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Revolutionizing Drug Delivery Through Chitosan Biowaste: A Review of Recent Patented Innovations

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Abstract: Chitosan, a biopolymer derived from the partial deacetylation of chitin, has attracted significant interest as a sustainable pharmaceutical excipient due to its biodegradability, biocompatibility, and diverse functional attributes. Recent breakthroughs have explored the valorization of chitosan biowaste in pharmaceutical formulations, particularly in oral drug delivery, leveraging its tunable physicochemical properties. This review thoroughly examines recent advancements and patented innovations in chitosan-based drug delivery by conducting an extensive literature search using PubMed, Scopus, Google Scholar, and ClinicalTrials.gov, and analyzing patents from Espacenet and USPTO databases. Key findings reveal that chitosan's molecular weight, degree of deacetylation, and source critically influence its pharmaceutical applications, including drug encapsulation, mucoadhesion, and controlled release. Novel formulations, such as chitosan-silicate coprecipitates, polyelectrolyte complexes, and nanostructured chitosan carriers, have enhanced drug solubility, bioavailability, and stability. However, challenges persist in optimizing extraction methods, ensuring batch-to-batch reproducibility, and expanding its pharmaceutical applications beyond conventional uses. Future research should focus on eco-friendly extraction techniques, novel chemical modifications to enhance functionality, and clinical evaluation of chitosan-based drug formulations to maximize its potential as a sustainable pharmaceutical excipient.

Keywords: Chitosan biowaste, pharmaceutical excipient, molecular weight, degree of deacetylation, oral drug delivery, patented innovations

Introduction

Globally, approximately 6–8 million tons of marine crustacean shells (shrimp, crab, and lobster) are produced annually as waste. The disposal of these shells poses environmental challenges in developing countries, while developed nations incur substantial disposal costs. These marine shells contain valuable biomaterials, including chitin (poly N-acetyl-D-glucosamine), proteins, and calcium carbonate [1], as the second most abundant natural polysaccharide after cellulose. Chitin presents significant potential for sustainable pharmaceutical and industrial applications, necessitating efficient valorization techniques [2-4]. Scientists should work out sustainable ways to make useful products from chitin. Governments and industry should invest in using this abundant and cheap renewable resource. In addition to chemical-based chitin extraction techniques, several other methods—such as bio-based approaches, ionic solvents, deep eutectic solvents, and ultrasound-assisted techniques are also emerging as effective alternatives. Microbial fermentation, which utilizes lactic acid-producing microorganisms or biologically derived organic acids, is proving to be an efficient system for obtaining high-quality chitin [2]. The partial deacetylation of chitin produces chitosan. Chitosan is a hydrophilic, nontoxic, biodegradable and biocompatible natural material. It is a linear polysaccharide consisting of β(1-4)linked D glucosamine residues with a variable number of randomly located N-acetyl-glucosamine in a glucosamine backbone [5] , Figure 1. These properties make chitosan a preferred polymer for various applications in the pharmaceutical and biomedical fields. Various biological activities are also exhibited, including antibacterial, antifungal, antitumor, and antioxidant properties. The relationship between chemical structure and biological activity is demonstrated in chitosan molecules with different degrees of acetylation (DA), molecular weights (MW), and a uniform distribution of acetyl groups. Many researchers studied the wound healing activities of chitin and chitosan and recently nano-based materials from both polymers are developed for wound healing applications [3]. Furthermore, incorporating dispersed chitosan into protein has been shown to significantly enhance the mechanical strength of nanofilms, making them more viable for industrial applications in the food industry [4]. Chitosan can be transformed into fibers, films, coatings, and beads, which are also useful in industries such as paper manufacturing, photography, textile finishing, heavy metal chelation, and water treatment [2,4].

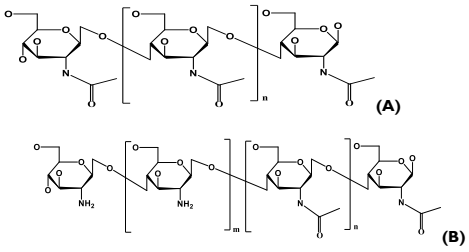

Figure (1): Chemical structures of (A) Chitin and (B) Chitosan. The degree of deacetylation (DD) of chitosan determines the amount of acetyl groups that have been removed from the chitin structure, leaving behind free amino groups on the polysaccharide.

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Methodology Search Strategy and Selection Criteria

To ensure a comprehensive and structured evaluation of recent patented innovations in chitosan-based drug delivery systems derived from biowaste, this review employed a thorough literature search across multiple academic and patent databases. Primary databases utilized included PubMed, Scopus, Google Scholar, and ClinicalTrials.gov, chosen for their extensive coverage of biomedical, pharmaceutical, and interdisciplinary research relevant to chitosan applications in drug delivery.

