Chitosan-Infused Nanocarriers for Targeted Drug Delivery and Localized Treatment of Atopic Dermatitis

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Abstract: Chitosan, a biopolymer obtained from chitin through deacetylation, is acknowledged as a cornerstone in advanced drug delivery research due to its biocompatibility, biodegradability, and natural mucoadhesive properties. This minireview consolidates recent advances in modification techniques, including quaternization, hydrophobic grafting, and thiolation, as well as their incorporation into nanoparticles, hydrogels, films, and nano emulsions. We analyse essential fabrication techniques (ionic gelation, emulsification, nanoprecipitation, and reverse micellization) and detail how these methods tailor particle size, surface charge, and release kinetics to achieve optimal therapeutic effectiveness. Special attention is directed towards the transdermal and topical management of atopic dermatitis, highlighting the effectiveness of hydrophobic ally and thiol-modified chitosan nanocarriers. These carriers have demonstrated enhanced skin adhesion, pH-responsive drug release, and significant reductions in lesion severity and cytokine expression in preclinical studies. Finally, we examine emerging trends in chitosan-based composites and nano-formulations, highlighting opportunities for multifunctional delivery systems, targeted therapies, and scalable manufacturing aimed at clinical translation.

Keywords: Biopolymer, Chitosan, Chitin nano formulation, Atopic dermatitis, Nanoparticles, hydrogels, transdermal delivery, ionic gelation, emulsification

Introduction

Chitosan, a polysaccharide derived from chitin, has garnered significant attention in recent year due to its diverse applications in the pharmaceutical and drug delivery sectors. Due to the presence of protonated amino groups, it exhibits cationic

characteristics, which allow interactions with negatively charged biological membranes and macromolecules through electrostatic forces. This enables mucoadhesion and facilitates targeted drug release. Additionally, the modification of chitosan through nanocomposite formation further enhances its versatility and functionality, opening up new avenues for advanced drug delivery systems and biomedical applications. As depicted in figure 1.Chitosan (CS), has significant attention for its versatility, availability, and unique properties in the field of medical applications (Sharma, Porat and Gedanken, 2021),(Khan and Alamry, 2021). It consists of units of 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose, and it is the 2nd most abundant co-polymer, following fibre such as cellulose (Cheba, 2020),(Mahmood et al., 2019),(Noshirvani et al., 2017). It is commonly produced by partially removing acetyl groups from chitin in an alkaline setting (Soni et al., 2018),(Upadhyaya et al., 2014).Chitosan is widely utilised in various applications due to its polyelectrolytic character and its ability to form complexes with substances via amino groups (Ahmed and Ikram, 2016). Chitosan and its derivatives are considerably search compounds due to their advantageous physicochemical properties, which facilitate the development of surfaces that can respond to stimuli (Ziegler-Borowska et al., 2016). Chitosan is employed in agriculture as a bio-pesticide, in the eatable products and pharmaceutical industries as a packaging material, and in wastewater treatment as a membrane filtration device (Hoang et al., 2022). Figure 2 illustrates the categorization of biopolymers based on the presence and covalent linkage of monomers.The inherent mucoadhesive and biocompatible properties of chitosan make it an excellent scaffold for topical treatments of atopic dermatitis in dermatologic clinics(Amisha et al., 2024). Attaching hydrophobic groups like oleic or linoleic acid to chitosan nanocarriers enhances their affinity for the stratum corneum and prolongs their residence time on the skin(Noor et al., 2020). Thiolation of CS also enhances adhesion through disulfide linkage with keratinocyte surface proteins, whereas quaternized derivatives facilitate pH-sensitive swelling and controlled drug release in the mildly acidic AD microenvironment(Huang and Lin, 2025). Composite CS–lipid nano emulsions and in situ–gelling hydrogels combine occlusive hydration with extended anti-inflammatory delivery, effectively restoring barrier function. In preclinical models of dermatitis induced by oxazolone and DNCB, nanoparticles based on CS that were loaded with tacrolimus, resveratrol, or tetra methylpyrazine significantly reduced the severity of lesions, scratching behaviour, and pro-inflammatory cytokine expression at doses considerably lower than those of conventional drugs(Dartoraet al., 2023)(Garg et al., 2025).

