A Review on Utilization of Chitosan Nano-composite for Biomedical Application

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ABSTRACT: The research and development in recent polymer nano-composites materials utilization has significantly impacted its biomedical application. Particularly, polymers that are biodegradable gives considerable benefit of being capable to be busted down and removed after it has served the function. Degradable polymers have broad range of clinical applications such as surgical sutures and implants. It is observed from the review of literature materials with desired biological, physical, chemical, degradation properties and biomechanical should be selected to fulfill the functional demand. To fulfill new challenges in biomedical applications with new materials, a large range of natural and synthetic degradable polymers have been continuously searched by scholars. In this paper the use of Chitosan Nano-composite for bio-medical application such as drug delivery, tissue regeneration, and wound healing is discussed. The biomedical activity of chitin and chitosan compounds is affected by their physicochemical nature which is robustly linked to conditions of chitin and chitosan production process as its source.

INTRODUCTION

Any natural or artificial substance engineered to interact with biological systems in order to direct medical treatment is known as biomaterial. Biomaterials should be biocompatible which means they carry out their role with a suitable host reaction. Materials composed of everything from metals and ceramics to glasses and polymers have been researched to meet the requirements of the biomedical community. Polymers acquire considerable potential because of flexibility in chemistry gives rise to materials with large physical and mechanical property diversity. Degradable polymers are of greatest interest as these biomaterials are able to be busted down and excreted or resorbed without removal or surgical revision. [1]

After cellulose, Chitin is one of the most abundant polysaccharide. Chitin and chitosan are an significant family of linear polysaccharides consisting of changeable amounts of β-(1→4)-linked 2-acetamido-2-deoxy- β-D-glucopyranose (GlcNAc) and 2- amino-2-deoxy- β-D-glucopyranose (GlcN) units. Chitin samples are insoluble in water and common organic solvents because they contain a high content of GlcNAc units. On the other hand, they dissolve only in solvents such as N, N-dimethylacetamide, hexafluoroacetone or hexafluoro-2-propanol. The term “chitosan” represents a group of fully and partially deacetylated chitins; however a rigid nomenclature with respect to the degree of Ndeacetylation between chitin and chitosan has not been established. Chitin and chitosan must be classified on the basis of their insolubility and solubility in 0.1 M acetic acid in which the insoluble material is called chitin, whereas the soluble one is Chitosan. Figure 1 shows the structures of ideal chitosan, ideal chitin, and the real structures of these compounds [2].
Owing to versatile biological activities of Chitin and Chitosan such as biocompatibility, biodegradability, non-toxicity and adsorptive abilities and chemical applications, mainly in the medical and pharmaceutical fields, they have immense economic value. The biological properties of these compounds depend closely on their physicochemical parameters, particularly their solubility in water and other generally used solvents. Chitin has far fewer applications though they are highly insoluble and chemically somewhat unreactive material than compared to Chitosan. For increasing their range of biomedical applications, Solubility chitin and Chitosan in water and organic solvents can be improved by chemically modifying free hydroxyl and the primary amino groups of them. Chitin or chitosan based materials with different structures demonstrate dissimilar biological activities, and not all the biological activities were found in one kind of chitin or Chitosan material. Therefore for an understanding of the structure–property–activity relationships and special emphasis in this respect should be placed on the chitosans and chitin used in biomedical applications, Knowledge of the microstructure of chitosan and chitin samples is essential. Chitin and chitosan possess very interesting biological properties (Figure 2); thus, they have been used in lots of applications, mainly in the medical and pharmaceutical fields [3]

Salient finding from review:
Ulery et al. [1] summarizes the modern advances in the field over the past 4 years, specially highlighting new and interesting discoveries in drug delivery applications and tissue engineering. A wide range of degradable polymers that hold potential as biomaterials are currently exists. With advancements in polymer synthesis techniques, the paradigm of utilizing a few well characterized polymers (e.g. PLGA and collagen) for all biomedical applications has shifted to using polymers, both heavily researched and newly developed, that can fit certain niches (e.g. DNA and RNA association with phosphoesters and...
inherent bioactivity of chitosan). The field of degradable polymeric biomaterials will only continue to progress if the recent creation of strong collaboration teams composed of chemists, biologists, material scientists, engineers and clinicians is encouraged. Kumirska et al. [2] concluded that Chitin and chitosan are natural aminopolysaccharides with unique structures, multidimensional properties, highly sophisticated functions and wide ranging applications, especially in the biomedical and pharmaceutical fields. The chemical modification of these polymers improves their solubility in water or organic solvents, which in turn enhances their biological activities and raises the number of potential biomedical applications.