The search strategy was meticulously designed to maximize retrieval of relevant literature by employing a combination of controlled vocabulary and terms. Primary keywords incorporated into the search were: "chitosan biowaste," "pharmaceutical excipient," "molecular weight," "degree of deacetylation," "oral drug delivery," "patented innovations," "nanostructured chitosan carriers," and "polyelectrolyte complexes." Boolean operators (AND, OR) were strategically applied to refine the search, ensuring the inclusion of studies addressing various extraction methods, chemical modifications, physicochemical characterizations, pharmaceutical formulations, and clinical applications of chitosan in drug delivery.

To maintain focus on recent advancements and patented innovations, the search was restricted to publications and patents from January 1994 to December 2024. This timeframe effectively captures the dynamic evolution and recent commercialization of chitosan-based drug delivery technologies, reflecting current developments and their translation into clinical and industrial applications. Additionally, literature was screened based on relevance to pharmaceutical excipients, particularly emphasizing innovative formulation strategies, novel material composites, and eco-friendly extraction methods.

Although this review is not a systematic review, it adheres rigorously to robust methodological standards to enhance the reliability and comprehensiveness of its findings. A qualitative approach was adopted to synthesize the extracted literature, prioritizing studies that provided pharmaceutical validation, comparative analyses of chitosan formulations, patented technological developments, and discussions on scalability, reproducibility, and regulatory considerations. This structured approach ensures methodological transparency and replicability, facilitating future extensions and deeper investigations into chitosan-based pharmaceutical innovations.

Chitosan Sources, Extraction, and Classification

Chitosan can be classified into different categories depending on many factors.

Sources of Chitosan: Marine and Non-Traditional Origins

Chitin is traditionally sourced from the exoskeletons of crustaceans, mollusks, and insects; however, alternative non-animal sources, including mushrooms and fungal biomass, have recently emerged. These distinct origins yield chitosan variants differing significantly in molecular weight (MW), nitrogen content, degree of deacetylation (DD), solubility, and viscosity, thereby broadening their applicability in food, cosmetic, pharmaceutical, and biomedical industries [6-10].

Classification of Chitosan Based on Molecular Weight and Degree of Deacetylation

Based on its MW chitosan can be classified into three different types: high molecular weight chitosan (>1000 kDa) (HMWC), medium molecular weight chitosan (100–1000 kDa) (MMWC) and low molecular weight chitosan (<100 kDa) (LMWC) [8-9].

Comparative studies have emphasized notable differences in pharmaceutical performance between marine-derived and fungal-derived chitosan. Marine chitosan, primarily sourced from crustaceans, often demonstrates high viscosity and strong film-forming capabilities, making it ideal for certain controlled-release formulations. Conversely, fungal chitosan, notable for its consistent molecular weight and lower allergenic risk, has exhibited superior solubility at physiological pH levels and enhanced antimicrobial properties, positioning it advantageously for applications requiring rapid dissolution and bioactivity, such as antimicrobial coatings and rapidly disintegrating tablets.

DD of chitosan can be grouped into low DD (47%–53%), medium DD (74%–76%), and high DD (95%–98%) categories [12], as shown in Figure 2. Different MW and DD can be obtained through simple chemical modifications that results in different solubility and viscosities which can be employed in versatile pharmaceutical applications [13,14].

Further comparative analysis has also been conducted to investigate the effect of chitosan's DD on drug encapsulation and release kinetics. For example, formulations containing high-DD chitosan (>95%) exhibited superior drug loading efficiency and sustained release behavior compared to lower-DD variants, attributed to increased solubility in acidic environments and enhanced polymer-drug interactions. Additionally, comparative cytotoxicity studies on nanoparticles formulated from varying DD chitosan indicated notably improved biocompatibility and cellular uptake efficiency with higher DD, demonstrating its preference in designing targeted nanocarrier systems.

Despite the extensive research on chitosan's pharmaceutical potential, a comprehensive synthesis of patented innovations remains limited. While numerous studies have explored its physicochemical properties and drug delivery capabilities, the translational gap between fundamental research and commercial pharmaceutical applications persists. This review bridges that gap by thoroughly analyzing patents from Espacenet and USPTO, alongside scientific literature from PubMed, Scopus, and ClinicalTrials.gov. We highlight recent advances in chitosan-based drug formulations, including novel polyelectrolyte complexes, nanostructured carriers, and chitosan-silicate coprecipitates, which have enhanced drug solubility, bioavailability, and stability.

Unlike previous reviews that primarily focus on chitosan's fundamental characteristics, our work identifies key challenges in regulatory standardization, pharmaceutical scalability, and batch-to-batch reproducibility. Furthermore, we discuss strategies for eco-friendly extraction, novel chemical modifications, and the integration of biotechnological valorization approaches to enhance chitosan's role as a sustainable excipient in next-generation drug delivery systems. By merging scientific advancements with intellectual property insights, this review provides a roadmap for future innovations, addressing both technical and commercial hurdles in chitosan-based pharmaceutical development.

