1. Introduction

Due to their great biocompatibility and biodegradability, biopolymers are crucial in biomedical applications [1, 2]. Biopolymer-based nanoparticles are the most promising nano carriers for delivering various therapeutic drugs to tumor cells such as ovarian cancer cell lines because they have good biodegradation and biodistribution in biological systems [3, 4]. Additionally, biopolymers are utilized in a number of biomedical applications, including genes delivery [1], tissue engineering, and drug delivery [5, 6]. Due to their usage and limitations, biopolymers are a major chemistry and biology interface [7, 8]. There is a need to create awareness and create novel ways for biomedical and agricultural applications given the variety of biopolymer applications [1, 9]. The research community is currently very interested in biopolymers such as chitosan, alginate, pectin, cellulose, agarose, and gelatin [10, 11].

Chitosan (CS), a biopolymer, has drawn a lot of interest due to its adaptability, accessibility, and special qualities in medical applications [12, 13]. It is made up of 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose units and is the second most prevalent copolymer after cellulose [14, 15, 16]. It is often created from chitin by partial deacetylation in an alkaline environment, as shown structurally in Figure 1 [17-20]. The polymer is digested by human enzymes and is used for a range of medical and agricultural applications, including genes delivery [1], tissue engineering, and drug delivery [5, 6]. Due to their usage and limitations, biopolymers are a major chemistry and biology interface [7, 8]. There is a need to create awareness and create novel ways for biomedical and agricultural applications given the variety of biopolymer applications [1, 9]. The research community is currently very interested in biopolymers such as chitosan, alginate, pectin, cellulose, agarose, and gelatin [10, 11].

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Due to its antibacterial action, chitosan and its nanoparticles (NPs) are beneficial for a range of biological applications, including food preservation [27]. They also affect fish and crustaceans in an immunomodulatory manner, which directly benefits the aquaculture and fish farming industries [28]. Additionally, CS NPs are now being used to treat illnesses in fish and other animals [29]. Chitosan NPs are attractive candidates for a variety of uses in fish medicine due to their many beneficial biological features, including safety, biocompatibility, biodegradability, and antibacterial capacity [30].

Due to its polyelectrolytic nature and its capacity to chelate substances because of the presence of amino groups, chitosan is used for the majority of applications [31, 32]. As a result of its beneficial physicochemical features, which enable the creation of reactive surfaces, chitosan and its derivatives are the materials that are most heavily investigated [33, 34]. Chitosan has numerous uses as a bio-pesticide in agriculture, a packaging material for the food and pharmaceutical sectors, and a membrane filtration system for wastewater treatment [28, 35, 36]. Chitosan is amenable to modification because of the presence of functional groups like amino (NH2+) and hydroxyl (OH-) [37, 38, 39]. Furthermore, chitosan is distinguished by its substantial biological and chemical characteristics and safety [40]. Figure 2 illustrates how distinct...
groups of biopolymers can be categorized according to the presence and covalent bonding of monomers.

2. Physicochemical and biological properties of chitosan biopolymer

Chitosan has a wide range of physicochemical and biological properties, which are listed in Table 1. It can be used in its natural state or in a modified state produced through physical or chemical methods to produce novel qualities and functionalities.

3. Synthesis of chitosan nanoparticles

Due to their low prices, eco-friendly, and non-toxic natures, metal oxide nanoparticles (NPs) have been created utilizing green chemical technologies in recent decades, and they are good therapeutics for animals and people [43, 44]. Chemically produced metal oxide NPs including hazardous chemical reducing agents such as hydrazinium hydroxide, sodium hypophosphite, and sodium borohydride, on the other hand, have had an environmental impact. The precursors would cling to the broad surfaces of NPs, increasing their toxicity and negatively impacting the environment and biological applications [17, 44, 45].
Chitosan nanoparticles (CNPs) are nontoxic, biocompatible, biodegradable, and functionalized nanostructures derived primarily from by-products of the seafood industry. CNPs have shown potential as green fillers in biodegradable composite reinforcement for food packaging and biomedical applications [44, 46]. In the following section, the majority of the common methods for synthesizing chitosan nanoparticles are thoroughly explained, with their benefits and drawbacks.

