

A Review on Chitosan Derivative Polymers and Its Application Towards Drug Delivery Carrier

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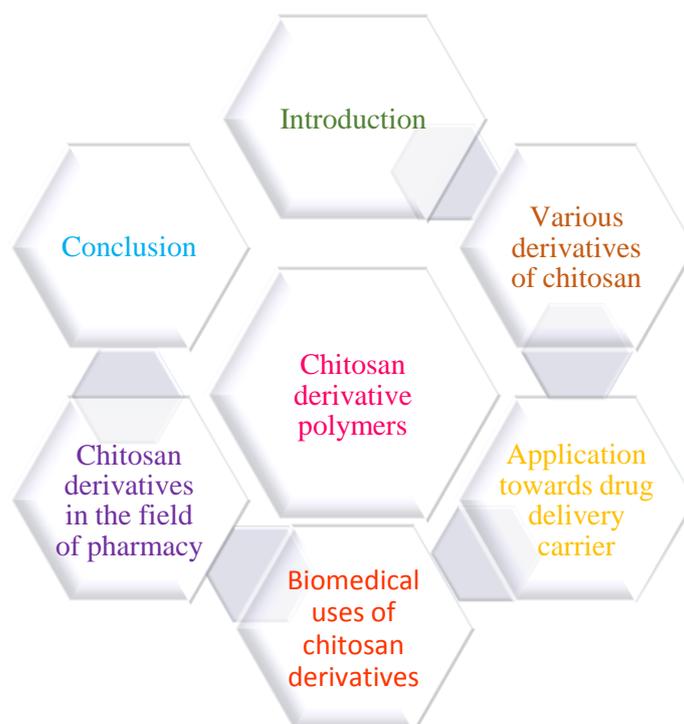
Abstract: Chitosan is a versatile biodegradable natural polymer and most studied aminopolysaccharide nowadays with many advantages such as nontoxicity, biocompatibility, and biodegradability. Chitosan is incredibly hard to solubilize in water, yet it tends to be solubilized in acidic arrangement. Deacetylation degree (DDA) and atomic weight (MW) are the most unequivocal boundaries since the essential amino gatherings are the key useful gatherings of chitosan where grants to connect with different atoms. Chitosan derivatives will be obtained through the chemical modification exploitation techniques like chemical process, alkylation, sulfation, hydroxylation, quaternization, esterification, graft copolymerization, and etherification. Altered chitosan has substance properties better than unmodified chitosan. For instance, nanoparticles created from chitosan subsidiaries can be utilized to convey tranquilizes because of their strength and biocompatibility. Modification of chitosan has been a crucial side of chitosan analysis, showing an improved solubility, pH-sensitive targeting, an exaggerated variety of delivery systems, etc.. This review focuses on chitosan derivatives, its application as a drug delivery system and in the biomedical field. Chitosan derivatives will have a huge impact and show greater potential in drug delivery systems for the development of drugs in future.

Keywords: Chitosan, chitosan derivative, drug delivery carriers, biomedicines

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Figure 1: Schematic Illustration Of Chitosan Derivative Polymers Towards Drug Delivery Carrier



I. Introduction

Chitosan is an inexhaustible common soluble polysaccharide composed of β -(1-4)-linked 2-amino-2-deoxy-D-glucose and 2-acetamido-2-deoxy-D-glucose units that has no harmfulness and no side impacts, and it includes great saturating and adsorption properties¹⁻³. Chitosan is solvent in acidic media for instance the generally utilized acidic answers for dissolving chitosan are acetic acid, hydrochloric acid, lactic acid, and formic acid. The polymer chain are charged emphatically when it is disintegrated in a fluid arrangement of $\text{pH} < 6.5$. The degree of deacetylation and the normal sub-atomic load of polymer just as low harmfulness and great bioavailability make it a novel excipients in pharmaceutical definition as a moderately new turn of events⁴. The United States Food and Drug Administration (FDA) has affirmed that chitosan is protected in the utilization of nourishments and medications.

