Recent advances of chitosan-based polymers in biomedical applications and environmental protection

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Abstract
Interest in polymer-based biomaterials such as chitosan and its modifications and also the methods of their application in various fields of science is uninterruptedly growing. Owing to unique physicochemical, biological, ecological, physiological properties, such as biocompatibility, biodegradability, stability in the natural environment, non-toxicity, high biological activity, economic affordability, chelating of metal ions, high sorption properties, chitosan is used in various biomedical and industrial processes. The reactivity of the amino and hydroxyl groups in the structure makes it more interesting for diverse applications in drug delivery, tissue engineering, wound healing, regenerative medicine, blood anticoagulation and bone, tendon or blood vessel engineering, dentistry, biotechnology, biosensing, cosmetics, water treatment, agriculture. Taking into account the current situation in the world with COVID-19 and other viruses, chitosan is also active in the form of a vaccine system, it can deliver antibodies to the nasal mucosa and load gene drugs that prevent or disrupt the replication of viral DNA/RNA, and deliver them to infected cells. The presented article is an overview of the nowaday state of the application of chitosan, based on literature of recent years, showing importance of fundamental and applied studies aimed to expand application of chitosan-based polymers in many fields of science.

Keywords Polymers · Chitosan · Properties · Applications · Environmental protection

Introduction
Biopolymers, having unique properties, ease of using and processing, variety in combination with economy and environmental friendliness, differ from other classes of materials. These are high molecular weight natural materials that constitute the structural basis of all living organisms and play a significant role in vital processes [1]. They can be obtained both from living organisms (plants, animals, bacteria, fungi) and by synthesis method. New developments in the production of biopolymers are aimed at using these biomaterials as medical materials, food additives, adsorbents, packaging, cosmetics, fabrics for clothes, chemicals for water purification, industrial plastics, biosensors, etc. [2].

Production of biodegradable carbohydrate biopolymers, which are both a structural material (cellulose, chitin), an energy reserve (starch, glycogen), and also perform numerous biological functions, shows a special interest [3, 4]. Thus, the role of biomaterials synthesized on the basis of carbohydrate biopolymers has been studied in intercellular interactions, cell differentiation, the formation of multicellular systems, the development of malignant neoplasms, etc. [5]. Cellulose-, chitin-, and chitosan-based materials in the form of fibers, membranes, hydrogels, sponges have been developed and implemented in such important areas as pharmaceuticals, biomedicine, the food industry, etc. [6–12]. The combination of properties such as solubility, viscosity, gelation, mechanical, surface and interfacial properties, composition, degree of
polymerization, types of bonds and structure allows to create biomaterials that are promising compounds which meet the requirements of environmental friendliness and economic sustainability for a variety of applications [13].

The aim of some modern studies is to obtain highly effective drugs with sorption activity towards toxic metals, which are dangerous environmental pollutants that can be accumulated and negatively affect the vital functions of the human organism, leading to various pathologies. From the literature data it is known that enterosorbents (drugs of various structures that bind exo- and endogenous substances in the gastrointestinal tract by adsorption) based on polysaccharides and used for purification and binding of various toxins in the internal medium of the organism are very promising for these purposes [14]. In addition, these compounds possess a wide range of pharmacological properties. Removal of toxic metals from the organism is one of the important directions of modern science as well. In this regard, our research carried out on synthesis and application of enterosorbsents obtained on the base of chitosan and poly-N-vinylpyrrolidone, with the aim of removal of toxic metals from the human organism is very topical and practical; we are going to present the obtained results in our further publications.

The aim of this review is to present the recent scientific advances in properties and applications of various chitosan-based polymers. Synthesis, study and practical application of chitosan-based polymers in many biomedical fields and as the important environmental treatment materials for removal of toxic metals from different media are one of the achievements of scientific progress in the search of new promising materials in recent years.

**Production and structure of chitosan**

**Source and production of chitosan**

Chitosan is produced from chitin, which is present in the bodies of crustacean, molluscs, insects, fungi, etc., by the chemical or enzymatic partial N-deacetylation process [15, 16]. Production process of chitosan (Fig. 1) consists of deproteinization (heat at 60–100 °C for 1–72 h in the presence of 0.125–2.5 M of NaOH, Na₂CO₃, KOH, K₂CO₃, Ca(OH)₂, Na₂SO₃); demineralization (HCl, HNO₃, H₂SO₄, CH₃COOH and HCOOH at 100 °C for 1–48 h);

![Fig. 1 Scheme of chitosan production from chitin [21](https://example.com)](https://example.com)
decolouration (dissolve in organic solvents, bleach with KMnO₄, heat at 20–60 °C for 0.25–12 h); and deacetylation (30–50% solution of NaOH) [17–20].

**Structure of chitosan**

Chitosan is a natural linear polysaccharide composed of randomly distributed β-(1–4)-linked D-glucosamine and N-acetyl-D-glucosamine (Fig. 2a), namely it is consisted of two monosaccharide units: 2-amino-2-deoxy-β-D-glucopyranose and 2-acetamido-2-deoxy-β-D-glucopyranose linked by β-(1–4) glycosidic bonds, in which about 50% of the acetyl groups will be removed from the chitin by a hydration process or enzyme hydrolysis [22, 23]. When the deacetylation degree is higher than 50%, the polymer is called chitosan (in case of less than 50% it is called chitin) [24–26]. To avoid depolymerization and the formation of reactive particles under the influence of oxygen, sodium borohydride is added or the system is purged with nitrogen [27]. Jang et al. [28] found that chitosan has α, β and γ crystal structures (Fig. 2b).