Kumirska et al. [3] concluded that (1) Chemical methods of modification can generate completely new chitin/chitosan-based biofunctional materials. (2) The biological properties of chitin/chitosan materials used directly in biomedical applications (e.g., antimicrobial effects) could be different that observed for materials obtained after preparation of nanoparticles, microspheres, hydrogels, films, fibers or tablets, (3) Chitin/chitosan properties are interrelated and many times they could influence the bioactivity in a conflicting manner. Sonia et al. [4] comprehensively integrate the recent applications of chitosan nano/microparticles in oral and/or buccal delivery, stomach-specific drug delivery, intestinal delivery, colon-specific drug delivery, and gene delivery, giving special emphasis to oral drug delivery. Honarkar et al. [5] explained that Chitosan and its derivatives are suitable for tissue engineering applications. Various type of chitosan derivatives have been used in skin, bone cartilage, liver, nerve, and blood vessels. This material is also a good candidate for use as a carrier of drugs for controlled release and other pharmaceutical applications. This polysaccharide has shown high potential for absorption of dyes, metal ions, and proteins. So, it might also be a good candidate for removing pollutants from water and wastewater.

Dash et al. [6] summarized the chemical structure and relevant biological properties of chitosan for regenerative medicine. Also the methods for the preparation of controlled drug release devices and their applications. Aiman Omar Mahmoud Abbas [7] researched on modifying and optimizing chitosan for applications in gene delivery, enzyme immobilization and tissue engineering Chen et al. [8] focuses on the versatile modifications of chitosan matrices (ionic or chemical crosslinking) and the most modern research activities in drug-eluting devices, including vascular stents, artificial skin, bone grafts, and nerve guidance conduits. Yuan et al. [9] studied the potential application of this hybrid nanocomposite carrier in biomedical applications, including tissue engineering and controlled drug delivery Anitha et al. [10] focuses on the diverse applications of CT and CS membranes and scaffolds for drug delivery, tissue engineering and targeted regenerative medicine.

Cai et al. [11] investigated the morphological and compositional properties of composites. As well as studied the interaction between the organic matrix and the inorganic crystallite and the formation mechanism of the rod-like nanoparticles. Hule et al. [12] discusses current efforts and key research challenges in the development of these materials for use in potential biomedical applications. Jayakumar et al. [13] emphasized recent research on different aspects of chitin and chitosan based nanomaterials, including the preparation and applications of chitin and chitosan based nanofibers, nanoparticles and nanocomposite scaffolds for tissue engineering, wound dressing, drug delivery and cancer diagnosis. Jayakumar et al. [14] reviewed the recent reports on the preparation, properties and biomedical applications of chitin and chitosan based nanofibers in detail Jayakumar et al. [15] took a closer look on the wound dressing applications of biomaterials based on chitin, chitosan and their derivatives in various forms in detail

Khor et al. [16] surveyed to demonstrate the utility of chitin and chitosan as potential materials for various implant applications and some of the challenges in demonstrating biocompatibility as well as sterility that must be addressed. The eventual realization of real implants awaits the take-up of these materials on a more commercial basis that would see the introduction of chitin-based implantable devices. Venkatesan et al. [17] discussed the preparation, mechanical properties, chemical interactions and in vitro activity of chitosan composites for bone tissue engineering. Peter et al. [18] prepared Nanocomposite scaffolds using nBGC disseminated chitosan matrix by lyophilization technique. The prepared composite scaffolds were characterized using FT-IR, SEM, XRD and EDS studies. In addition, swelling, density, degradation, bioactivity, cytotoxicity and cell attachment studies of the composite scaffolds were also performed.