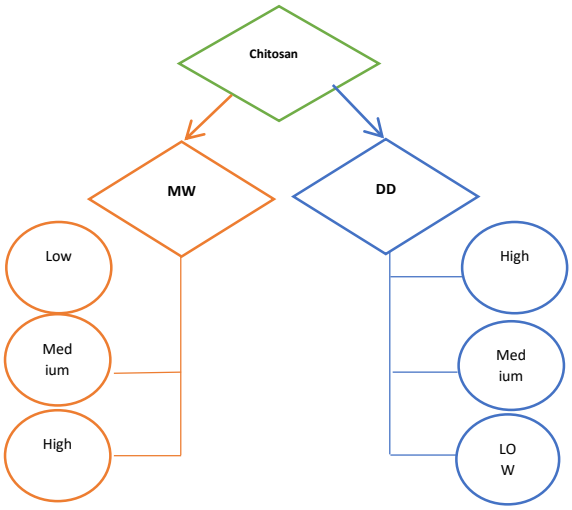

Figure (2): Chitosan classification based on molecular weight (MW) and degree of deacetylation (DD).

Pharmaceutical Properties of Chitosan Structural and Functional Differences

The physicochemical properties of chitosan are closely related to the taxonomy of its source. Chitin extracted from crab and shrimp shells predominantly exhibits an α-crystallographic structure, whereas chitin from squid pens displays a β-crystallographic structure, characterized by enhanced solubility and swelling due to weaker intermolecular bonds. Consequently, β-chitin-derived chitosan exhibits higher chemical reactivity compared to α-chitin derivatives [4, 15 -18]. Sources, including squid pens, spiny lobsters, squilla, crab, and shrimp, are viable for industrial-scale production of HMWC [18- 19]. Nonetheless, marine-derived chitosan production faces limitations such as seasonal variability, labor-intensive processes, and essential demineralization steps [10, 17, 20].

Chitosan Extraction and Purification Techniques

Nontraditional sources of chitosan with less limitations are fungi, protists and algae. Chitin is a major constituent of the mycelial cell walls of fungi like Aspergillus niger, Mucor rouxii and Penicillium notatum. Chitosan derived from fungal sources shows no seasonal variations and it is free from heavy metals and allergenic animal protein. Also, fungal chitosan can be produced with a wide range of MW compared to crustacean chitosan [10,16, 21]. It can be produced with superior physicochemical properties by manipulation of the fungal growth medium, fermentation process and extraction method. The resultant chitosan MW is dependent on the growth phase of fungi [2]. Fungal chitosan high solubility in physiological pH ranges together with its poly-cationic characteristics and lower antigen effect allow its usage in versatile applications for vegetarian people and those with crustacean allergy. Furthermore, it can be used in food, water purification and in pharmaceuticals as a potential drug carrier, coating material, non-viral gene delivery system, wound dressing, antimicrobial agent and preservative [10, 17]. Different chitosan sources yield variability in drug-release characteristics due to the heterogeneous distribution of acetyl groups along the polymer backbone, affecting solubility profiles. Additionally, antimicrobial efficacy differs significantly among sources; animal-derived chitosan generally exhibits limited antimicrobial activity, effective only at high concentrations, whereas non-animal (fungal or plant-based) chitosan demonstrates potent bactericidal and fungicidal activities at lower concentrations [7]. Nevertheless, marine-sourced chitosan remains more commercially appealing to pharmaceutical industries due to its large-scale availability [9]. On the other hand, the HMWC obtained from crustaceans shows higher viscous solutions than fungal chitosan due to its poor solubility at neutral pH values. This makes it preferable to act as thickening agent and film forming substance. Similarly, insect derived chitosan has uniform particle size, homogenous low MW, unique viscosity and free from heavy metals while chitosan obtained from squid pen is free from calcium carbonate, carotenoids, and minerals [22].

Pharmaceutical properties of chitosan with different degrees of deacetylation

Deacetylation of chitin produces chitosan with more exposed NH2 groups. DD of chitosan is an important intrinsic property that affects its pharmaceutical properties and results in different biomedical applications. Depending on its DD, chitosan shows different characteristics such as solubility, electrostatic features, biodegradability, sorption characteristics, chelation power and acid base behavior [22]. Chitosan solubility in water is directly proportional with DD. As number of positively charged amino groups increases, solubility in acidic media increases [9, 23]. Wang & Xu studied the effect of DD of chitosan on the viscosity and flow properties of chitosan concentrated aqueous acidic solutions, they noticed that viscosity and non-Newtonian flow properties increased as DD increased [24].