α-Chitosan (main form) has a tight structure with strong intermolecular forces and is formed by two parallel and inversely arranged polysaccharide chains [29]. β-Chitosan is formed by two parallel and aligned polysaccharide chains with poor intermolecular hydrogen bonds [30]. γ-Chitosan is composed of three parallel polysaccharide chains, two of which were aligned in the same direction and the other was arranged in the opposite direction [31]. The sources of α-chitosan are crabs and shrimps, β-chitosan are squids, and γ-chitosan are loligos [32].

**Properties and modifications of chitosan biopolymers**

**Properties of chitosan biopolymers**

Chitosan is white odourless powder (or flakes) with different molecular weight (MW), degree of deacetylation (DD), insoluble in water and organic solvents, soluble in dilute hydrochloric, formic and acetic acids. Melting point is approximately 290 °C [33, 34]. Thus, the reason for the dissolution of chitosan in dilute hydrochloric acid is explained by the interaction of amino groups with hydrogen cations and converting it into a positively charged polyelectrolyte [35, 36].

Cations in the composition damage hydrogen bonds among the chitosan molecules, and it leads to dissolving them in water. The solubility of chitosan depends on MW and DD. The higher the DD of chitosan, the higher the degree of protonation of amino groups in the molecule, and the easier it dissolves. The larger MW of chitosan, the large number of hydrogen bonds formed in its polymer chain, and more difficult it dissolves. DD and MW greatly determine many properties of chitosan, in particular, antimicrobial and anti-biofilm activities, DD determines chitosan solubility and viscosity [40]. Therefore, at the application of chitosan biopolymers in practice (for example, as biomaterials, biopesticides, in drug delivery, immunology, etc.), it is necessary to have information about the main characteristics and control some parameters, such as the content of heavy metals, radionuclides, residual protein content, the presence of endotoxins, allergens bacteria and yeast, and other impurities [41].

Unlike other representatives of polysaccharides (cellulose, pectin, agar, dextran, etc.) chitosan possesses many important properties (Fig. 3), including non-toxicity, chelating activities, biocompatibility, biodegradability, adsorption capacities, film-forming ability, bacteriostatic action [42].

The antiviral, antibacterial activity of chitosan has been proven, the immunostimulating, adjuvant, adjuvogenic, antihypoxic, cholestric, radioprotective, hemostatic effects of chitosan and its derivatives have been confirmed [43–45]. The antibacterial effect of chitosan is explained by the interaction of its positively charged amino groups.

**Fig. 2** Structure (a) and polymeric forms (b) of chitosan
with negatively charged phosphoryl groups of phospholipids of the bacterial cell wall, changes in metabolism, which leads to cell death [46].

It is known that chitosan is capable of interacting with nucleic acids, which, in turn, leads to the disturbance of synthesis of vital proteins and enzymes, and damaging the structure and function of the bacterial cell [48]. The fungicidal properties of chitosan are described by identical mechanisms [49]. The analgesic effect of chitosan has been established due to its ability to absorb bradykinin [50]. Chitosan sulfate, the structural analogue of chitosan, is similar in structure to the heparin—natural blood anticoagulant [51, 52]; the possibility of a synergistic effect of chitosan allows to create the drugs with anticoagulant and anti-sclerotic action [53]. Furthermore, sulfated chitosan is a natural antioxidant, which absorbs hydroxyl and superoxide anion radicals, and can be a substrate for creating drugs and biologically active additives as well [51, 54]. Chitosan can be used for treatment of diabetes because it increases insulin levels [55]. Possibility of using as a polymer matrix for the delivery and dosage release of drugs and anti-allergic properties of chitosan are proven [56]. Application of chitosan in immunotherapy is proposed as an antitumor agent that suppresses the growth of tumor cells, pathogens, stimulates humoral and cellular immunity, for gene therapy with the aim of targeted delivery of genetic material [45]. Chitosan has wound healing properties, stimulates the formation of granulation tissue and the activity of fibroblast proliferation [57, 58] and suppresses fibrosis [44]. Chitosan and its derivatives can be used to create biodegradable carriers of pharmaceuticals in the form of films, which provides the prolonging effect of their action [53, 59, 60].

**Modifications of chitosan biopolymers**

In order to improve the solubility, rheological properties, thermal stability, and oxidation resistance, chitosan is subjected to chemical modifications (Fig. 4) [61].

Amino groups, hydroxyl groups at C₃ and C₆ positions are the active groups in the chemical structure of chitosan. As a rule, the NH₂-amino group is more reactive than the Cβ-OH primary hydroxyl group (due to the free rotation),
and the primary hydroxyl group is more reactive than the 
C3-OH secondary hydroxyl group. Chemical modification of
chitosan could be carried out on amino, hydroxyl, or both 
amino and hydroxyl groups to form N-, O- or N,O-modified 
chitosan derivatives [63, 64]. Etherification, esterification, 
crosslinking, graft copolymerization and O-acetylation are 
reactions carried out on hydroxyl groups, while acetylation, 
quaternization, Schiff's base reaction and grafting are carried 
out on amino groups [65].

**Schiff bases formation reactions**

Modifications of chitosan biopolymers via reactions of 
Schiff bases formation are well-known. Chitosan reacts 
readily with most aliphatic and aromatic aldehydes to produce 
Schiff bases—imines. The Schiff base formed after the reac-
tion of aldehyde and chitosan could be reduced by sodium 
borohydride to synthesize N-derivatives of chitosan [66, 67]. 
They could chelate transition metal ions in aqueous solution 
to form insoluble metal chelates, which could be separated. 
This reaction is very useful for the application of chitosan 
for removal of toxic metals.