Singh et al. [19] successfully synthesized monodispersed α-Fe2O3 nanoparticles through a simple hydrothermal method and dispersed it in chitosan (CH) solution using glycolic acid as organic surfactant to fabricate nanocomposite film.
The methods and magnetic nanoparticles described in the paper have provided a novel approach for the preparation of CH based nanocomposite films which may be applied to the magnetic field assisted drug delivery systems, cell/enzyme immobilization, biosensors, magnetic resonance imaging (MRI), tissue engineering and many other industrial processes. Shelma et al. [20] suggested that the tensile strength of the chitosan films can be increased up to a significant level by incorporating chitin nanofibres without appreciable change in water vapor permeability. However, the percentage swelling of the composite chitosan films decreased with increase in chitin whisker content. Tamura et al. [21] presented the preparation and biomedical applications of novel chitin membranes and scaffolds prepared from chitin hydrogel.

**Bio-Medical applications of Chitosan Nano-composite:**

Owing to its unique physicochemical properties, chitosan has great potential in a range of biomedical applications, including drug delivery, tissue regeneration, wound healing, blood coagulation, and immune-stimulation.

1. **Drug Delivery Perspective:** Biopolymers are capable materials in the delivery of protein drugs due to their compatibility, degradation behavior, and nontoxic nature on administration. On appropriate chemical modification, these polymers can provide better materials for drug delivery systems. Owing to favorable biological properties, Chitosan is extensively used for dental, colon-specific, buccal, gastrointestinal, and gene delivery applications. It is used in the form of tablets, gels etc. Figure 3 shows the different types of chitosan-based drug delivery systems [4]

In recent years, significant effort has been devoted to the development of biodegradable materials for drug delivery systems. Among the various biodegradable polymers used for the progress of controlled-release formulations, chitosan has been reported to be advantageous since it is a natural, nontoxic, biocompatible product with the potential for biodegradability. A type of amphiphilic derivatives of chitosan has been synthesized by incorporating (2-hydroxypropyl-3-butoxy) propyl into succinyl–Chitosan. The N-chitosan-derivative-based ophthalmic drug delivery systems can be easily and capably used for patients. Self-aggregated nanoparticles from methoxy poly(ethylene glycol)-grafted chitosan (mPEG-g-Ch) have been synthesized by a formaldehyde linking method. These nanoparticles were chosen as a transporter for badly water soluble methotrexate (MTx), an anticancer drug. MTx is a folate antimetabolite and has been used in the treatment of various malignancies. However, it may cause adverse effects such as bone marrow suppression, interstitial pneumonitis, chronic hepatotoxicity, acute, and chronic interstitial obstructive pulmonary disease. So, it is essential to decrease its toxicity and side-effects. Therefore, mPEG-g-Ch self-aggregated nanoparticles have been used as a transporter for MTx to sustain its release, prolong its circulation time, increase its therapeutic index, and reduce its toxic effects. The obtained outcome show continuous release of more than 50% MTx in 48 h from MPEG-g-Ch.

![Figure No 3: Different types of chitosan-based drug delivery systems [4]](image-url)
In a new study, dry powders were prepared by spraydrying of aqueous ethanol solution of chitosan (drug release modifier), leucine (aerosolization enhancer), and terbutaline sulfate (model drug). A new combination coating material of HPMC and ChA has potential for use in colonic drug delivery. The system is enzyme controlled due to the degradation of ChA by the colonic enzyme. Also, Chitosan acetate may interact with the acidic drug but has no effect on the drug release in this system. Preparation of enteric-coated chitosan-prednisolone conjugate microspheres (Ch-SP-MS) and in vitro evaluation of their potential as a colonic delivery system have been studied. Sonication was utilized to prepare finer Ch-SP-MS and the addition ratio of eudragit was reduced to obtain eudragit-coated Ch-SP-MS with higher drug content. The eudragit coating can protect Ch-SP-MS morphology at gastric pH of 1.2 and allow almost complete regeneration of Ch-SP-MS at intestinal pH of 6.8 a few hours after exposure at this pH. Drug release is also suppressed at gastric pH and raised at intestinal pH. Recently, water-soluble N-(c-bromopropanoyl amino acid)-chitosan derivatives have been synthesized. Nanocomposite films from chitosan/organic rectorite (chitosan/OREC) have been synthesized by a casting solvent-evaporation method. Addition of OREC to pure chitosan film enhances many of the properties related to the amount and interlayer distance of the layered silicate in the chitosan/OREC. In vitro drug controlled-release studies show a slower and more continuous release for the nanocomposite films in comparison with pure chitosan film, and the drug delivery cumulative release is proportional to the amount and interlayer distance of OREC. [5]