Chitosan derivatives can be acquired by the substance adjustment of chitosan-responsive functional groups. Here, the -OH and -NH₂ dynamic gatherings on the chitosan particle are inclined to chemical responses⁵⁻⁷. Synthetic modifications cannot just improve the physical and concoction properties of chitosan, it can likewise hold the novel properties of chitosan and grow the application scope of chitosan derivatives. Chitosan derivatives have better biocompatibility, bioactivity, biodegradability, and non-poisonousness, they despite everything have bactericidal, antibacterial, anticancer, and antiviral pharmacological effects, including the capacity to prompt erythrocyte conglomeration, advance platelet initiation, and enact supplement frameworks other than that of chitosan⁸⁻¹³.

At present, chitosan derivatives have been generally utilized in both clinical materials and biomedicines. With the advancement of nanotechnology, chitosan subordinates have been set up as nanomaterials, including nanoparticles, hydrogels, microspheres, and micelles. Chitosan subordinates can be utilized as focused conveyance vehicles for drugs, just as adjuvants and conveyance bearers for vaccines¹⁴⁻²⁰. This review focuses various derivatives of chitosan, its application towards drug carriers (tablets, capsules, hydrogels, nanoparticles, microspheres) and their use in the field of biomedicine have been discussed. We trust that the survey can give some direction to inquire about on improving and extending the potential uses of chitosan derivatives in drug delivery systems.

II. Derivatives Of Chitosan

Chitosan has dynamic hydroxyl and amino gatherings that can experience different compound responses counting hydroxylation, carboxylation, alkylation, acylation, and esterification. These responses bring pendant gatherings into the chitosan, decimating the crystal structure of chitosan and thus expanding the dissolvability of the altered chitosan. These chitosan subsidiaries with improved physicochemical and natural properties are more qualified for use as bearers in the medical field²¹. **Table 1** illustrates chitosan derivatives and its biomedical application.

The utilization of chitosan and its derivatives has been proposed in various territories of biopharmaceutical research, for example, mucoadhesion, penetration upgrade, antibody innovation, quality treatment and wound healing, colon-specific, gene carriers, transdermal delivery, mucosal vaccines, buccal, periodontal, etc.,. It can likewise be utilized in the pharmaceutical industry in direct tablet pressure, as tablet disintegrants, for the creation of controlled discharge strong dose structure or for the improvement of medication disintegration. Chitosan derivatives were created to improve organic exercises as well as water-solvent property, on the grounds that the water-insoluble property was a significant restricting component for mechanical application regardless of its one of a natural aspects²².

Currently, chitosan and its derivatives have sensible applications within the sort of solutions, suspensions, particles, e.g. beads, resins, spheres, nanoparticles and sponges, hydrogels, foams, films, fibers, microscopic threads, and scaffolds in several fields: drugs and biomedicine, pharma, cosmetics, hygiene and private care, food industry and nutrition, agriculture and agrochemistry, textile and paper industries, edible film industry, packaging, biotechnology, chemistry, and chemical change, action, drink trade and art, photography and different rising fields such as nutraceuticals, useful textiles and cosmeceuticals, technology, and cultivation²³⁻²⁸.

The various derivatives of chitosan developed by completely different researchers throughout the recent years area unit shortly represented as:

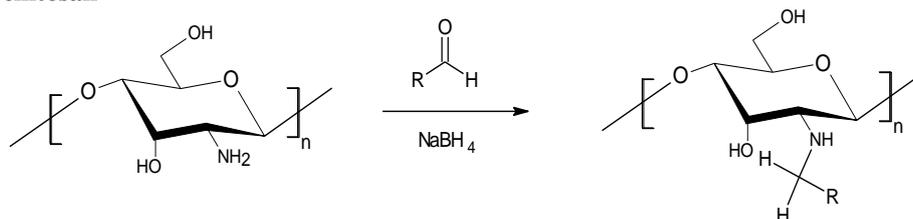
Alkylated Chitosan: Both the utilitarian gatherings – NH₂ (amino) and C3, C6–OH (hydroxyl) can be engaged with chitosan alkylation. Hence, chitosan alkylation happens primarily through the amino gathering to supply N-alkylated chitosan subordinates²⁹. Hemolysis and toxicity measures demonstrated that N-alkylated chitosan has great biocompatibility. From the effects of in vitro blood coagulation tests, N-alkylated chitosan would be wise to hemostatic movement than unmodified chitosan³⁰. Hydrogen holding between chitosan atoms is essentially decreased by the nearness of the alkyl gatherings, making the changed alkylated chitosan more water dissolvable and all the more encouraging in clinical applications.