Comparative evaluations focusing on molecular weight differences have further underlined the implications for chitosan's pharmaceutical applications. Studies comparing LMWC against HMWC in drug delivery revealed distinct advantages of LMWC in terms of permeability enhancement, improved bioavailability, and faster mucoadhesion profiles, making it especially beneficial for oral and buccal delivery systems. In contrast, HMWC was demonstrated to have superior mechanical properties and slower biodegradation rates, making it favorable for sustained and controlled drug delivery applications where prolonged release profiles are necessary.

Other researches evaluated degradation, hydrophilicity and mechanical characteristics of different DD of chitosan. Results confirmed that higher DD make chitosan more suitable for tissue engineering since it positively affects hydrophilicity, biocompatibility and cell attachment of the chitosan films [25]. On the other hand, it was reported that DD of chitosan influences the cellular uptake and cytotoxicity of chitosan nanoparticles via the zetapotential effect of those particles. Huang et al noticed that chitosan nanoparticles uptake by A549 cells decreased by 41% when DD decreased from 88% to 46% [26,27]. Other researchers assessed the antitumor activity of different DD chitosan. They confirmed the importance role of this property through its effect on increasing solubility of chitosan in water as well as ensuring reproducibility of the pharmacological action [28]. Jung et al studied the antibacterial activities of different degrees of deacetylated chitosan on many Gram-positive and Gram-negative bacteria. Chitosan with 99% DD showed the highest antibacterial activity against all tested bacteria. This is due to low viscosity (17.9 mPa s) of its solution [29]. DD affects crystallinity of chitosan preparations. Higher DD showed higher tensile strength of chitosan membrane this is due to higher level of crystallinity that results in higher elongation at break [30].

Other researches assessed the effect of DD on other pharmaceutical properties of chitosan such as reactive oxygen species scavenging activity that depends mainly on free amino groups [31], prolyl endopeptidase inhibitory activity where 50% DD exhibited the highest inhibitory activity [32], chitosan microspheres loading, swelling and drug release that depend on hydrophobicity and pore size [33], Capacity of adsorption of Pb2+ and Ni2+ from aqueous solutions [34] and cellular attachment of chitosan coated orthopaedic implants where surface roughness and fibronectin adsorption increase as DD increases [35].

Pharmaceutical properties of different molecular weight chitosan

Chitosan MW is a critical parameter that affects its physicochemical and pharmaceutical properties [23,36]. Usually, commercially available chitosan is high MW. Since lower MW chitosan has more bioactivities and solubility than higher MW chitosan., many methods were developed for chitosan depolymerization [11, 23,36]. Huei & Hwa studied effect of chitosan MW on permeability of chitosan membrane. Results showed lower permeability from HMWC. However, higher tensile strength, tensile elongation and enthalpy were reported for HMWC membranes [37]. Mucoadhesion properties of membranes prepared from different MW chitosan were evaluated for quaternized N-trimethyl chitosans. Results confirmed the influence of chitosan MW on its properties. Lower chitosan MW shows better mucoadhesive and penetration enhancement of hydrophilic and large MW drugs through the buccal route [38]. Nanoparticles prepared from low and medium MW chitosan were evaluated for antimicrobial activity against different microorganisms. Results showed minor differences in activity observed between different MW [13]. However other researches confirmed a correlation between chitosan MW and its antibacterial activity. They reported that this correlation influenced by the type of the tested bacteria. Depending on the site of action of chitosan whether it acts on the cellular membrane or cross the membrane. HMWC remains on the cellular surface that leads to cell lysis via blocking nutrients transport inside the cell while LMWC can penetrate the cell and cell nucleus, binds to DNA and inhibits mRNA synthesis. Other factor is the pH that affects chitosan solubility and cellular binding. Higher antibacterial activity was observed at lower pH values. High molecular chitosan was effective against more bacterial strains. Other researchers reported that a minimum MW of 10KDa is required for bactericidal effect [9,22]. Younes et al reported that antibacterial activity of chitosan against Gram-negative bacteria increases with deceasing MW while for gram positive bacteria it increases with increasing MW. Similarly, the antifungal activity of chitosan depends on the particular type of fungus [39]. Chitosan radical scavenging activity depends on its MW [40]. LMWC is more active than high MW. Many researches assessed other biomedical properties of different MW chitosan like anticancer activity, gene transfer and antioxidant activity [36,41].

Advanced and patented pharmaceutical applications of chitosan in oral drug delivery

Chitosan-Based Polyelectrolyte Complexes and Nanostructured Carriers

Chitosan-based pharmaceutical applications differ notably based on MW, as illustrated in Figure 3.