2. Tissue Engineering: There is also a special place for chitin or chitosan in the field of tissue engineering. The mechanical properties of chitosan membranes deteriorated when the molecular weight of chitosan increased, whereas it is precisely the high molecular weight of chitosan that gives the chitosan scaffold its better mechanical strength. The reduced proliferation of human skin fibroblast cells on a collagen/chitosan scaffold with increasing chitosan molecular weight was observed, while the MW of chitin and chitosan samples had no appreciable influence on the proliferation of tissue fibroblasts or on keratinocytes [2]. Chitosan scaffolds are promising materials for the design of tissue engineered systems owing to their low immunogenic activity, controlled biodegradability and porous structure. The influence of DA on the structural and biological properties of chitosan scaffolds for cell culture and tissue engineering was studied. The mechanical strength of chitosan was better with lower DA and that chitosan with lower DA favored cell adhesion. Also observed that chitosan scaffolds with DA (15-25%) displayed a more regular structure in comparison to scaffolds with very low DA (<15%). Moreover, the lateral pore connectivity was much lower for chitosans DA 15-25% than for scaffolds with DA <15%. Both observations were very important, because it is very well known that the microstructure of the matrix has an important influence on cell intrusion, proliferation and functioning in tissue engineering. Freier et al. prepared and characterized chitin and chitosan tubes for nerve regeneration. The compressive strength of these tubes was found to increase with decreasing of DA [2].

3. Wound-healing applications: An ideal dressing should protect the wound from bacterial infection as well as promote healing in wound-healing. Chitosan-based materials which are produced in varying formulations have been used in a number of wound healing applications. Chitosan induces wound-healing on its own and produces fewer scarring. It seems to enhance vascularization and the supply of chito-oligomers at the lesion site, which have been implicated in better collagen fibril incorporation into the extracellular matrix. While different material dressings have been used to improve endothelial cell proliferation, the delivery of growth factors involved in the wound-healing process can enhance that process. In addition to the reparative nature of the chitosan hydrogels, they can also deliver a therapeutic payload to the local wound, for example, fibroblast growth factor-2 (FGF-2) which stimulates angiogenesis by activating capillary endothelial cells and fibroblasts. To sustain FGF-2 residence at the wound site, FGF-2 was incorporated into a high molecular weight chitosan hydrogel, formed by UV-initiated cross linking. A chitosan hydrogel scaffold impregnated with-FGF loaded microspheres were developed by Park et al. that accelerates wound closure in the treatment of chronic ulcers. Films of chitosan, in combination were found to promote accelerated healing of incisional wounds in a rat model. The wounds closed within 14 days and mature epidermal architecture observed histological with keratinized surface of normal thickness and a subsided inflammation in the dermis. [6]

CONCLUSION: In this exhaustive review it is found that vast scope exists in application of Chitosan nano-composite in biomedical field. Biomedical applications such as drug delivery, tissue engineering, and wound healing are
discussed in this paper. Chitosan is used as a biomaterial for its biodegradability and biocompatibility properties. Chitosan has an immense potential in variety of biomedical applications. Chitosan’s physicochemical and mechanical properties are utilized in fabricating particles and films it can be modulated for specific purposes. The chemical modification of chitosan polymers improves their solubility in water or organic solvents, which in turn enhances their biological activities and increases number of potential biomedical applications. Chitin and chitosan has an intrinsic structural and physicochemical variability due to its natural origin and manufacturing process. Furthermore, the poor physicochemical characterization of the chitin and chitosan-based products used in biomedical experiments makes it very difficult to compare results and set up relationships between the physiological behavior of these compounds and its properties.

REFERENCES


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