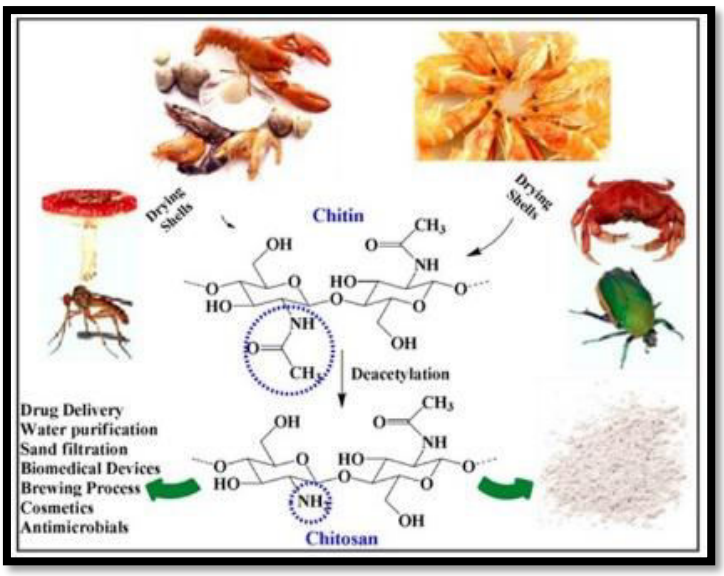

Figure 1. Diagrammatic representation of chitin origins, the process of deacetylation to form chitosan, and primary fields of application (2)

Therapeutic application of Chitosan in drug delivery: System for drug delivery offer numerous advantages in treatment, including reducing toxicity, enhancing therapeutic effectiveness, and minimising the need for frequent dosing. Controlled drug release mechanisms, a hallmark of modern drug delivery, ensure precise, localised distribution of medication over time, optimising therapeutic outcomes while avoiding the pitfalls of traditional dosing methods (Kedir et al., 2022). Traditional drug delivery often results in fluctuating drug levels, leading to potential overdoses or suboptimal efficacy between doses. In contrast, controlled release mechanisms maintain consistent drug levels, mitigating the risk of under- or overdosing and enhancing patient safety (Farokhzad and Langer, 2009). Chitosan, a biocompatible polymer, holds immense promise as a drug carrier due to its ability to facilitate controlled drug release. Its metabolic breakdown in the body ensures safe elimination, particularly when tailored to the appropriate molecular weight. Enzymatic breakdown, facilitated by chitinase enzymes, further enhances its biodegradability (Nanaki et al., 2012). In drug delivery formulations, chitosan serves as an inert filler or diluent, regulating drug release kinetics. Whether incorporated into pills, capsules, or other dosage forms, is vital for drug release and improving solubility, bioavailability, and tissue penetration (Li et al., 2022). Utilizing the distinctive characteristics of chitosan, drug delivery systems can attain targeted and prolonged release of therapeutic drugs, presenting a viable approach for addressing many illnesses(Yang et al., 2023).

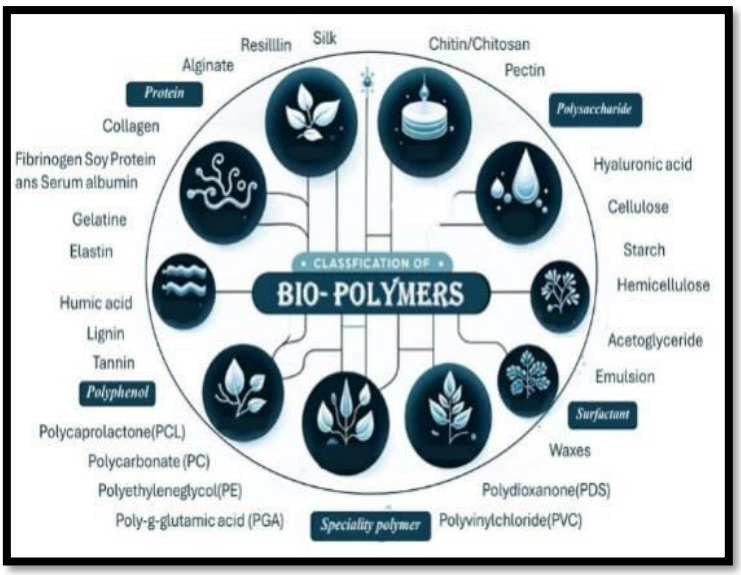

Figure 2.Bio-polymers be classified based on their chemical composition and origin: proteins, polysaccharides, polyphenols, specialty polymers, and surfactants