**Quaternization reactions**

Modifications of chitosan biopolymers via quaternization 
reaction are carried out by means of a free amino group on 
the chitosan. It includes introduction of quaternary ammo-
nium groups or small molecule quaternary ammonium salts 
on the amino group of chitosan. These groups have strong 
hydration ability and large steric hindrance. The quaternized 
chitosan has increased solubility in water and good antibac-
terial properties [68–70].

**Alkylation and acylation reactions**

Modifications of chitosan biopolymers via alkylation and 
acylation reactions are carried out with halogenated hydro-
carbons, anhydrides, acid halides as acylating agents in a 
certain reaction medium. Synthesized compounds destroy 
the hydrogen bonds among chitosan molecules, change the 
original crystal structure, greatly improving the solubility 
and widening application range of chitosan [71–74].

**Carboxylation and carboxymethylation reactions**

Modifications of chitosan biopolymers via carboxylation 
and carboxymethylation reactions involve the introduction 
of acid groups into the main chain of chitosan in order 
to improve the solubility, moisturizing and film-forming 
properties of the compound [75, 76]. Carboxymethyla-
tion can occur both at the hydroxyl and amino groups 
of chitosan with the formation of O-carboxymethyl and 
N-carboxymethyl derivatives, respectively. Carboxymethyl 
chitosan, a water-soluble anionic polymer was selectively 
modified to prepare antitumour drug conjugates [77, 78], 
also was reported as a potential vehicle for targeted drug 
delivery to the liver due to its preferentially located and 
long retention in the liver and spleen after intravenous 
injection [79]. The modification of chitosan with sugars 
on amino groups allows to introduce cell-specific sugars 
recognized by cells, viruses and bacteria into carriers of 
specific drugs, DNA and antibodies [80, 81].

**Graft copolymerization reactions**

Modifications of chitosan biopolymers via graft copoly-
ermerization reaction improve the solubility and biological 
activity of the polymer [82] and are used for medical and 
pharmaceutical applications as orthopedic/periodontal, 
wound-dressing materials, tissue engineering and contro-
led drug/gene delivery [83–86]. Based on this modi-
fication and a molecular imprinting technique, chitosan 
could be used for special absorption of template molecules 
mimicking natural recognition materials such as antibodies 
for diagnostics [87]. Recently composites of chitosan with 
various polymers (polyethylene glycol, polylactic acid, 
polypyrrole, collagen, starch) and with inorganic materials 
(bioactive glass, ceramics) have been intensively studied 
for drug delivery systems, tissue engineering, and other 
medical applications [88–91]. Hyaluronic acid, alginate, 
chondroitin sulfate, hydroxyapatite are used with chitosan 
for preparation of multilayer-structured biomaterials based 
on the layer-by-layer technique for applications in tissue 
engineering [92–96].

**Cross-linking reactions**

Modifications of chitosan biopolymers via cross-linking 
allow to obtain chitosan derivatives with stable chemi-
cal properties, insoluble in acids and bases and which 
are used as a carrier for the adsorption of drugs, immo-
obilized enzymes, heavy metal adsorbents, etc. Research-
ers have compared the composition of metal complexes 
formed by the coordination of chitosan with some 
heavy metal ions before and after cross-linking. The 
ability of chitosan to adsorb metal ions was as follows: 
Hg > Cu > Pb > Zn > Cd > Mn [97].

Other chemical modifications of chitosan such as esteri-
fication, hydroxyalkylation, sulfonation, etc. are known 
and studied [98–101]. At present, chitosan is also physi-
cally modified through mechanical grinding, ionizing radi-
ation and ultrasonic treatment to prepare biomaterials for 
the various applications [102].
Recent researches of chitosan biopolymers

The presence of amino and hydroxyl groups in chitosan opens the great opportunities for many industrial and biomedical applications. Use of chitosan biopolymers is uninterruptedly growing in such fields as medicine, pharmaceutical research, paper, textile, agriculture and food industries, cosmetology, tissue engineering, ecology, biotechnology, wastewater treatment (Fig. 5). Chitosan-based materials have also found application in veterinary medicine, medical nutrition, production of dietary supplements, biosterecides, biosensors, chromatographic materials [103–112]. The use of chitosan has been described in direct tablet compression, as tablet disintegrant, for the production of controlled release dosage form or for the improvement of drug dissolution [113].

Application of chitosan biopolymers in biomedical practice

Recent applications are in ophthalmic, nasal, sublingual, buccal, periodontal, gastrointestinal, colon-specific, vaginal, mucosal-vaccine and gene carrier fields. Chitosan, being an adsorbable and nontoxic polymer, is favored in drug delivery because of antiulcer and antacid properties, which help in preventing drug irritation [114, 115]. During the last years the use of chitosan composite-based scaffolds as a biomaterial has been reported for tissue engineering [116, 117] due to the cationic nature and ability to form interconnected porous structures. Chitosan with other biomaterials such as hydroxyapatite, bioactive glass ceramic are used for bone repair and reconstruction to form a carbonated apatite layer to enhance the mechanical properties [118–122]. Owing to unique properties (toughness, biocompatibility, oxygen permeability) chitosan-based biomaterials in the form of fibers, mats, sponges have been used for burn treatment and wound dressings [123]. Influence of chitosan biomaterials on the synthesis of collagen for wound healing was studied [124]. Chitosan has been modified by authors [125] for using as a dressing material for treatment of wounds and burns. It was found that dressing materials based on chitosan and its modified forms, having haemostatic and analgesic properties, and also possessing properties of high strength, non-toxicity, good water absorption capacity and biocompatibility, together with other polymers (both synthetic and natural) accelerate the process of wound contraction and healing [126].

