaced water besides highly viscous sugar hinder labile materials from disruption via freezing. This plasticizer added to chitosan formulations can manipulate water-uptake capacity/hydrophilicity and mechanical strength that consequence prolonged and controlled drug release profile. Metal ions like Zn(II) are also added to enlarge colloidal stability of chitosan polyelectrolyte formulations due to imparted stabilization attributed to coordinate bondings tune to morphological alteration and swelling properties.

### 2.8.2 Blends/hybrids

Chitosan blends/hybrids are obtained via nonionic additives responsible to improve physicochemical properties than both constituting agents. Mixtures of chitosan with starch, poly-vinyl alcohol, poly-ethylene oxide and polyvinylpyrrolidone enhances material stability of resultant blended matrix. Chitosan undergoes specific interactive blendings as achieved via hydrogen, ionic and/or dipolar interference with residual component's dependent miscibility display decreased moisture sensitivity. Blended modification controls water-uptake capacity and own higher thermal degradation compared to pure chitosan and proportionated addition. Such blending controls and improves thermal/hydrolytic stability besides biodegradability which conveys resistive enzymatic degradation.

### 2.8.3 Physicochemical crosslinking

Chitosan skeleton undergoes significant modifications via various physicochemical crosslinking. Added agents-chitosan blends forms chemical crosslinking via covalent bonding and physical crosslinking via ionic bonding. Chemical guard the physicochemical stability of chitosan since gelation is irreversible higher stability is achieved through more covalent bonds besides hydrogen/hydrophobic bondings. Rather chemical crosslinking changes biological properties and limits practical pharmaceuticals utility. Crosslinking level markedly influenced swelling ability, mucoadhesiveness, acidic stability of microparticulates and color alterations.

While ionic/physical crosslinking bridges negative charged components like citrate, sulfate, phosphate groups binds faster onto cationic chitosan which prevents protonation of chitosan amino groups to yield polyelectrolyte complexes. Physical modification is simple, facile and mild requires no catalysts and extra purification in contrast to chemical crosslinking. Chitosan-acyclovir crosslinking are achieved via solvent change with sodium citrate salting shown better physical stability to drugs viable for its controlled release. Microparticulate delivery systems derived from chitosan are strongly depends on surface electrostatic charges that gets altered upon storage, so strategies are developed to prevent aggregation and corresponding zeta potential changes. Improved microparticles stability is attributed due to added non-ionic stabilize polyoxyethylene sorbitan sodium monooleate over ionic crosslinkings.

Despite the great potential of using chitosan in drug delivery or tissue engineering systems, its poor long-term stability is a substantial drawback in the scaling-up of chitosan pharmaceutical applications. Upon storage, chitosan undergoes gradual chain degradation followed by destruction of its functional groups which as a consequence leads to irreversible loss of its physicochemical properties. Both intrinsic (degree of deacetylation, molecular weight, purity, and moisture level) and extrinsic factors (environmental storage conditions, thermal processing, sterilization, and processing involving acidic dissolution) are acknowledged as crucial parameters affecting the stability of the chitosan-based formulations. To improve chitosan stability, several strategies (addition of the stabilizing agent during the preparation process, blending with hydrophilic polymer, and use of ionic or chemical cross-linkers) have also been reported. As there are no universal principles to preserve chitosan-based products upon storage, preformulation studies and selection of the most proper storage conditions are essential to provide their maximal stability.

## 2.9 Chitosan formulation for water treatments

### 2.9.1 Case study of defluoridation/fluoride removal

Chitosan is facile to sophisticated biological and physicochemical adaptations in its inherently flexible skeleton so as to yield novel composite/blend which own huge and widespread applications than its contemporary cellulose [1–4, 25]. Qualitative and quantitative framework changes in chitosan matrix can offer highly facile industrial grade suitable formulations/fabricated products and solutions have provided ever demanding exertion in water and wastewater treatments. Biosorption of fluoride from water onto fabricated chitosan-graphite novel composite is illustrated.

### 2.9.2 Synthetic scheme of chitosan doped bio-composite

Chitosan gelling obtained via dissolution in acetic acid at mild acidic pH gets intertwined via invasive hydrophilic/phobic interaction and induces impulsive entanglement in self-standing microsphere hydrogel as shown in **Figure 2**.