Acylated Chitosan: The $-NH_2$ and $-OH$ bunches on the chitosan particle can take an interest in an ester or amide response with natural corrosive anhydride or natural corrosive chloride. While planning acylated chitosan, consideration should be paid to the response temperature and the sort of impetus utilized. The dissolvability of acylated chitosan in water or in a natural dissolvable is commonly improved by presenting diverse atomic loads of fats or aromatic acyl gatherings. In one investigation, N-succinylated chitosan was produced through the presentation of succinyl in the N-position of the chitosan glucosamine unit³¹. N-succinylated chitosan atoms contain $COOH$, $C2-NH_2$; $C3-OH$, $C6-OH$, and other dynamic gatherings, which permit it to all the more likely adsorb divalent copper particles. Acylated chitosan has great handling properties and a continued discharge impact. It is another kind of assistant material that can be utilized for oral insoluble skeletal formulations.

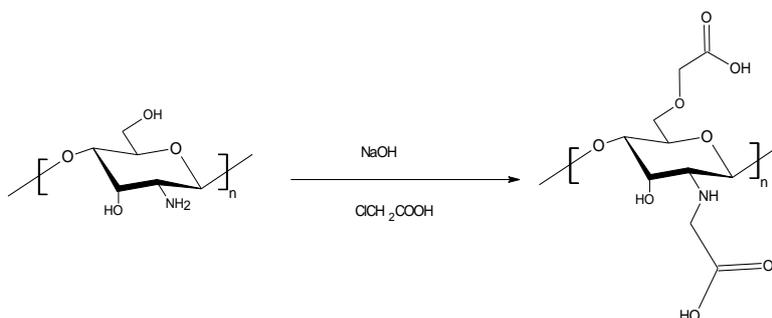
Carboxylated Chitosan: So as to get carboxyl-changed chitosan subordinates, carboxylated chitosan responses by and large happen through both the $-NH_2$ and $-OH$. Carboxylation can be accomplished utilizing glyoxylic acids. Chitosan has been treated with monochloroacetic acids under various conditions to get carboxymethyl chitosan. The water dissolvability of carboxymethyl chitosan is reliant upon the states of alteration and the level of carboxymethylation³². The carboxylation of chitosan improves the water dissolvability that is attained at pH values above or below the isoelectric point, In order to increase the water solubility of chitosan, Toh et al. grafted carboxylic acid onto chitosan reportage a better solubility in water at pH scale seven that is unconcealed through mensuration of the cloud purpose (when twenty mildew of primary alkanes were converted into carboxylic acid), yet in addition produces amphiphilic chitosan subsidiaries with both $-NH_2$ and $-COOH$ gatherings. These subordinates have great water dissolvability and surface movement, just as film-shaping, moisture assimilation, dampness maintenance, antibacterial³³, antioxidant³⁴, and other natural properties which render them valuable for different applications in beautifying agents, nourishment and pharma industries.

Figure 2 represents chitosan derivatives:

N-alkylated chitosan



Carboxylated chitosan

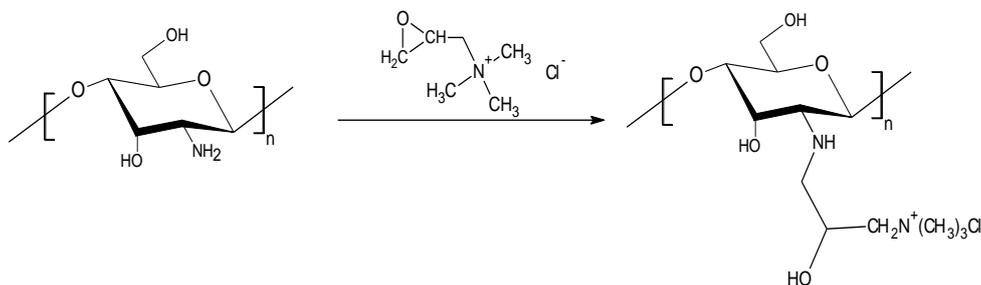


Quaternary Ammonium Chitosan: Chitosan quaternization responses can happen through both the $-NH_2$ and $-OH$ gatherings. Quaternization for the most part includes response of chitosan with methyl iodide, despite the fact that it might include synthetic concoctions other than methyl iodide³⁵⁻³⁷. The subsidiaries are incorporated by chitosan and quaternary epoxides; it is conceivable to get ready cationized derivatives (quaternary ammonium chitosan) with different hydrophobicity/hydrophilicity through the different alkyl chains on quaternary epoxides³⁸. The most straightforward subsidiary of chitosan is the trimethyl ammonium salt. The treatment of chitosan in N-methyl-2 pyrrolidone containing sodium iodide and methyl iodide with chloride particle in nearness of sodium hydroxide coming about into the trimethyl ammonium salt of chitosan having high level of substitution³⁹. The anionic changes of iodide with chloride particles are vital for adjustment bringing about water dissolvable item at unbiased pH⁴⁰.

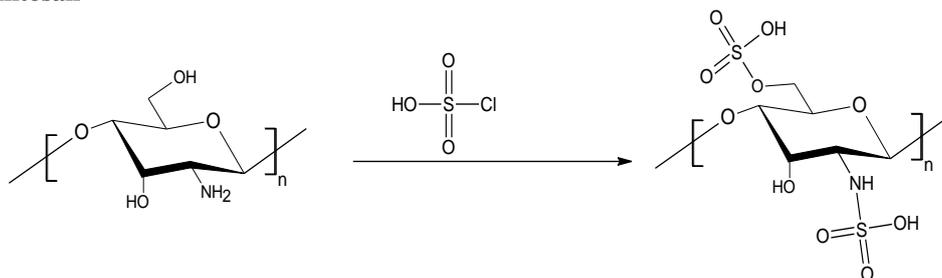
Quaternized chitosan has impressive application in the planning of anticoagulant materials, useful protein materials, and functional polymers because of its high water dissolvability and wellbeing⁴¹.

Figure 3 some chitosan derivates illustrated below

N-2-hydroxypropyl trimethyl ammonium chloride chitosan



Sulfated Chitosan



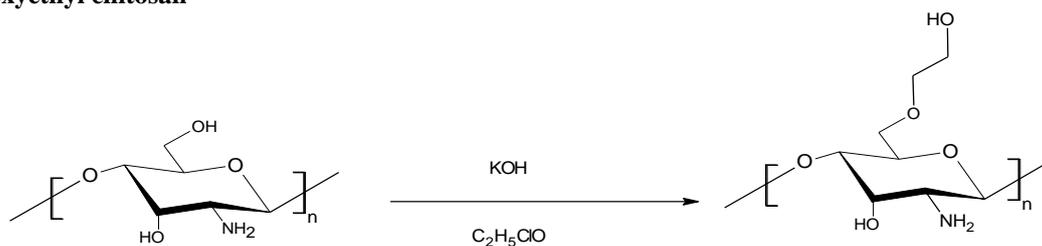
Esterified Chitosan: The esterification of chitosan happens with a portion of the oxygen-containing inorganic acids (or their anhydrides) on the chitosan particle. Sulfated chitosan has a wide scope of uses alternative for heparin or heparin sulfate in the field of science, including as anticoagulant and as antiviral medications, to advance osteogenic separation and explicit authoritative of proteins⁴²⁻⁴⁴. The administrative mechanism of sulfated chitosan is equivalent to heparin. In vivo investigations show that the movement of proteins and cells is affected by vicious response with specific cells and naturally dynamic mixes⁴⁵⁻⁴⁶. Chitosan derivatives acquired through esterification can be utilized for high-quality strands.

Graft Copolymer Chitosan: Chitosan graft copolymerization confers some new phenomenal properties to chitosan through the presentation of opposite side chain gatherings. The subsequent changed chitosan can be utilized to change the outside of textures or cellulose and furthermore improve the antibacterial properties of chitosan⁴⁷⁻⁴⁹. Altered chitosan got through join change can likewise be utilized on the surface of tissue-building materials to improve the anticoagulant properties⁵⁰⁻⁵¹. Chitosan can be coupled to oligo-lactic corrosive containing terminal aldehyde gathering to produce a unite copolymer that is dissolvable in N,N-dimethylformamide (DMSO), dimethyl sulfoxide dimethyl sulfoxide (DMF), and acidic corrosive. The graft copolymerization of chitosan copolymer holds extraordinary guarantee for boundless use in the creation of continued discharge drugs and different biopharmaceuticals⁵².