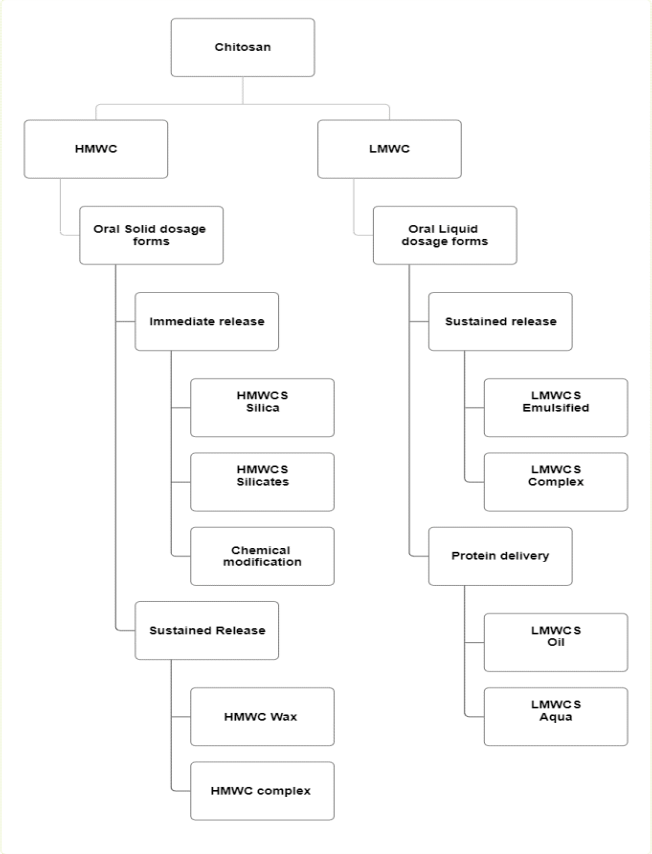

Figure (3): Scheme of publications based on chitosan molecular weight and pharmaceutical applications.

HMWC, characterized by limited water solubility, is primarily used in solid dosage formulations to achieve sustained drug release. Conversely, LMWC, possessing greater aqueous solubility, is suitable for liquid pharmaceutical formulations [42-45]. The cationic nature of chitosan, arising from positively charged amino groups under acidic conditions, facilitates sustained-release properties, particularly through the formation of polyelectrolyte complexes with negatively charged polymers [46- 47]. The best pharmaceutical excipients were obtained as a composite of HMWC polymer with either inorganic or organic material. The self-assembly of anionic and cationic polysaccharides into polyelectrolyte complex (PEC) hydrogels has been recognized as an effective method of crosslinking. A smart nutrient delivery system through self-assembly of salecan and HMWC was used as a safe carrier that can protect vitamin C from the gastric fluid and sustain its release in intestine. A controlled and pH-dependent release was noticed with a mechanism agreed with Ritger-Peppas model [48]. A good pharmaceutical excipient must be easily compressed into tablets and such tablets do not disintegrate upon exposure to dissolution media and produce a sustained release system. Different methods were adopted to attain sustained release behavior. Complexation approach is one of these methods. A matrix tablet composed of binary mixture of chitosan as a positively charged polymer and xanthan gum as a negatively charged polymer formed water-insoluble coat upon exposure to simulated gastric fluids. This coat served as a drug release retarding system. The proper proportion of HMWC and xanthan gum to produce tablets with suitable mechanical properties was determined based on percolation theory. Terbutaline sulfate was used as a model drug

to investigate the sustained release behavior of this system [43,49]. The sustained release technology using HMWC and xanthan gum was also applied to other model drugs such as metronidazole and ambroxol HCl, tramadol, ibuprofen, ampicillin, minocycline and rifampicin [50-54].

Nunthanid et al assessed the release of theophylline from tablets formulated with 3% w/w of spray-dried chitosan acetate as a binder. Chitosan of high viscosity grade, MW of 814 kDa with 88% DD was used. In vitro release study demonstrated sustained drug release in all media with cumulative release of 100% in acidic, neutral (pH 6.8) and distilled water media within 6,16 and 24 hr, respectively [42]. Halloysite nanotubes were loaded with norfloxacin, formulated with chitosan as nanocomposite films and evaluated for anti-bacterial activity. The nanocomposites films were effective against gram-positive and gram-negative bacteria. Release studies showed a sustained release behavior of norfloxacin from the flexible nanocomposite films prepared with kinetics followed Weibull and Korsmeyer-Peppas models. [55].

Chitosan-Silicate Coprecipitates for Controlled Release

In another study, NaX/Fe3O4 and Doxorubicin were successfully incorporated into the PLA/chitosan nanofibers and the magnetic system evaluated for sustained release delivery of doxorubicin. The kinetic studies showed that the drug release mechanism from nanofibers followed by the Fickian diffusion. This release pattern resulted in a killing of 82% of H1355 cells after 7 days [56].