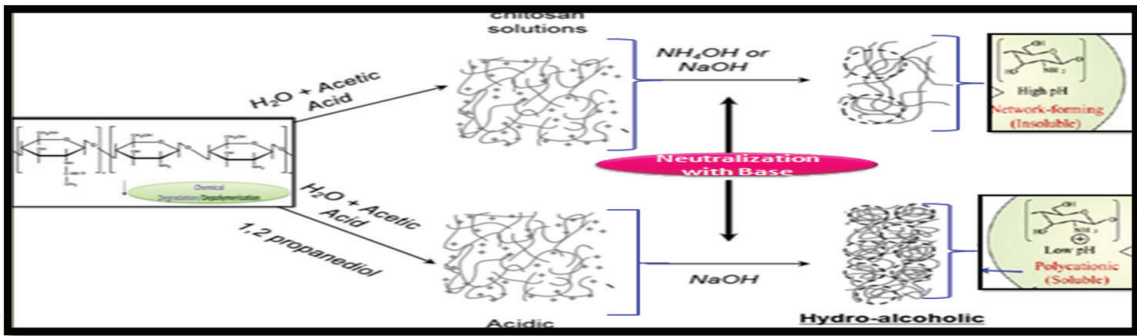


Figure 2. Preparation scheme for chitosan gelling (scale-5 mm).

This phenomenon followed by coagulation in alkaline solution which subsequently yields viscous droplets/bids are further treated with graphite resulting desired fabricated chitosan doped graphite composites FCDGC. Chitosans hydrogel on drying or evaporation causes dramatic shrinkages in its pore size to impart porosity owing elevated specific surface area. This micro-porosity is attributed to space zones of contacts between chitosan fibrils though impregnation onto  $\text{—OH/—NH}_2$  by doped graphite surfaces as shown in **Figure 3**.

2.9.3 Fluoride biosorption onto FCDGC

The fluoride anions are facile to sorbed by FCDGC due to diffusive interaction via weak intermolecular forces as bridge to connect fluoride onto activated surfaces of adsorbent that ultimately enhanced sorption capacity. Although, amine/ hydroxyl groups of FCDGC plays vital role in bio-sorption of fluoride, however, other functionalities also affect fluoride sorption may be due to surface complexation, physic-sorption and chelation affinity suitable for scavenging fluoride at pH 6.5. Further, decreased in fluoride sorption in above pH > 6.5 is interpreted due to ligand-exchange between fluoride and counter anion hydroxide coordinated on immobilized FCDGC. This developed FCDGC displayed a surface controlled