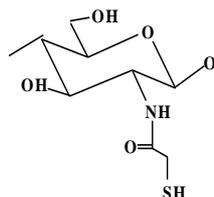
Etherified Chitosan: Chitosan etherification response happens through the –OH bunch on chitosan, prompting the arrangement of the relating alkylating operator (alkyne subordinates). The delivered alkyne subsidiaries at that point experience a deacetylation response to get chitosan ether subordinates. Chitosan ether derivatives are not cytotoxic, don't affect the development of fibroblasts, and don't cause huge disturbance, however they do cause deferred extreme touchiness and postponed provocative reaction. Hydroxyethyl chitosan has fantastic execution biocompatibility and biodegradability and is proper for applications in the medical field. They likewise have incredible bacteriostatic and hygroscopic saturating impacts and are alright for use as common textile softening and completing agents. Hydroxyethyl chitosan can likewise be utilized as an additive in beautifying agents where they show antibacterial impacts on regular microscopic organisms, for example, *Escherichia coli*⁵³.

Figure 4 examples of chitosan derivatives

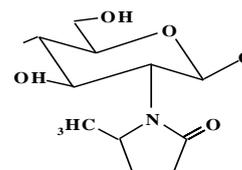
Hydroxyethyl chitosan



Thiolated Chitosan



Methyl pyrrolidinone chitosan



N-benzyl Derivatives Of Chitosan:Chitosan was responded with 2-formylbenzene Na salt and 4-formyl benzene Na disulfonate among the sight of Na cyano borohydride to yield N-benzyl subordinates. Chelant amino polymers like chitosan have a low proficiency in metal take-up in the acidic pH range (because of the protonation of the amino gatherings). Progressively finished, the amino polymers, as chitosan, are solvent in acidic media and subsequently can't be utilized as sorbents in these conditions. Be that as it may, their action is as the solid cation exchanger can be improved by derivatizing chitosan with N-benzyl sulfonate for the expulsion of metal particles as sorbents in acidic medium. These sulfonated subsidiaries prompts the adsorption of substantial metals (Cd^{2+} , Zn^{2+} , Ni^{2+} , Pb^{2+} , Cu^{2+} , Fe^{3+} , and Cr^{3+})⁵⁴.

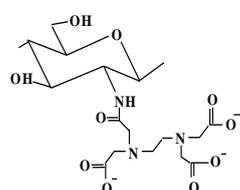
Chitosan-Triphosphate Nanoparticles: Ionotropic gelation techniques are the most widely recognized to accomplish a pharmaceutical item with wanted attributes. Super-paramagnetic iron oxide nanoparticles (SPIONPs) were exemplified by Sanjaia, et al. at different fixations inside chitosan-triphosphate (SPIONPs-CS) utilizing the ionotropic gelation technique. Ionotropic gelation depends on the capacity of polyelectrolytes counter particles to cross connect to shape hydrogels. Normally happening polysaccharides, for example, chitosan which have important use as biopolymers has been expanded in the novel region, for example, hydrogel supported discharge plan, subsequently giving an eco-accommodating pharmaceutical item improvement process.

The dispersion capacity of CS nanoparticles is enhanced by encapsulation of SPIONP's. SPIONP's CS nanoparticles showed super-paramagnetic properties at room temperature. These SPIONP's CS nanoparticles is applied as tissue specific MRI contrast agents. SPIONP's CS nanoparticles demonstrated low cytotoxicity against skin fibroblast cells and good stability for long periods⁵⁵.