3.1. Emulsification method

As depicted in Figure 3 below, emulsions interior phase is made up of a semi-hydrophobic organic solvent like benzyl alcohol or ethyl acetate. Both phases were pre-saturated with water to ensure that they were in thermodynamic equilibrium at ambient temperature [12, 44]. The approach is based on emulsifying a polymer organic solution into a water phase, then evaporating the organic solvent [44, 47]. Following dilution with a large amount of water, solvent diffusion from the dispersed droplets into the outer phase causes the formation of colloidal particles. Finally, evaporation or filtration can be used to remove the organic solvent depending on their boiling point Figure 4 [39,48]. Emulsification reduces the size of the emulsion droplet by using a high-shear force. Following emulsification, the system evaporates the organic solvent under vacuum, resulting in polymer precipitation and the formation of nanoparticles [49]. Finally, NPs with diameters ranging from 80 to 900 nm can be obtained. Despite the need for a large volume of aqueous phase to be removed from the colloidal dispersion and the risk of hydrophilic drug diffusion into the aqueous phase, this method is frequently used for the production of polymeric NPs [39, 50].

3.2. Ionic gelation method

Ionic crosslinking is used to create chitosan NPs (Figure 4). A positively charged amine group and a negatively charged polyanion, such as tripolyphosphate (TPP), make up the ionic compound [51, 52]. Chitosan was made into a cationic solution by dissolving it in diluted acetic acid, while TPP was made into an anionic solution by dissolving it in distilled water. The TPP solution was then added one drop at a time to the cationic chitosan solution [48, 53]. At room temperature, mechanical churning created NPs rapidly. Adjusting the amount of chitosan and crosslinking agent, as well as the pH value of the solution, can affect the physiochemical parameters of the resultant NPs, such as particle size and surface charge [54, 55].

3.3. Reverse micellar method

Making chitosan NPs using the reverse micellar technique entails producing NPs in the aqueous core of reverse micellar droplets and then crosslinking them with glutaraldehyde (Figure 5). A surfactant was dissolved in an organic solvent to form reverse micelles in this manner [56]. To prevent turbidity, an aqueous chitosan solution was introduced while constantly whirling [57]. This transparent solution was given a crosslinking agent while being constantly agitated. To complete the cross-linking process and ensure that the free amine group of chitosan was conjugated with glutaraldehyde, the system was kept stirred overnight [56]. The organic solvent was removed by evaporation under low pressure. The surplus surfactant yields and cross-linked chitosan NP yields were achieved. By precipitating the surplus surfactant with an appropriate salt and centrifuging the precipitate, the excess surfactant

Figure 3. Schematic representation of the emulsification/solvent diffusion method.

Figure 4. Preparation of chitosan NPs by ion gelation technology.
was removed. The final NPs suspension was dialyzed before lyophilization. This approach yielded chitosan NPs with a size of less than 100 nm and a high degree of mono dispersing [48, 56].

3.4. Nanoprecipitation method

Fessi’s group was the first to develop and apply nanoprecipitation, also known as solvent displacement or interfacial deposition [58, 60]. The nanoparticles are made in a colloidal suspension using the nanoprecipitation method, which entails adding the oil phase to the aqueous phase slowly while stirring moderately (Figure 6). It has the advantage of being rapid and simple to utilize because the production of the NPs is instantaneous and takes only one step. The rate of organic phase injection, the rate of aqueous phase agitation, and the oil phase/aqueous phase ratio are all critical manufacturing parameters that have a significant impact on the nanoprecipitation process [50, 59, 61]. Particles with an incredibly narrow dispersion can be created because there is no shearing tension. Entrapment of hydrophobic and hydrophilic medicines is a common application of this method [50, 62]. The polymer and medication are dissolved in a water miscible organic solvent such as acetone or methanol. The solution is then dropped into an aqueous solution containing surfactant one drop at a time. Due to rapid solvent diffusion, the NPs are formed quickly. Following that, the solvents are extracted at a reduced pressure [61, 63].