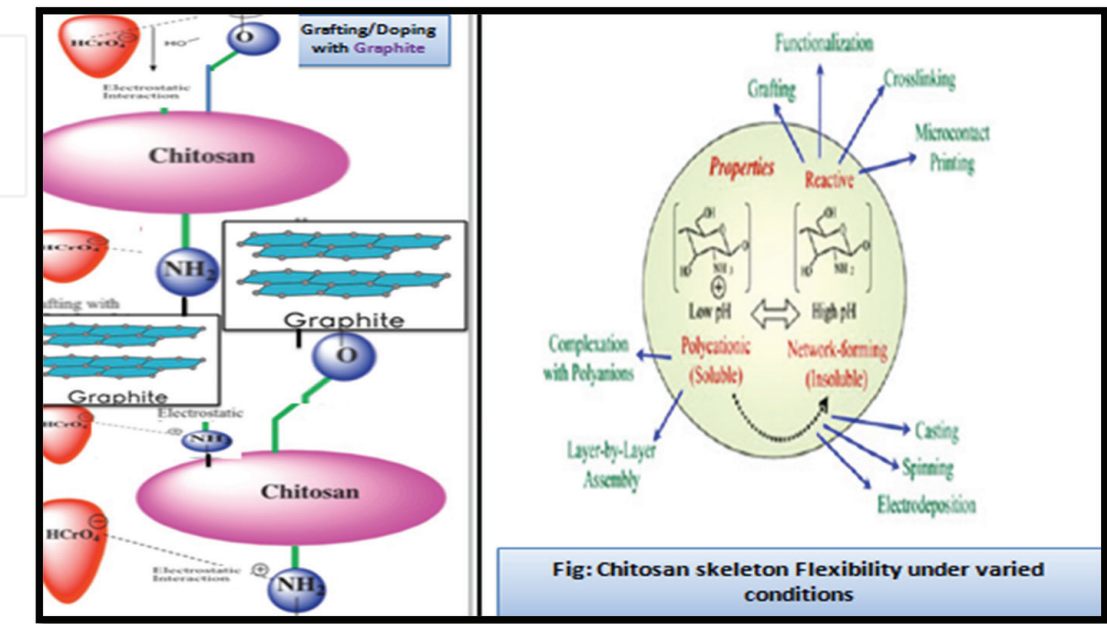
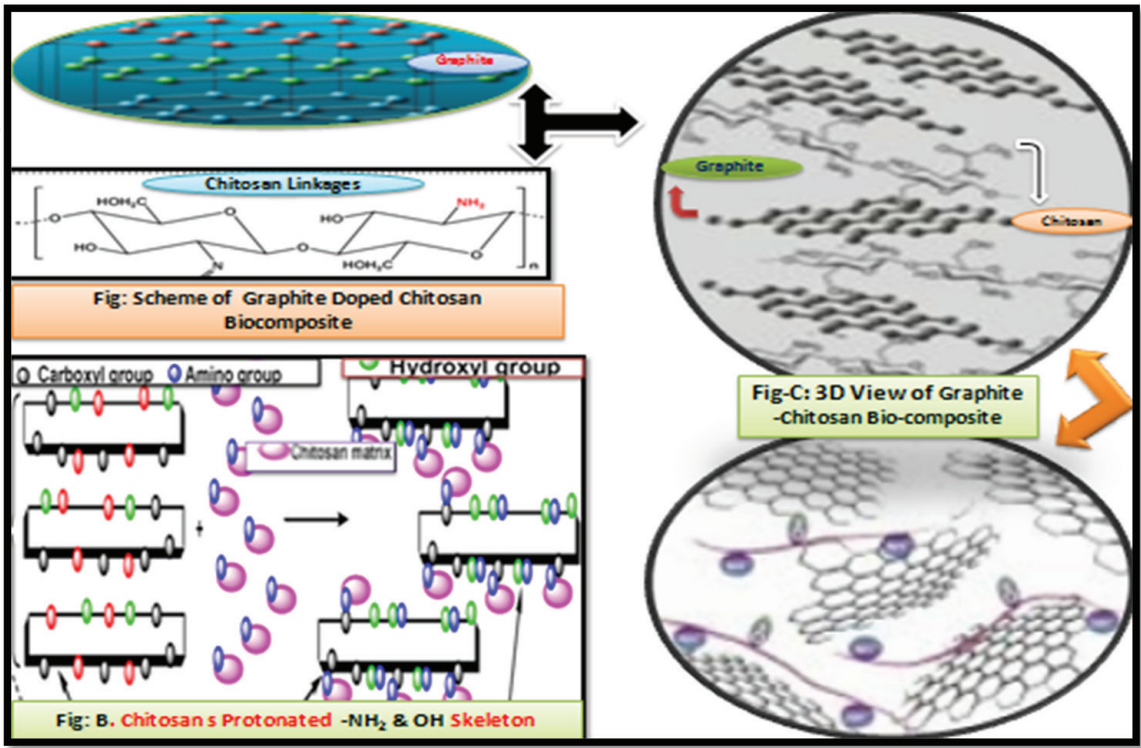


Figure 3. Mechanistic layers of graphite and chitosan yielding doped bio-composite illustrated inset flexible change in chitosan skeletons.

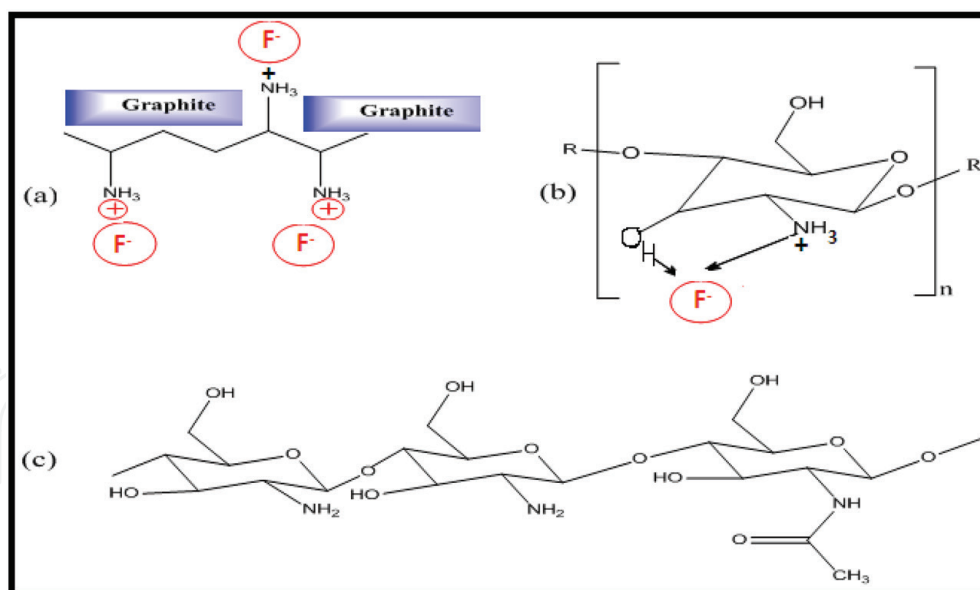
monolayer sorption of fluoride with interactive heterogeneous distribution and diffusion to cationic sites/surface of adsorbents. The mechanistic view of fabricated chitosan doped graphite biocomposite FCDGC and insight for elevated bio-sorption is depicted in **Figures 4** and **5** respectively.