Chitosan Conjugates:CS can be conjugate with a bioactive excipients for conveyance of dynamic fixings, for example, calcitonin. CS conjugates, for example, 5-methylpyrrolidone chitosan, chitosan-4-thiobutylamidine conjugates have demonstrated upgraded ingestion just as mucoadhesive properties. Guggi and Bernkop joined a chemical inhibitor to CS. The subsequent polymer held mucoadhesive property and attached catalyst inhibitor forestalls the debasement of medications by repressing proteins, for example, trypsin and chymotrypsin. this conjugates CS exhibited guarantee conveyance of sensitive peptide drugs, for example, calcitonin⁵⁶⁻⁵⁸. Examples of some chitosan conjugates are mentioned in **Figure 5**

Figure 5

Chitosan EDTA conjugates



Chitosan-NTA conjugates

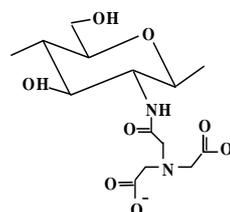


Table 1: Chitosan Derivatives And Examples Of Biomedical Applications

Some Chitosan Derivatives	Important Properties	Biomedical Applications	References
Carboxymethyl-chitosan O-carboxymethyl-chitosan N-carboxymethyl chitosan O,N-carboxymethyl chitosan N,N-carboxymethyl-chitosan n-Lauryl-carboxymethyl-chitosan	Amphoteric products Water soluble in wide range of pH Film and gel forming abilities Clarifying agents Solubility depends on pH	Excipients Dental care Carriers for hydrophobic cancer drugs Drug delivery systems Surfactants Bracket preparation Treatment of irregular small bone defects Cosmetics Oral absorption enhancers	Mourya and Inamdar (2008), Elsabee et al. (2009), Jimtaisong and Saewan (2014), and Farion et al. (2018) ⁵⁹⁻⁶²
Chitosan 6-O-sulfate O-sulfated chitosan N-sulfated chitosan N-octyl-O-sulfate chitosan 2-N,6-O-sulfated chitosan N-palmitoyl-O-sulfate chitosan	Anticoagulant activity Antimicrobial agents Hemostatic agents Anti-HIV activity	Drug delivery Blood anticoagulant Hemagglutination inhibition activity Antitumor and antioxidant activity Tissue engineering Hemo-compatibility Neural repair treatment Lipoprotein lipase-releasing activity	Jayakumar et al. (2007), and Elieh-Ali-Komi and Hamblin (2016) ⁶³⁻⁶⁴
Quaternized derivatives Trimethylammonium chloride chitosan N,N,N-trimethyl-chitosan chloride Triethyl chitosan chloride Trimethyl chitosan	Cationic derivatives Water soluble at neutral pH Good moisture retention and absorption Mucoadhesion	Antifungal agents Antistatic agents Drug delivery Antibacterial coating Flocculating agent Dental care Anti-tuberculosis Enzyme inhibition Biomedical devices Gene delivery Gene transfection Permeation enhancers Oral absorption enhancers Bionic periosteum	Kedjarune-Leggat and Leggat (2011), Huang et al. (2014), Muñoz-Bonilla et al. (2014), LogithKumar et al. (2016), and Pardeshi and Belgamwar (2016) ⁶⁵⁻⁶⁷

III. Chitosan Derivatives As A Drug Delivery Carrier

Chitosan and its derivatives have been principally investigated as excipients in sedate details, and in medicate conveyance systems. The new methodology comprised of supplanting conceivably harmful mixes by common items, which quickly end up being promising. The pharmaceutical industries quickly comprehended the benefits of utilizing chitosan⁶⁸.

The primary properties utilized in the pharmaceutical field are: controlled medication discharge, for example, mitigating naproxen, mucoadhesive properties, in situ gelling properties, transfection improving properties (deoxyribonucleic corrosive and little meddling ribonucleic corrosive ribonucleic corrosive based medications structure stable buildings with chitosan), and penetration enhancing properties.

Chitosan and its derivatives might be utilized in oral, ocular, nasal, vaginal, buccal, parenteral, intravesical, and transdermal administrations, and as inserts for medicate conveyance in both implantable and injectable forms. Drug delivery applications incorporate not just controlled medication discharge frameworks, for example, site-specific antibiotic conveyance in the stomach, and controlled arrival of proteins, yet in addition vaccine and gene conveyance. Chitosan is intriguing to be utilized for buccal conveyance because of its

mucoadhesive bioactivity and assimilation enhancing property. Solid penetration enhancing properties are too referenced.

The properties of chitosan as resulted in the development of vaccine delivery and injectable preparations. The transmucosal retention advertiser impact of chitosan is significant for nasal and oral conveyance of polar medications to administrate peptides and proteins, and for immunization conveyance⁶⁹.