Researches carried out in the field of infectious diseases show the effectiveness of the use of chitosan in this area. Systems developed on the base of chitosan with different properties have been proposed [127]. It has been shown that these systems reduce the side effects of drugs and increase the effectiveness of treatment. Taking account the current situation in the world with COVID-19 and other viruses, chitosan is also active in the form of a vaccine system, for example, it can deliver antibodies to the nasal mucosa and load gene drugs that prevent or disrupt the replication of viral DNA/RNA, and deliver them to infected cells. Further work on the development of systems is proposed that will be widely used in clinical practice, in particular, for the treatment of infectious diseases (Fig. 6).

From year to year, the spread of dangerous pathogenic bacteria is very serious for all mankind and that requires the creation of new materials for the treatment of bacterial infections. Thus, antibacterial and antibiotic properties of the chitosan biomaterial with grafted ferulic acid (CFA) against Listeria monocytogenes (LM), Pseudomonas
13. Chitosan biomaterials having good biocompatibility, bioactivity and biosafety, demonstrate great potential in the field of infection control.

14. Chitosan-based biomaterials in infection diseases [127]. Chitosan biomaterials having good biocompatibility, bioactivity and biosafety, demonstrate great potential in the field of infection control.

15. A new antifungal denture base material was proposed by modifying polymethyl methacrylate (PMMA) with chitosan salt (chitosan hydrochloride (CS-HCl) or chitosan glutamate (CS-G)) [133]. When studying its properties in vitro, the analyses carried out showed that, despite the antifungal effect of CS salts in solution, modification of the PMMA polymer with these CS salts does not improve the antifungal, antibiofilm and antiadhesive properties of the base material of PMMA dentures.

16. Possible applications of biomaterials based on chitosan, antibiotics and antifungal drugs, considering the factors and mechanisms of the antimicrobial and antifungal action of chitosan, and also clarifying the question of the genetic response of microorganisms to chitosan are described [134, 135]. It was established that there are electrostatic interactions between positively charged chitosan and negatively charged cell surface of the microorganism (teichoic acid in gram-positive bacteria, lipopolysaccharide (LPS) in gram-negative bacteria and phosphorylated mannosyl in fungi). In addition, chitosan chelates environmental ions and nutrients which are necessary for the survival of bacteria. It was found that low-molecular-weight chitosan and oligo-chitosan exhibit an extracellular antifungal action, inhibit mitochondrial activity and ATP production, and are also able to penetrate the cell wall, inhibiting DNA/RNA and protein synthesis. The research indicates that despite the fact that chitosan exhibits a high antimicrobial effect, its use on a large scale is limited by some of its properties, such as low solubility in water, lack of a certain molecular weight and purity.

17. Nanoparticles based on chitosan and its modified forms are widely tested as drug carriers in ophthalmology for the treatment of bacterial and viral infections, glaucoma, age-related macular degeneration and diabetic retinopathy. Authors summarize recent advances in chitosan-based nanotherapy for drug delivery to the eye and the problems that arise during this process [136]. It has been shown that a high degree of cross-linking in chitosan nanoparticles allows to increase drug retention and facilitates penetration into the eyes.

18. The following research describes in detail the recent developments of chitosan blends with an emphasis on electrospun nanofibers, which represent a new class of biomaterials, in the field of biomedical applications (drug delivery, wound healing, tissue engineering, biosensing, regenerative medicine) (Fig. 7) [137].

19. New method (electrospinning) for the production of chitosan nanofibers with a large surface area and porosity was considered [138]. Specialists working with this material can optimize the properties of these fibers and expand their range of applications. Thus, it is indicated that the development of complex organ structures will be achieved by the method of electrospinning in combination with 3D printing technology, three-dimensional scaffolds will be designed,
integrated with growth factors and cells with high viability. It is noted that despite the fact that specialists were able to simulate the structure and morphology of natural tissue, these studies need further clinical trials until they can be reliably applied in medical practice.

Chitosan-g-poly(acrylic acid)/attapulgite/sodium alginate composites were synthesized as drug delivery matrices [139]. It was found that the composite hydrogels displayed high pH-sensitivity. The cumulative release ratios of diclofenac sodium from the hydrogel were 3.76% at pH = 2.1 and 100% at pH = 6.8 within 24 h, respectively. It has been noted that such pH-sensitive polymeric materials can be offered for the development of new controlled drug delivery systems.

Hydrogels based on different ratios of chitosan and sodium alginate were synthesized by gamma irradiation in the presence of glutaraldehyde, as a cross-linking agent. It was found that these blend hydrogels exhibited high water swelling and showed high thermal stability. Also, pH responsive release character of ketoprofen drug was studied in this research [140].

The recent developments in chitosan delivery systems for the treatment of brain tumors and neurodegenerative diseases are presented [141]. It has been found that chitosan nanoparticles improve therapeutic efficacy in various brain diseases due to their biocompatibility, biodegradability, low toxicity, controlled release, mucoadhesiveness and effective absorption by nasal mucosa and tumor cells. Chitosan nanoparticles are also often used as carriers for the delivery of therapeutic agents, successfully increasing their concentration in the brain, and when administered intranasally chitosan nanoparticles are commonly used to deliver drugs to the brain and can increase nasal residence time and absorption by the nasal mucosa.