**2.10 Chitosan smart materials: viable for copious challenges**

Micro to nanoscale smart materials own certain multi-dimensional switching characters ever utilized in advancement of science due to repetitive self-healed auto-altering of temperature, pressure, heat, electricity and light environments [26]. Smart approaches aid designing of rational chitosan materials that convey salutary purpose and usage including piezoelectric, shape memory polymers, thermo-responsive polymers, photomechanical stuff, self-healing materials and thermoelectric resources, besides hydrogels, nanoassemblies, super-active surfaces and bio-conjugates. Biopolymer chitosan based fabricated materials owe auto-adjustable mechanical strength and depth by virtue of intrinsic cenotaph ability along with inventive status on stress disburses. This chapter sum up revolutionary growth and interest to supply various vital applications. Typically designed parameters can formulate stylish compatibility in chitosan skeleton that can able to counter slight changes in adjustable environment. Chitosan permits rapid changes/transitions via synergic merge of individual characters of foreign components in resultant matrix so as to yield enviable properties which hold uniqueness to carry innovative functionalizations. Thus, smart and responsive nanoassembly/nanoparticles are sensibly designed by means of advanced nanobiotechnology. Chitosan based 3D hydrogels are able to absorb enormous water while sustains invariable stability to bear volume phase/gel-sol phase transitions due to adoptable alterations. These hydrogels possess various physic-chemically stimulated characters viable to bring various responses. Smart surface/interface own two-phase intermolecular force discontinuity, and thus attain very unique high energy point. Chitosan based



**Figure 4.**  
*Mechanistic view of fabricated chitosan doped graphite composite/FCDGC.*



**Figure 5.**  
View of fluoride interactive adsorption mechanism on of FCDGC active sites.

“smart surface/interface are designed with dynamically controllable properties to be utilized for assorted biomedical applications viz.; adsorption of biomolecules, tissue engineering and bio-separations besides biocompatible materials at the biotic/abiotic interface.

Chitosan based stimulus-responsive smart nanofibers are obtained for their ‘on–off’ reversible switching actions owing exclusive advantageous of nanodimensions imparting peculiar features like huge surface area, high porosity and enhanced external stimuli sensitivity, besides simplistic bulk manipulations in their resultant skeleton. Such stimulus-responsive smart chitosan derived nanofibers own dynamic and reversibly tunable structures with potential ‘on–off’ actions crucial for efficient delivery of drug/cell/gene in assorted medical applications. Smart bio-conjugates based on chitosan possess superior features and unique properties to original chitosan and added versatile new values due to generation of nanoscale switching. Bio-conjugate smart polymeric matrix are employed for enormous applications viz.; proteins affinity separations, enzyme bioprocesses, drug/cell/gene carrier, diagnostics purpose, biomarkers, biosensors and cell cultured tissue engineering besides DNA motors. Chitosan based shape-memory materials comprise the capability to change from a temporary to memorized permanent shape via peripheral stimulus responses. Such shape-memory polymers (SMPs) can act as a cheap and efficient alternative to well-known metallic shape-memory alloys due to facile manufacturing and easy programming. Thermally induced chitosan based SMPs own self-repairing/rewritable features which owe special weightage in development of environmentally benign technologies [1–4, 27].

### 3. Summary

Chitin/chitosan matrix is favored to derive sophisticated formulations to be used for its promising risk-free functions in assorted fields like clinical, biomedical, and pharmacological, besides designing/fabrication of advanced nano/biotechnological smart materials. Chitosan template infringes many organic as well inorganic cationic and anionic materials in its flexible/amicable framework so as to get hybrids, hydrogels, composites, coatings, films and nanostructures owing ample utilities in modern S&T. Chitosan still seek methodical R&D to dope/blend interactive fillers/

dopants or additives which can offer improved formulations with split wide open revolutionary and advanced applications.

Nanotechnology integrated chitosan derived smart formulations possess wide, multitasking and thematic portfolio in nanotechnology way from “biosensor/bio-marker matrixes” to artificial atoms called “quantum dot”. These advanced technologically designed characteristics chitosan materials initiated new modality owing innovative utilities including DNA/RNA/cell/gene nano-carriers, quantum dots for disease diagnosis/therapeutics besides tissue scaffold designing as templates and devices for benefit of man and nature.

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