4. Characterization of chitosan biopolymer and its modified nanocomposites

According to the degree of deacetylation (DD), which is assessed by the percentage of D-glucosamine and N-acetyl-D-glucosamine, the biopolymer is classified as either chitin or chitosan [64, 65]. Table 2 shows the most widely used methodologies for characterizing chitosan and its modified nanocomposites. Chromatographic and spectroscopic techniques can be used to analyze chemically modified chitosan derived from chitin, as shown in Figure 7 which is taken from our previous work.

5. Pharmaceutical applications of chitosan biopolymer, chitosan derivatives and its modified nanocomposites

Chitosan is used in a wide range of sectors, from agriculture to advanced biotechnology and nanotechnology professions (Table 3). Figure 8 shows chitosan derivatives and modified composites applications in wastewater treatment, cosmetics, textiles, biomedical, food

![Figure 5. Preparation of chitosan NPs reverses micellar method.](image)

![Figure 6. Preparation of chitosan NPs by nanoprecipitation method.](image)

### Table 2. Instruments commonly used for characterization of chitosan and its modified nanocomposites, as well as their applications.

| No. | Instruments | Application | Ref. |
|-----|-------------|-------------|------|
| 1   | Thermogravimetric | Thermal stability of chitosan and its nanocomposites | [66] |
| 2   | FT-IR spectroscopy | elucidate the structure of a compound | [67] |
| 3   | Viscometric analysis | Molecular weight determination | [68] |
| 4   | X-ray diffraction | Crystallinity and phase purity | [69] |
| 5   | Scanning electron microscopy | Morphology | [70, 71] |
| 6   | $^1$H NMR | Characteristic peaks of proton | [71] |
packaging and processing, and other applications [72, 73]. Bacterial and viral infections can be life-threatening as a result of drug overuse and the emergence of antibiotic-resistant pathogens. Biopolymers are currently considered to be the most promising medicinal materials [74, 75]. Chitosan is a surface-modified polysaccharide that is used in drug delivery systems [76, 77]. It has attracted a lot of attention because of its

Table 3. Reports chitosan based nanocomposite and their pharmaceutical applications.