It is known that chitosan composites are widely used in medical practice (treatment of burns, artificial kidneys, blood anticoagulation and bone, tendon or blood vessel engineering), and also developed for use in biosensors, packaging, separation processes, food or agricultural industries, and catalytic processes. It is planned to create modulated three-dimensional structures of chitosan using cross-linking processes that improve its use in various fields of medicine, as well as the development of porous catalysts based on chitosan in order to increase the efficiency of catalytic processes by increasing the number of available active sites [142].

The presence of electron-donating amino and hydroxyl groups allows to use chitosan biopolymers in the separation and purification of biologically active compounds (nucleic acids and products of their hydrolysis, steroids, amino acids). Recent studies have indicated usage of chitosan-based compounds as effective materials to inhibit biofilm formation and attenuate of virulence properties by various pathogenic bacteria [143].

**Application of chitosan biopolymers in environmental protection**

Environmental pollution with heavy toxic metals is dangerous for all living organisms. Currently, methods (such as bioadsorption, solvent extraction, remediation by plants
and microbial communities, green separation by hydrogel polymers, immobilization, and others) are being developed for the extraction of heavy metals from soil and wastewater. Taking into account the ingestion of heavy metals by humans with food and to prevent serious risks to human health, development of effective methods for removal of heavy toxic metals and to eliminate the toxicity of these metals in air, soil, and water is of great importance. The food chain of the adsorption process of heavy toxic metals by humans is shown in Fig. 8 [144, 145].

In work [147] it was shown that chitosan hydrolysates obtained by hydrolysis of high-molecular-weight chitosan by the fenton reaction can be used as potent agents that block or form tight complexes with fine dust in the air, containing some solid particles and unknown species of microorganisms. This data can be used in the future for the production of various dust-proof masks and filters for the purpose of human healthcare.

Nanomaterials prepared on the basis of chitosan and its modified forms together with carbon nanotubes have been used as bacterial disinfectors of various pollutants in the field of water purification [148]. The use of these materials compared to ozonation, chlorination and other disinfection methods has demonstrated the absence of treatment by-products. In the future, the authors plan to develop materials with increased stability and low toxicity, and pay special attention to the design of nanomaterials, which affects the properties and efficiency of the material, in order to eliminate undesired adsorption of biomolecules and increase antibacterial activity.

A promising direction for application of chitosan biopolymers is the sphere of environmental protection, for development of drugs with radioprotective properties, sorbents for the isolation of radionuclides [149]. Chitosan can also be used as a flocculant for water treatment, surfactants and membranes in ultrafiltration, reverse osmosis and evaporation, purification of industrial effluents containing heavy metal ions [150–154]. Chitosan is capable of forming complexes with transition metals [155, 156]. The heavy metal complexes are formed as a result of donation of a nonbonding pair of nitrogen or oxygen electrons on the -NH2 and/or -OH groups, respectively, to a heavy metal ion. Chitosan granules obtained by cross-linking chitosan with tripolyphosphate have significant adsorption properties towards the metal ions and could be effectively used in wastewater treatment [157–159]. The nature of the cation is very important in the mechanism of interaction; the affinity of chitosan for cations absorbed on film shows selectivity in the following order [160]:

\[
\text{Cu}^{2+} >> \text{Hg}^{2+} > \text{Zn}^{2+} > \text{Cd}^{2+} > \text{Ni}^{2+} > \text{Co}^{2+} ~ \text{Ca}^{2+}
\]

One of the important applications of chitosan biopolymers is connected with their ability to bind heavy and toxic metal ions. The adsorption capacity values of modified chitosans (MChs) for metal ions removal were reported by Zhang et al. [161]. It has been noted that adsorption process depends not only on adsorbent structure (modifications of chitosan) but also on conditions of the process (pH, temperature, adsorbent dosage, contact time, co-existing ions). The following results for Cu(II) ions adsorption were observed on various MChs (Table 1).

Authors of research [162] developed monodisperse microspheres of chitosan by the microfluidic method and carried out experiments to study the adsorption characteristics to remove copper ions from waste water. The adsorption mechanism was developed based on various adsorption kinetics and isotherms models. The research results showed a high adsorption capacity (75.52 mg/g) and a readsoption efficiency of 74% after 5 cycles. The adsorption capacity in the presence of other competing ions was also studied by the density functional theory (DFT) analysis. It was shown that the most energetically favorable structure of the studied metal complexes is the central model, where metal ions are coordinately bound to several amino groups (Fig. 9).

Pb(II) imprinted magnetic biosorbent was prepared by means of lead ion imprinting technology and cross-linking reactions between chitosan, Fe3O4 and Serratia marcescens in order to remove of Pb2+ ions. The influence of solution pH, adsorbent dosage, selectivity of sorption and desorption processes were studied on the adsorption of lead ion. Kinetics and thermodynamics of adsorption process were investigated and adsorbent was studied by XRD, VSM, SEM, EDS, FTIR, XPS and BET analyses. It has been established that nitrogen of amino group and oxygen of hydroxyl group in Pb(II) imprinted magnetic biosorbent were coordination atoms [163].

A method of heavy metal ions removal by biodesorption with hybrid 3D printing technology was proposed [164]. For this purpose, 3D chitosan composite of a monolithic structure of reusable application was prepared, which showed high efficiency in contrast to conventional biosorbtents. The
adsorption capacity of this material was about 13.7 mg/g at T = 25 °C and pH = 5.5. The analyses performed showed that the –NH₂ and –OH functional groups of chitosan are actively involved in the adsorption process, which indicates the possibility of this sorbent using to remove numerous metal ions from different solutions.