Refinement and Formulation Strategies for Chitosan: Within this segment, a variety of tactics are examined, all aimed at augmenting the properties of chitosan and converting it into highly effective delivery systems. It encompasses chemical, physical, and enzymatic modifications of chitosan to tailor its characteristics for specific applications which is shown in Figure 3. Chemical modifications involve altering chitosan's structure through reactions with various compounds, such as quaternisation or grafting of hydrophobic groups, ionic group, polymerizable group, hydrophilic groups, and cross linkable group to improve its solubility and stability (Saikia and Gogoi, 2015),(Sievalet al., 1998),(Ercelenet al., 2006),(Zhang et al., 2007). Physical modifications, including mix with other polymers or electrospinning, offer ways to modify chitosan's physical properties without altering its chemical structure (Lee et al., 2002),(Seidi et al., 2021). Enzymatic modifications utilise enzymes to catalyse specific reactions, enabling precise control over chitosan's properties (Antaby, Klinkhammer and Sabantina, 2021). Additionally, this explores formulation strategies that incorporate modified chitosan into drug delivery systems, such as nano-micelles, hydrogels, or films, to optimise release kinetics, improve bioavailability, and enhance healthful efficiency. Each strategy offers unique advantages and contributes to expanding the versatility and applicability of chitosan-based formulations in the pharmaceutical and biomedical fields (Ahmed and Aljaeid, 2016).

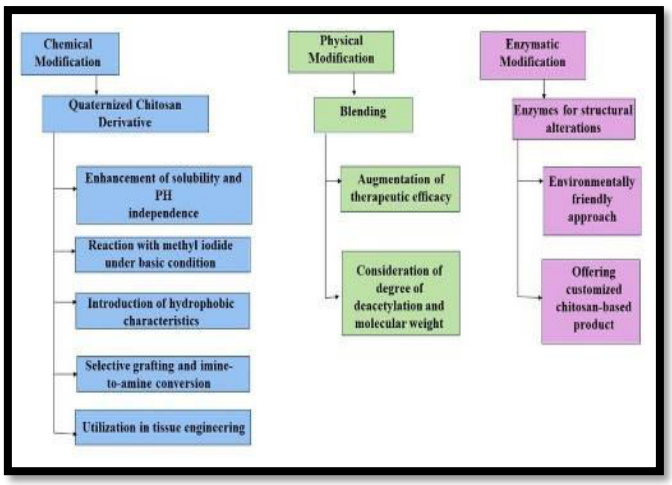

Figure 3. Analysis of Chitosan Modification Approaches: Chemical, Physical, and Enzymatic(Seidi et al., 2021)

Chitosan nano-formulation: Chitosan nano-formulations exemplify a sophisticated technique in delivering medication systems, regulating pharmaceutical release timings meticulously, and improving bioavailability(Sangnimet al., 2023). These formulations typically involve encapsulating therapeutic agents within chitosan nanoparticles, which can be tailored to achieve specific drug-loading capacities and release profiles, as shown in Figure 4 (Sun et al., 2019). Various synthesis methods are employed to fabricate chitosan nanoparticles, including nanoprecipitation, emulsification, and ionotropic gelation, each presenting distinct benefits regarding of particle size, stability, and scalability (Bashir et al., 2022).