Chitosan is a highly porous polymer that can absorb waxy material such as beeswax and so can produce water-insoluble and low density excipient able to be compressed into tablets to produce sustained release dosage forms floating system. HMWC/beeswax composition was used as a controlled release mixture [57].The optimal ratio of beeswax to HMWC was determined in terms of flowability, compaction, tablet floating ability and controlled release behavior. Solid Pickering microparticles system of beeswax with chitosan nanoparticles encapsulated with ibuprofen and lidocaine as model drugs showed a slow and extended release over time profile [58]. However, HMWC can be formulated as a pharmaceutical excipient that can be easily compressed into tablets and such tablets disintegrate rapidly upon exposure to dissolution media and to produce an immediate release matrix when combined with silica or silica salts [59-62]. Chitin/chitosan polymers are organic water insoluble materials with relatively high elastic behavior. When processed with an inorganic water-absorbent brittle material such as colloidal silica in suitable proportions, the processed chitin/chitosan could produce an excipient with favorable mechanical and disintegration properties. Although HMWC possesses relatively good compaction properties, it has a weak disintegration power and so to enhance its ability to disintegrate, HMWC was co-processed for the first time with colloidal silica to produce a highly compressible superdisintegrant [59]. The “intimate” physical association between HMWCS and silica creates an insoluble, hydrophilic, highly absorbent material, resulting in superiority in water uptake, water saturation for gelling formation and compactability among all other known commercial superdisintegrants. The work on HMWC silica or Mg silicate salts lead to the development of a new type of pharmaceutical excipients that can be used as a tablet binder and at the same time superdisintegrant in all proportions. This could facilitate pharmaceutical production of oral disinitegrating tablets (ODT) using high speed tableting machines and decrease the number of excipients used during manufacturing of immediate release tablets. The advancement in method of preparation and improving quality and functionality of pharmaceutical excipient could be considered as an outstanding finding in the science of pharmaceutical excipient. Such new pharmaceutical additives lead to the development of natural, robust and cheap multi-functional pharmaceutical excipients and thus facilitated the manufacturing of tablet dosage forms [59].

The prepared HMWC silica coprecipitate was shown to bind more strongly to fatty materials compared to HMWC in conditions simulated to gastrointestinal tract. This could be attributed to the existence of primary amino functional groups attached to the structural backbone of chitosan. Such property made HMWC-silica a therapeutically active composition suitable to bind to lipids and bile salts present in gastrointestinal tract. This finding was published elsewhere [63].

Comparative studies examining chitosan-silicate coprecipitates with other super-disintegrants and controlled release excipients, such as croscarmellose sodium and sodium starch glycolate, highlighted the unique properties of chitosan-based excipients. Coprecipitates of chitosan with silica exhibited superior mechanical stability and enhanced water absorption capabilities, notbly improving tablet disintegration times and uniformity of drug release compared to traditional super-disintegrants. Moreover, comparative analyses of controlled-release profiles using chitosan-beeswax combinations versus traditional lipid-based formulations indicate notable improvements in floating characteristics and prolonged gastric retention times, underscoring the potential of these novel composites in gastro retentive drug delivery systems.

Consequently, HMWC silica co-precipitate could be considered as an active agent suitable to bind to fatty acid moieties [64-65]. It is known that the ideal excipient should be inert pharmacologically, therefore, HMWC silica would be not a favorable choice and other approaches should be adopted. In order to demonstrate that the process of co-precipitation with colloidal silica was responsible for such superdisintegration behavior, several inert water-absorbable polymers other than chitosan were used. Thus, a generalized form was published indicating the importance of co-precipitation of the polymers with colloidal silica to produce superdisintegrating excipient [66].

Recent Patents on Chitosan Drug Delivery Systems

Two water-absorbable inert polymers, chitin and starch, were investigated thoroughly. Chitin coprecipitation was prepared and evaluated as superdisintegrant and published as a co-precipitate of chitin and silicon dioxide for the use as tablet excipient [67].

Chitin-silica coprecipitate has an outstanding functionality that does not depend on swelling properties, as in the case of most conventional superdisintegrants. Chitin–silica offers good compressibility and compactability characteristics that may allow it to function as a superdisntegrant and pharmaceutical filler at the same time [68]. The advantage of colloidal silica is water absorption ability which results in superdisintegration upon precipitating onto chitin/chitosan surface. This comes from its high surface area and the existence of an interaction with water due to the locally strained bonds, with reduced bond energy of silicon dioxide at the molecular level. This effect could be

enhanced more upon the use of silicate salts due to their higher surface area and the higher ability to interact with water molecules [68].