Table 1 Experimental conditions and adsorption capacities of MChs for the removal of Cu(II) ions from aqueous solutions [161]

| Modified chitosan                                                                 | Characterization methods          | Amount of Cu(II) mg/g | Optimum conditions |
|----------------------------------------------------------------------------------|-----------------------------------|-----------------------|--------------------|
| Chitosan/sulhydryl-functionalized graphene oxide composite                        | FTIR, TG, SEM, XRD                | 425.00                | pH 2.0 T(K) 293     |
| Carbonaceous sulfur-containing chitosan–Fe(III)                                  | FTIR, SEM, NEXAFS                 | 413.20                | T(K) 6.0 contact time(min) 298 15 |
| Chitosan/poly(vinyl amine) composite beads                                       | FTIR                              | 192.57                | pH 4.5 T(K) 298     |
| Epichlorohydrin o-crosslinked maleic acyl chitosan adsorbent                      | FTIR, XRD                         | 132.50                | T(K) 5.0 contact time(min) 303 90 |
| Chitosan–epichlorohydrin–triphosphate adsorbent                                  | FTIR, EDS, TGA, DSC               | 130.72                | pH 6.0 T(K) 298     |
| Grafted chitosan beads                                                           | FTIR, SEM                         | 126.00                | T(K) 6.0 contact time(min) 303 300 |
| Cross-linked magnetic chitosan-2-aminopyridine glyoxal Schiff’s base resin       | SEM, FTIR, TGA, XRD               | 124.00                | pH 5.0 T(K) 303     |
| 8-Hydroxyquinoline-2-carboxaldehyde chitosan                                     | FTIR, 13C-NMR, DSC, SEM           | 88.07                 | T(K) 5.0 contact time(min) 303 360 |
| Chitosan-modified MnFe₂O₄ nanoparticles                                           | XRD, TEM, FTIR, zeta potential    | 65.10                 | pH 6.5 T(K) 298     |
| Epichlorohydrin cross-linked xanthate chitosan                                    | FTIR, 13C-NMR, XPS                | 43.47                 | T(K) 5.0 contact time(min) 323 1440 |
| Chitosan/poly(vinyl alcohol thin adsorptive membranes modified with amino functionalized multiwalled carbon nanotubes | FTIR, SEM, permeability           | 20.10                 | pH 5.5 T(K) 313     |
| Chitosan/sporopollenin microcapsules                                              | SEM, FTIR, TGA                    | 1.34                  | T(K) 5.5 contact time(min) 298 120 |

Fig. 9 Structures of investigated divalent metal-CS complexes [162]
In work [165, 166] recent data on removal of lead (Pb), cadmium (Cd), mercury (Hg) and arsenic (As) by chitosan-based magnetic adsorbents from various aqueous solutions are presented. It has been shown that these adsorbents have a high adsorptive capacity towards toxic metals and can be reused in consecutive adsorption–desorption cycles. Langmuir isotherm model confirms good monolayer capacity values of 341.7 mg/g for lead, 152 mg/g for mercury, 321.9 mg/g for cadmium and 65.5 mg/g for arsenic (Fig. 10).

Removal of cadmium ions from waste water was studied using polypropylene/sisal fiber/banana fiber (PP/SF/BF) and chitosan/sisal fiber/banana fiber (CS/SF/BF) composite materials as adsorbents. It has been established that sorption capacity of CS/SF/BF composite (419 mg/g) is higher than PP/SF/BF composite (304 mg/g), and permits multilayer adsorption. The carried out tests have shown that adsorption process was best satisfied with the Freundlich isotherm [167].

Modified chitosan-based nanocomposites (MCS/GO-PEI) were prepared for removal toxic heavy metals and organic compounds from environmental water. The results of research showed that sorption process was characterized by pseudo-second-order kinetic and Langmuir isotherm model. High adsorptive capacities of these samples for arsenic, mercury ions, congo red, amaranth (220.26, 124.84, 162.07, 93.81 mg/g, respectively) were presented and the possibility of re-using these nanocomposites as promising adsorbents was shown [168]. Preparation of graphene oxide/chitosan (GO/CS) composites as new promising sorbent materials for removal of heavy metal ions, dyes and other organic molecules from aquatic environment is presented in paper [169, 170]. Sorption of copper (II), cobalt (II) and iron (III) ions, using chitosan composite sponges prepared by ice-segregation procedure, was studied for purification of waste water [171]. It has been determined that iron (III) ions were mainly adsorbed from two-component mixtures with cobalt (II) ions at pH = 4, whereas copper (II) ions were removed from two-component mixtures with cobalt (II) ions at pH = 6. Carried out experiments showed high chemical stability and reusability of these sponges in sorption–desorption processes.

Nitrogen-enriched chitosan-based activated carbon biosorbent was prepared for separation of Cr(VI) and Pb(II) ions from contaminated water. Thermodynamic parameters have been studied, and kinetics of adsorption of these metal ions is well-fitted by a pseudo-second-order model. High efficiency, availability, recyclablility, and cost effectiveness make it possible to use this biosorbent for wastewater treatment [172, 173].

Magnetic phosphorylated chitosan composite (P-MCS) as an adsorbent for Co(II) ions was prepared by authors [174]. Adsorption capacity for Co(II) was equal to 46.1 mg/g. Adsorption isotherms and kinetic models of these ions well fitted the Langmuir model and the pseudo-second-order model, respectively. The carried out experiments have shown dependence of Co(II) adsorption process on surface chelation between functional groups and metal ions, and possibility of use P-MCS for treatment of wastewater.