| Chitosan derivatives and chitosan based nanocomposite | Properties | Pharmaceutical applications | Reference |
|--------------------------------------------------------|------------|-----------------------------|-----------|
| Chitosan/Polyvinyl alcohol and modified thiabendazoleum-montmorillonite. | Biodegradable and antimicrobial activities | Show a good antibacterial activities against S. aureus and E. coli) and active packaging applications | [98] |
| Carboxylic acid functionalized carbon nanotubes dispersed in chitosan as a selective layer on the polsulfone membrane (CNTs-COOH/CHIT/PS) | Eco-friendly adsorbent | Efficient rejection of heavy metal ions from aqueous solutions. Less efficient than (CNTs-COOH/CHIT/PS) in rejection of heavy metal ions from aqueous solutions. | [97] |
| Porous nickel molybdate nanosheets/chitosan (NiMoO4/CHIT). | Sensitive, selective, reproducible, biocompatible & biodegradable | As biosensor and practical pharmaceutical analysis (detection of amiodipine drug). | [91] |
| Gold nanoparticles and a chitosan nanocomposite film coated on a screen printed electrode (Au-NPs/CHIT/SPE) | Sensitivity, stability, reproducibility, immune sensor & cancer biomarkers | Exhibited potential in clinical screening of cancer biomarkers. Diagnosis of prostate cancer using prostate-specific antigen. | [92] |
| (Nickel Ferrite cores/bovine serum albumin/chitosan/folic acid) NPs-BSA-CS-FA or BSA-CMC-FA conjugates. | Hydrophilicity, nontoxicity, cancer-specific capability and biocompatible | Green approach for breast cancer MR imaging, treatment, tumor diagnosis and therapy. | [93] |
| Six novel N,N,O tridentate water soluble hydrazide based O-carboxymethyl chitosan Schiff base derivatives | Anti-inflammatory, antioxidant & antidiabetic agent | Could be used for treatment of body pain, as anti-diabetes and cancer. | [94] |
| Gold and silver-based chitosan nocomposites | Antimicrobial, antitumor, anti-inflammatory and antioxidant effects | Possess potential applications in nanomedicine. Used as wound dressing and anti-bacterial activities. | [95] |
| N,N,N-Trimethyl ammonium chitosan (TMC) | Water solubility, pH sensitivity antibacterial, anti-inflammatory agents | Widely used in medicine as antibacterial, anti-inflammatory drugs, filler fiber in materials for dressing wounds | [96] |
| Chitosan (CS) Deacetylation Degree (DD) + Alginate (ALG) | Biocompatibility, bioadhesion and blood glucose lowering properties. | Used as effective insulin oral delivery for treatment of diabetes | [97] |
| Chitosan beads & Chitosan stabilized bimetallic Fe/Ni nanoparticles, Grafted chitosan hydroyl with acrylic acid, MgO/Chitosan/Graphene oxide and Chitosan-g-poly(glycidyl methacrylate) | Adsorbents of antibiotic pharmaceuticals | Removal of Amoxicillin, Enrofloxacin, Norfloxacin and Cephapirin respectively from aquatic environment. Used for waste water treatment by removing antibiotic pharmaceuticals. | [98] |
| 2,6-Diamino chitosan (2,6-DAC) | Biodegradable, biocompatible and synergistic activity | Exhibit broad bactericidal efficacy toward both Gram-positive and Gram-negative bacteria with minimum inhibitory concentrations and has synergistic activity with antibiotics including amikacin, tobramycin, novobiocin, rilampicin, and tazobactam. | [100] |

Figure 7. Characterization of chitin and chitosan. (a) FTIR, (b). XRD, (c). SEM, (d and f). ¹H NMR and (e). Thermogravimetric analysis. Reproduced with permission from [88].
biocompatibility, low cost, nontoxicity, environmental friendliness, absorbability, biodegradability, recyclability, and superior antibacterial characteristics [72, 78]. Chemical modifications to the chitosan structure have sparked a lot of attention because they improve transfection efficiency and stability [79, 80].

The -NH2 and -OH groups of chitosan molecules make them a good base for interacting with other monomers, biological molecules, polymers, and nanoparticles [20, 81]. A variety of methods can be used to make quality films, fibers, gels, microspheres-microcapsules, and micro-/nanoparticles [82, 83]. Because of their physicochemical properties, chitosan and its derivatives are good materials for biomedical and pharmaceutical applications, and they are also compatible with the human body environment [84, 85]. In biological systems, chitosan-based nanoparticles have good biodegradation and bio distribution, making them one of the most promising nano carriers for delivering various therapeutic medicines to tumor cells, particularly ovarian cancer cell lines [4, 79].