Water-insoluble silicate salts were used instead of colloidal silica, namely Mg silicate. Mg silicate was precipitated within the intimate structure of the water-absorbable polymers by salt replacement reactions to produce a solid in solid dispersion. [69]. The basic concept of such technology of chitin metal silicates precipitation was first discussed by Rashid et al [70] . Unlike the use of acidic and basic reagents for the industrial preparation of chitin–silica particles, coprecipitation of metal silicates is dependent on simple replacement reaction between sodium silicate and metal chlorides. The performance of such novel chitin metal silicates co-precipitates as a single multifunctional excipient in tablet formulation using direct compression and wet granulation methods was evaluated [71]. When, coprecipitated onto chitin particles, metal silicates produced in non-hygroscopic, highly compactable/disintegrable compacts. The neutral, acidic, and basic drugs were used as model drugs mixed with chitin-Mg silicate co-precipitates to form compacts. For all compacts containing the model drugs, the novel excipient has the potential to be used as filler, binder, and superdisintegrant, all-in-one, in the design of tablets by the direct compression as well as wet granulation methods [71].

Chitin-Mg silicate excipient proved to have preferable advantages over a known pharmaceutical filler i.e. Avicel® 200 in terms of compaction, disintegration and sensitivity to Mg stearate lubricant [72].

Chitosan-Based Microneedles and Injectable Systems

Another approach which modified significantly HMWC properties was chemical structure modification. This important track depends on chitosan degree of substitution and type of substituent, was also followed [73-76]. Chitosan amino functional groups were substituted with N-hexoyl group and the degree of substitution was crucial in determining the physico-mechanical properties. Superdisntegration attained at high degree of substitution of LMWC was utilized for liquid dosage forms [77]. A pharmaceutical excipient was obtained by co-processing LMWC with oleic acid /surfactant system to act as drug nano-carrier suitable to deliver protein molecules via oral route. LMWC was utilized for liquid dosage forms because of its high-water solubility [74, 78]. There are very few liquids sustained release products available commercially in the market. The major challenge with liquid sustained release dosage forms would be to produce sufficient release retardation and to maintain the stability throughout the shelf life. Therefore, there is a necessity to conduct more studies for the development of pharmaceutical liquid sustained release products. LMWC was used to sustain the release of certain drugs having suitable physico-chemical properties that favors interactions with LMWC. Several patents and articles were published and proved the ability to overcome the obstacles and to form a liquid sustained release dosage form for specific type of drugs.

Innovations in Chitosan-Based Drug Delivery

Pharmaceutical industry should build up on this knowledge and put more effort in the development of liquid sustained release products using LMWC to reach to the market. The objective is to formulate a pharmaceutical excipient that can be easily used as a soluble ingredient in liquid dosage forms and at the same time able to retard the release of active ingredients.

LMWC possesses different pKa values depending on MW and DD [79-80]. Thus, the degree of ionization is pH dependent. LMWC is a positively charged polymer when mixed with negatively charged drug molecule could produce a polymer-drug complex. The degree of dissociation of drug from LMWC complex could be pH dependent. The gastrointestinal tract pH varies during drug transit which permits LMWC drug complex to dissociate slowly based on pH variations in the gut [81-82].

LMWC can be prepared by hydrolysis of HMWC in acidic conditions to produce different positively charged LMWC fractions [83]. The method of interacting different fractions of LMWC with negatively charged molecules such as diclofenac sodium to produce a liquid with a sustained release behavior was published elsewhere [84].

Further study on glucosamine HCl, the monomer of LMWC, to produce sustained release behavior upon complexing with ibuprofen sodium was evaluated [85]. The interaction between LMWC and ibuprofen as a model of an ionic drug in liquid dosage form was investigated. Results showed that complexation of ibuprofen with LMWC involved ionic interaction between the ammonium group of LMWC and the carboxylate ion of ibuprofen. It was also shown that it is more efficient to prepare the complexes using low concentration solutions of the polymer [45]. The physico-chemical properties of the produced LMWC in aqueous solution was investigated thoroughly in aqueous solution [86]. Further study using potentiometric titration was carried out to determine the variability in pKa and degree of acetylation of LMWC in solution [80].The surface activity properties of LMWC and some of its derivatives in aqueous solution was also investigated [87].

The previous approach of complexation to produce sustained release liquid made little retardation in the release of active ingredient in the liquid dosage form. In order to increase the drug retardation power out of the polymer complex; the drug polymer complex was dispersed in an oil emulsified system. The LMWC drug complex was dispersed in an oleic acid/polysorbate emulsified system and diclofenac potassium was used as model drug [88]. The MW of chitosan, concentration and type of polysorbate used are considered important factors that affect drug release behavior.

Additionally, LMWC used in protein drug delivery. Several studies on formulation of oral insulin using nano-sized delivery systems were carried out [89-92]. The studies included microemulsion in oily medium, nanocapsules dispersed in aqueous medium, lipoamino acid in aqueous medium and liposomal nanovesicles in aqueous medium [93]. Almost all studies included in-vitro and in-vivo evaluation using diabetic animal models. The studies revealed clearly the possibility to give insulin orally with the aid of LMWC, which served as an important factor in protein stabilization and permeation enhancement throughout the gastrointestinal tract.