In order to eliminate the limitations in the use of chitosan as an adsorbent for the removal of heavy metals, such modifications as cross-linking, grafting, and the use of magnetic chitosan (modified with Fe₃O₄) were carried out [175]. It was suggested in further studies to focus attention on: issues of regeneration and desorption; replacing glutaraldehyde and epichlorohydrin as crosslinking agents with less toxic ones; the use of an adsorbent that does not depend on pH; the use of various optimization tools (for example, the response surface methodology) and other issues in order to use chitosan on an industrial scale.

New class of crystalline porous composite consisting of metal ions and multidentate organic ligands is metal organic framework (MOF), which showed an appreciable capability in wastewater treatment for the removal of heavy metal ions. Functionalization of chitosan with ionic liquids (new class of salts with combination of organic and inorganic ions and with very unique and novel properties) was found to have increased adsorption capacity. They are immobilized on a solid support or they chemically react due to their high reactivity in adsorption process. Analyses carried out in work [176] showed that introduction of ionic liquids in chitosan improves thermal stability and heavy metal uptake properties.

Chitosan conjugated magnetite nanoparticle (CH-MNP) as an effective adsorbent was synthesized for the removal of Pb(II) ions by means of controlled co-precipitation technique and studied by response surface methodology (RSM) for...
optimization of process parameters [177]. Optimum value of pH, adsorbent concentration and contact time were obtained as 5.1, 1.04 g/L, and 59.9 min, respectively. Adsorption isotherm data were correlated well with the Langmuir adsorption isotherm model, and the equilibrium data followed the pseudo-second-order kinetics and intraparticle diffusion kinetic model.

New EDTA modified γ-MnO₂/chitosan/Fe₃O₄ nanocomposite was produced for the removal of heavy ions from aqueous solutions. Experiments have been shown high adsorption capacities for Pb(II) and Zn(II) (310.4 and 136 mg/g, respectively). Results of thermodynamic tests (ΔG° < 0, ΔH° > 0, and ΔS° > 0) showed that the nature of adsorption by this nanocomposite for Pb(II) and Zn(II) ions is spontaneous and endothermic, and is favored at higher temperatures [178].

Adsorption and removal of chromium (VI) ions from aqueous solutions, using chitosan hydrogel cross-linked with polyacrylic acid and N, N'-methylenebisacrylamide, has been studied in paper [173]. Evaluation of adsorption mechanism was carried out using Langmuir, Freundlich, Redlich-Peterson, and Sips nonlinear isotherms. The removal of chromium (VI) at pH 4.5 and an initial metal concentration of 100 mg/L was 94.72%. It was proposed to use chitosan hydrogel as an economical and environmentally friendly adsorbent of heavy metal ions for water and wastewater treatment.

A new efficient method of adsorption and removal of heavy metal ions with electric field-driven from wastewater has been proposed [179]. A composite adsorbent based on chitosan (CS) and sodium phytate (SP) deposited on a polyethylene glycol terephthalate (PET) material was used and placed near the cathode in a pair of titanium plate electrodes. Experiments have shown that the rate of copper ions removal adsorbed on the CS-SP/PET adsorbent increased from 56 to 88% for 10 mg Cu (II) solution per liter when the applied voltage was from 0 to 1.2 V (energy consumption was economical). The adsorption mechanism was correlated to the Langmuir isotherm model and the kinetic equation of the pseudo-second order.

Chitosan and silica gel-based composite was prepared with the purpose to study the adsorption of heavy metal ions in various solutions [180]. This composite was studied by FTIR and SEM–EDS methods in order to obtain information about the presence of active sites and surface morphology. The study of the adsorption process by this material showed the maximum percentage of removal of Cu (89.78%), Pb (96.9%) and Ni (69.33%) at pH = 5, Hg (92.78%) at pH = 6 with adsorbent mass of 1.5 g, temperature 30 °C and 120 min contact time. Adsorption of Pb is best satisfied to pseudo-first order, whereas pseudo-second order is best fitted to the adsorption of Cu, Ni and Hg. Obtained values of change in enthalpy testify to the effect that both physical and chemical adsorption occur in this process.

A highly adsorptive cross-linked carboxymethyl chitosan (CMC)/2,3-dimethoxybenzaldehyde Schiff base complex was synthesized for removal of heavy metals such as lead (II) and cadmium (II) ions from aqueous solutions and characterized using FTIR, XRD and SEM analysis [181]. It was confirmed that adsorption follows the Freundlich model and the pseudo-second order kinetic model. The cross-linked Schiff base has been found to be an effective, environmentally friendly and inexpensive adsorbent.

Development of a new economical and environmentally friendly chitosan nanoadsorbent has been proposed for water purification [182]. Use of inorganic nanomaterials, agricultural waste, adsorbents based on polymer nanocomposites for removing of heavy metal ions such as Hg (II), Cu (II), Cr (VI), Zn (II), Co (II), Cd (II), Pb (II) from wastewater has been studied. Experiments have shown that polymer-based materials have a strong chelating ability towards heavy metal ions, fast adsorption kinetics, and are well regenerated due to the synergistic effect of polymers and various nanofillers present in nanocomposites.

Hydrogels based on different ratios of carboxymethyl cellulose (CMC) and carboxymethyl chitosan (CMCh) and prepared by γ-irradiation showed high adsorption capacities for Pb and Au ions. It has been established that the effective sorption of these metal ions occurred with amino groups of the hydrogel with (CMC/CMCh) composition of 75/25 or 50/50. Properties of the obtained hydrogels (gel fraction, swelling ratio, gel strength) were also studied [183].