Subsequently, they can be easily processed into different forms such as solutions, gels/hydrogels, sponges, microparticles/nanoparticles, membranes and films (pure films or blends, adhesives), sponges, and fibers/nanofibers⁷⁰. **Table 2** represents chitosan and its derivatives based drug delivery systems. Films and filaments prepared utilizing chitosan and chitin were produced for tissue engineering and wound dressing, as oral mucoadhesive and water-resisting adhesive by righteousness of their discharge qualities and adhesion⁷¹⁻⁷². **Table 3** lists out the uses of chitosan derivatives in the field of pharmacy.

Table 2: List Of Chitosan And Its Derivatives Based Drug Delivery Systems

Types Of System	Method Of Preparation	Drug	References
Capsules/Microcapsules	Capsule shell	Insulin	Felt et al. (1998), Ravi Kumar (2000), Ravi Kumar et al. (2004), Dash et al. (2011), Ali and Ahmed (2008) ⁷³⁻⁷⁷
Microspheres/Microparticles	W/O emulsion cross-linking Coacervation Spray-drying Ionic gelation	Gentamicin sulphate, Aspirin, Hemoglobin, Clarithromycin, Propranolol HCL, Cimetidine, Bovine serum albumin, Famotidine	
Nanoparticles	Emulsion-droplet Coalescence Precipitation Ionic gelation Reverse micellar method	Gadopentetic acid, Ovalbumin, Ascorbic acid, Cyclosporin A, Insulin	
Beads	Coacervation/precipitation	Bovine serum albumin, Insulin, Salbutamol	
Films	Solution casting	Ofloxacin, Paclitaxel, Testosterone, Trypsin	
Gel/Hydrogels	Cross-linking method	5-Fluorouracil, Lidocaine	
Sponges/Foams	Freeze drying Reactions in supercritical fluids	Triamcinolone acetonide	

Table 3: Chitosan Derivatives In The Field Of Pharmacy

Topics	Available Forms	Uses	References
Drug delivery Drug release Excipients Biopharmaceutics Nutraceuticals Ophthalmology Cosmeceuticals Dermatology Vaccines Radiopharmaceutical agents	Solution Powder Beads Tablets Capsules Microspheres Nanoparticles Sponge Gels Nanocomposite	Encapsulation of sensitive drugs: to extend and to modulate drug unlease rate Excipients Controlled release of proteins and peptide carriers Gene delivery Dermatological product: to treat acne Hydrating and bacteriostatic agents Water-resisting adhesive In situ gelation Transfection Nutraceutical ingredients Permeation enhancer wound healing Efflux pump inhibitor	Goosen (1997), Illum (1998), Dodane and Vilivalam (1998), Hejazi and Amiji (2001), Agnihotri et al. (2004), Canh et al. (2004), Kang et al. (2009), Hamman (2010), Riva et al. (2011), Badwan et al. (2015), Mateescu et al. (2015b), Akbar and Shakeel (2018), Krishnaswami et al. (2018), Naskar et al. (2018), Lucio and Martínez-Ohárriz (2017) ⁷⁸⁻⁸⁹

IV. Conclusion

Chitosan is a compound of incredible enthusiasm because of its biocompatibility and biodegradability. Chitosan subordinates are promising medication excipients. A drug stacking framework, including micelles, nanoparticles, microspheres, and hydrogels, that is set up by chitosan derivatives, can expand the strength of medications and discharge tranquilizes n a continued and moderate way. Along these lines, chitosan derivatives conveyance frameworks for medications or antibodies can diminish side effects and improve the bioavailability of medications, which has expanded enthusiasm for chitosan derivatives in the field of medicine.

Chitosan derivatives appear to be progressively appealing and can be utilized for the controlled release of medications, and their adjustment with new solvents can be changed over into sedate conveyance frameworks, particularly for the controlled release and steadiness of the released medications. With extra research, it is believed that the physical and chemical properties of chitosan derivatives can be persistently improved by synthetic alteration techniques and can likewise be made to be increasingly appropriate for use in clinical materials and medication delivery systems. Chitosan derivatives will have more extensive possibilities in the field of medication later on.

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