LMWC polymer as a nano carrier for oral insulin delivery in liquid dosage forms was investigated. LMWC is able to interact with insulin. The mixture was dispersed in water and complexed with anionic surfactants and fatty acids to produce nano-sized particluates that can be dispersed either in oily or aqueous media. Oily based protein delivery system preparation includes the reaction of insulin with LMWC to form polyelectolyte complex [PEC]. The PEC has been characterized using suitable in-vitro tests [94]. The in-vitro test indicated that the PEC cannot withstand pepsin enzyme in the gastrointestinal tract, thus PEC was dispersed in an emulsified oily based medium. The factors

affecting formulation of oily based oral insulin system were studied [95]. The optimal preparation in terms of particle size, zeta potential and in vitro stability against pepsin enzyme was selected for further evaluation on diabetic rats [96].

The optimal oily formula was characterized and given orally to diabetic animals [97]. The encapsulated insulin was biologically active and stable as demonstrated by the remarkable reduction of blood glucose levels of the streptozotocin-diabetic rats after oral administration of the preparation. Moreover, hypoglycemic effect was sustained for a longer period of time compared to the subcutaneous injection. The effect of MW of chitosan was also evaluated on insulin release [98]. The study emphasized the importance of optimizing the MW along with the DD of the incorporated LMWC in oral insulin delivery preparations in order to ensure the highest performance of such delivery systems. The system was also evaluated on human volunteers [99]. The purpose of the study was to investigate oral absorption of oral insulin with different particle sizes in comparison with 0.1 U/kg subcutaneous product. The results confirmed the oral absorption of insulin through human gastrointestinal tract.

Aqueous based oral protein delivery nanoparticle system of LMWC with sodium lauryl sulfate was developed. An oral aqueous-based protein delivery system was developed as nanocapsules for oral delivery of proteins [100].

Other researches on peptides and growth hormone delivery using chitosan polymer were conducted. Chitosan based microneedles were used to deliver growth factors for wound healing via transdermal delivery [101-102]. Recently, chitosan attracts high attention as delivery system for vaccination [103].

Mesoporous silica nanoparticles coated with LMWC as an injectable controlled release carrier of insulin was investigated for subcutaneous delivery [104]. LMWC can interact with lecithin to produce liposomal nanovesicles for oral insulin delivery was also evaluated [105].

The reaction of unsaturated fatty acids [oleic acid] with LMWC produced an emulgel that has been also studied for its application as a low calorie diet [106]. Another research studied sorption power of LMWC oleoyl derivatives for ferrous ion and evaluated the resultant amphiphilic nanoparticles as carriers of iron for anemia treatment. Caco 2 cell model confirmed the efficacy and safety of the developed system for enhancing ferrous ion absorption through the intestinal mucosal cells [107-108]. A new adjuvant therapy for H. pylory treatment was introduced by developing a curcumin controlled released gastro retentive floating system based on chitosan and beeswax matrix formulated via hot melting. This approach showed a potential to enhance the therapeutic outcomes for H.pylori eradication [109].

Conclusion

Chitosan derived from bio-waste, particularly crustacean shells and fungal biomass, has demonstrated substantial pharmaceutical utility in oral drug delivery. Its molecular weight, degree of deacetylation, and origin significantly influence its physicochemical and functional properties, making it a versatile excipient for sustained drug release, mucoadhesion, disintegration enhancement, and protein delivery. Recent patented advancements, such as polyelectrolyte complexation, coprecipitation with silicates, and nanoformulations, have expanded its pharmaceutical applications, demonstrating improved bioavailability, stability, and controlled release profiles.

Despite its potential, several challenges remain. Future research should optimize extraction and purification methods to ensure molecular characteristics and pharmaceutical performance consistency. Further structural modifications and hybrid formulations with biopolymers or inorganic materials may enhance chitosan's functional properties for targeted drug delivery. Investigating its interaction with biological systems, including cellular uptake, degradation pathways, and long-term safety, is crucial for regulatory approval and clinical translation.

Moreover, eco-friendly processing and biotechnological valorization of chitosan bio-waste can improve sustainability and cost-effectiveness, addressing concerns related to seasonal variability and heavy metal content in marine-sourced chitosan. Developing standardized quality control parameters and expanding the application of non-marine chitosan sources could further support its adoption in pharmaceutical and biomedical fields. Addressing these gaps will enable chitosan bio-waste to serve as a sustainable, multifunctional excipient for next-generation drug delivery systems.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The raw data required to reproduce these findings are available in the body and illustrations of this manuscript.

Author's contribution

M. Al-Remawi: Conceptualization, Methodology, Investigation, Resources, Writing the original draft. **N. Jaber**: Methodology, Investigation, Writing the final version, Writing - review & editing, Visualization, Project administration.

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Conflicts of interest

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