### Table 3 (continued)

| Chitosan derivatives and chitosan based nanocomposite | Properties | Pharmaceutical applications | Reference |
|------------------------------------------------------|------------|-------------------------------|-----------|
| Chitosan/polyactic acid/calcium phosphate nanosheet  | Tough bone-resembling and osteoblast enlargement biodegradability and low cytotoxicity | Bone tissue engineering (bone implants) | [101] |
| Chitosan/calcium phosphate nanosheet                 | Nontoxicity and permeability | As topical administration drug delivery to the posterior segment of the eye. | [102] |
| Carboxymethyl chitosan (CMCs) + glutathione-glycylsarcosine (G-GS) & carboxymethyl chitosan (CMCs) + glutathione-valyl-valin (G-VV)-LDH hybrid | | |
| Fucoidan-based chitosan carrier                      | Non toxicity and biocompatibility | Used for Human breast cancer cell line and Colon cancer Caco-2 cells and treatment. | [103] |
| Chemically modified O-carboxymethyl chitosan Schiff base and their metal complex | Good solubility in water, high viscosity, low toxicity and biocompatibility | Possess better antibacterial, antifungal, anti-inflammatory, antidiabetic and antioxidant | [104] |
| Modified cellulose and cross-linked chitosan with covalently bound 8-hydroxyquinoline | Non-digestible, non resorbable, biocompatible | Potential for treatment of Wilson’s disease. | [105] |
| Chitosan-g-poly (N-isopropyl acrylamide)              | Biodegradable and injectable thermo gel, antioxidant and drug delivery | Suppressing oxidative stress, lowering ocular hypertension, reducing retinal ganglion cell loss and enhancing myelin growth and neuron regeneration. | [106] |

Figure 8. Chitin, chitosan and chitosan nanostructure formation and potential applications.

Figure 9. Schematic diagram of drug loading and delivery mechanism by biopolymer nanocomposites.
recent years, metal and chitosan composites have been a hotspot of antibacterial research, with the addition of metals to chitosan increasing its antibacterial activity and potentially having applications in nanomedicine [56, 87]. Antibacterial activity of metal-chitosan nanocomposite films was found to be superior to that of chitosan [88, 89]. Biotechnologists and microbiologists have created various types of chitosan nanocomposites for distinct uses in the biomedical and pharmaceutical industries due to its outstanding physical, chemical, and biological properties [56, 88]. Chitosan biopolymer is a remarkable substance for cosmetics, food, medicine, and pharmacy because of these properties [82]. As a result, a number of researchers in a variety of fields have contributed to the field of chitosan-based nanocomposites, and a variety of chitosan-based materials have been made and evaluated for bioactivity studies [89, 90].

5.1. Chitosan biopolymer and its modified nanocomposite for drug delivery system

Natural polymers are considered appropriate hosting materials for nanoparticles, particularly for biological applications, due to their sustainability, eco-friendliness, non-toxicity, biodegradability, and biocompatibility [107, 108]. The development of effective drug delivery techniques that allow bioactive molecules to reach their site of action despite avoiding non-target cells, organs, or tissues is becoming a public health research priority [109, 110]. Drug targeting and regulated drug delivery are concepts that are used to increase the therapeutic index of drugs by improving their localization to specific parts of the human body and reducing potentially detrimental side effects under normal circumstances [111, 112]. This method has a number of benefits, including easy drug adjustments after parenteral administration to achieve target disease sight, increased drug treatment efficacy, and less drug side effects [113, 114]. The medicines can be incorporated into the systems without passing through any chemical processes, which is important for preserving drug activity, and the system can be used for a range of administration routes, such as oral, nasal, parenteral, and intraocular [115, 116]. Figure 9 shows the schematic representation of the drug loading and delivery system for biopolymer nanocomposites.

Table 4. Chitosan biopolymer based drug delivery system with fabricated materials and loaded drugs.