Carboxymethylated chitosan hydrogels were obtained by γ-ray irradiation crosslinking method. Kinetic studies of sorption process were carried out with a purpose to determine favourable conditions for the adsorption of Fe(III) ions on these hydrogels and showed that maximum uptake of Fe(III) ions was equal to 18.5 mg/g at pH = 4.7 [184]. Favorable adsorption behavior was explained due to the coordination of Fe(III) ions with amino, hydroxyl and carboxyl groups in the structures of the proposed hydrogels.

Application of chitosan biopolymers in other spheres

Chitosan is widely used in cosmetology as a moisturizer, emulsifier, antistatic, emollient for hair and skin care. Chitosan biopolymers are polycation hydrocolloids that become viscous at interaction with acid and can act as abrasive film formers interacting with integuments and hair. Its use as an antioxidant agent and gelling agent in the food industry has also been proven [185, 186]. This biopolymer is used as a food wrap owing to its ability to form semipermeable tough, long-lasting, flexible films, thus extending the shelf life of...
food [187, 188], inhibiting microbial growth [189, 190]. Chitosan has been used in agriculture as antifungal agents and also to accelerate the growth of plant and decelerate root knot worm infestations [191].

In the paper and textile industry, chitosan is applied to cellulose fiber during the formation of paper, while the strength of the paper sheet is significantly increased, the resistance to bursting, tearing, and image stability are improved. Chitosan is used to improve the dyeing quality of fabrics made from various fibers. There are known data on the use of this biopolymer for the preparation of antistatic, stain-resistant, printing and finishing materials, for the removal of dyes and the manufacture of textile seams, threads and fibers as well [192].

**Commercial chitosan products**

Chitosan can be produced from different sources and the most traditional source of chitosan is from waste crustaceans’ shells from the seafood processing industry, such as crab or shrimp shells. While research has indicated the availability of other sources, these are currently the most sources actively explored on a commercial scale. Chitosan market volume is expected to reach $2.55 \times 10^9$ US dollar by 2022. Although many articles have been published during the last twenty years, chitosan applications in the biomedical field are still limited, mainly due to the difficulty of obtaining of the biopolymer with high purity and reliability at its source. Furthermore, production of new chitosan-based materials is quite limited, mainly due to their cost, which remains higher than that of petroleum-based polymers with similar properties [131]. It is required to develop more economical and environmentally friendly methods in order to obtain chitosan and convert it into useful products. On the other hand, the production cost of crustaceans based chitosan is cheap compared with fungal based chitosan. Crustaceans raw materials are readily available and cheap whereas the cost of raw materials is the main bottleneck for fungal chitosan production. Crustaceans chitosan can be found from 10 US dollar per kg to 1000 US dollar per kg. It also depends on product quality and application [193].

It should be noted that some commercial products of chitosan are known in the world market. Different forms of chitosan-based materials are used as wound dressing (Hem-Con® Bandage, ChitoGauze® PRO, ChitoFlex® PRO, ChitoSam™, Syvek-Patch®, Chitopack C® and Chitopack S®, Chitodine®, ChitosanSkin®, TraumaStat®, TraumaDEX®, Celox™), as hemostatic sealants (ChitoSeat™) in biomedical practice. Reaxon® (Medovent, Germany) is a chitosan-based nerve conduit which is resistant to destruction, prevents irritation, inflammation and infection, inhibits scar tissue and neuroma formation. Chitosan-based nutritional supplements (Epakitin™, Nutri + Gen®) are commercially available for use in chronic kidney disease in pets. Various chitosan-based products (ChitoClear®, Chitoseen™-F, MicroChitosan NutriCology®, etc.) are for sale as safe weight loss supplement, cholesterol-reducing agents, and also as antioxidant agents.

Many chitosan-containing products (Curasan™, Hydamer™, Zenvivo™, Ritachitosan®, Chitosan MM222, Chitoseen™-K, ChitoCure®, ChitoClear®, etc.) are also commercially available for cosmetic and hygienic usage. [131].

**Conclusion**

At present, chitosan due to the availability, renewability of raw material and the unique properties is a subject of researches and is widely used in various fields of biotechnology, medicine, pharmacy and industry.

In the coming years, demand for polymer-based biomaterials with better performance will be unquestionably the highest. Distribution of chitosan-based biomaterials at the larger scale can contribute as a sustainable and renewable material for the scientific developments in future. Furthermore, in the past decade in various fields of researches significant advancement has submitted but is still incomplete and applications of chitosan in the biomedical area are still limited. There are still many unresolved issues and challenges. Bioactivity of chitosan-based polymers has been studied for many years, however, the structure activity relationship and the mechanism of activity needs further investigation. This might be connected with poor bioavailability, and lacked of human clinical trials, and all these factors required further analysis.

At present time, there is not enough literature information on the application of polymer-based enterosorbents in medical practice, which is considered as one of the promising directions in the treatment and prevention of diseases of various etiologies [194, 195]. Preparation and application of enterosorbents reduces the intensity of antibiotic and hormone therapy. The development of this direction depends on both technological possibilities and the state of the environment.

**Author contribution** All authors contributed to the study conception and design. Material preparation and analysis were performed by [Sevda Fatullayeva], data collection by [Samira Mammadova] and [Elmira Aliyeva], review and editing by [Nizami Zeynalov] and [Dilgam Tagiyev]. The first draft of the manuscript was written by [Sevda Fatullayeva] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

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