| Natural polymer | Method of preparation | Modified material | Drug/model drug | Reference |
|-----------------|-----------------------|-------------------|-----------------|-----------|
| Chitosan        | Spray-drying          | -                 | Diphenylhydrazine and mebeverine | [121] |
| Ionic gelation  | Chitosan-β-cyclodextrin grafted N-maleoyl | Cyclodextrin | [122] |
| Ionic gelation  | Chitosan and Poly(Lactide-co-glycolide) (PLGA). | - | [60] |
| Carboxymethyl chitosan | Hydrothermal method | Carboxymethyl chitosan - folate/Fe3O4/CdTe nanoparticle | Adriamycin | [86] |
| Carboxymethyl chitosan | Precipitated and solvent method | Chitosan-Clay | Ibuprofen | [123] |
| Freeze-drying   | Chitosan and Calcium carbonate | Methotrexate | [7] |
| Esterification reaction | Folate modified chitosan/carboxymethyl | Paclitaxel | [90] |
| Freeze-drying   | Cyclodexin modified-Chitosan -Genipin | Sulfasalazine | [7] |
| N-maleoyl chitosan | Precipitation | N-maleoyl chitosan -β-cyclodextrin | Ketoprofen | [124] |
| Chitosan        | Dissolution           | Chitosan and 2-chloro-N,N-diethylethylamine hydrochloride | Quercetin | [19, 125] |
| Freeze-drying   | Chitosan/Succinic anhydride, glutaric anhydride | Paclitaxel and docetaxel | [122] |
| Oxidation       | Chitosan,Glycidyltrimethyl ammonium chloride, gelatin | Dopamine | [7] |
| Freeze-drying   | Chitosan, Poly(DL-lactide-co-glycolide) | Donepezil | [122] |
| Crosslinking methods | Chitosan,5-fluorouracil | 5-fluorouracil | | [62] |
| Encapsulation   | Chitosan nanoparticles loaded with plasmid DNA encoding Rhb1- GTase protein of Schistosoma mansoni. | - | [126] |
| Ionotropic gelation | Chitosan-fluorescein isothiocyanate-bovine serum albumin | fluorescein | [25] |
| Freeze-drying   | Chitosan,Gold nanoparticle | Curcumin | [127] |
| Chitosan,aspartate, glutamate, and hydrochloride | Dispersion | AgSD- incorporated bilayer chitosan wound dressing | silver sulfadiazine (AgSD) | [128] |
| Chitosan        | Ionic-gelation method | Chitosan and alginate | Amygdalin | [129] |
| Ionic cross-linking | Chitosan and Graphene | Ioxofamid | [18] |
| Ionic gelation  | Chitosan and xanthan gum | Ciprofloxacin | [130] |
| Complex coacervation | CS/Dx135Cr NPs | Insulin | [131] |
| Ionic cross-linking | Chitosan cross-linked-6-phosphogluconic Trisodium | - | [132] |
location or tumor [119, 120]. A number of recent research have established the capacity to synthesize and describe chitosan biopolymer modified with nano-clay, reduced graphene oxide, zeolites, SiO₂, hydroxypatite, and gold nanoparticle for use as a targeted drug carrier in drug delivery systems (Table 4).

6. Conclusion

Biopolymer nanocomposite have attracted a lot of research due to its special qualities, which include biocompatibility, biodegradability, and nontoxicity as well as better structural and functional features. The most difficult component of this technology is developing bio-based materials with equivalent quality and functions to synthetic materials. Various naturally occurring polymers, such as starch, collagen, alginate, cellulose, and chitin, are appealing candidates because they can reduce reliance on manufactured goods while remaining environmentally beneficial. Chitosan is one of the most exploited biopolymers in biomedical science, and it is the second most abundant next to cellulose. De-acetylated chitin and its amino-poly saccharide present in nature are used to make chitosan biopolymer. Because of its biocompatible and biodegradable nature, it has inspired a lot of interest in biological applications. Based on various reported study chitosan has been used in a variety of pharmaceutical application including antimicrobial, antioxidant, anti-inflammatory, anticancer and drug delivery systems throughout the last few decades. A range of chitosan sources, modification procedures, and manufacturing methods are also widely discussed. This review stated that chitosan and its nanocomposites have a bright future with improved distinctive qualities of their especial biocompatibility, biodegradability, mechanical and thermal stabilities, barrier, and nontoxicity, suggesting their uniqueness in the biomedical application based on numerous recent publications.

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