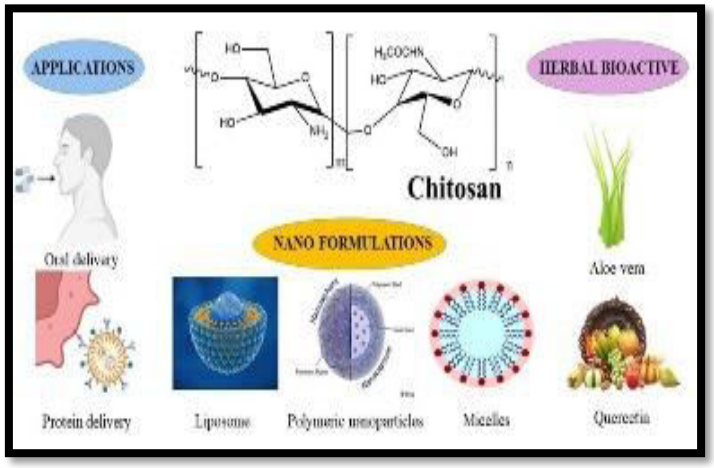

Figure 4. Chitosan Structure and Its Nano-Formulation Platforms for the Delivery of Oral, Protein, and Herbal Bioactive (Sangnim et al., 2023)

Chitosan Modification and Nano-Formulation: Polymers, which can be derived from nature, artificially created, or partially created, provide a wide variety of choices for developing nanoparticles used in the delivery of medication(Alves et al., 2020). Chitosan and its derivatives have remarkable properties that set them apart from other

polymers, rendering them very suitable for oral administration (Islam, Bhuiyan and Islam, 2017).

Synthesis approaches for Chitosan nano-formulations: In recent years, metal oxide nanoparticles (MNPs) have been synthesised utilising environmentally sustainable chemical processes, primarily due to their cost-effectiveness and lack of toxicity (Sathiyavimal et al., 2020). These nanoparticles have demonstrated efficacy as therapies for both animals and humans. The application of chemical methodologies to synthesise metal oxide nanoparticles, which entails the usage of potentially hazardous reducing substances that include sodium hypophosphite, hydrazinium hydroxide, and sodium borohydride, has had an adverse impact on the environment. The starting materials would adhere onto the extensive sides of tiny particles, augmenting their harmful effects and adversely affecting environmental and biological functions(Garavandet al., 2022). Chitosan nanoparticles (CNPs) are mostly derived from waste materials produced by the seafood industry. They are non-toxic, biocompatible, biodegradable, and functionalised. Carbon nanotubes have demonstrated promise as environmentally friendly additives in reinforcing biodegradable composites for uses in food packaging and biomedicine (De Mesquita, Donnici and Pereira, 2010). The subsequent section provides a comprehensive explanation of the predominant techniques used to produce chitosan nanoparticles, along with their advantages and disadvantages.

Emulsification method: Emulsification is the process of mixing two liquids that do not normally mix, such as oil and water, to create a stable emulsion. Emulsification is the process of dispersing one liquid into another by creating small droplets(Bancroft, 2002). Emulsification techniques are essential in the process of nano-formulating chitosan, as they offer an efficient way to improve its bioavailability and functional characteristics. These techniques entail dispersing chitosan in a compatible medium to form stable nanoparticles with nanosized dimensions, leading to notable enhancements in its solubility, stability, and controlled release characteristics (Mandpe et al., 2023). Figure 5 demonstrates that the emulsion's interior phase is composed of a somewhat water-repellent organic solvent that is like benzyl alcohol and ethyl acetate. Two stages were originally filled with fluid to achieve equilibrium thermodynamics at the ambient temperature. The procedure relies on the emulsification of a polymer-based volatile fluid into a aqueous phase, followed by evaporation of the organic solvent (Sathiyavimal et al., 2020). Upon dispersion over a substantial amount of distilled water, the organic solvent permeates through the distributed droplet into the surrounding phase, leading to the creation of colloidal particles (Moinard-Chécot et al., 2008). Ultimately, the organic solvent can be eliminated using either evaporation or filtering, depending on its specific boiling point Figure 5 (Wang et al., 2016). Wareeet al., (2018) conducted research that specificallyexamined. Preparation process and characterisation of chitosan

nanoparticles for encapsulation. The purpose of this study was to encapsulate curcumin within these nanoparticles in order to regulate and control its release rate. The nanoparticles were synthesised using the emulsification process, and several characteristics including particle size, zeta potential, and encapsulation effectiveness were assessed. The work showcased the capacity of chitosan nanoparticles as a vehicle for curcumin, providing controlled release characteristics for improved medicinal uses.

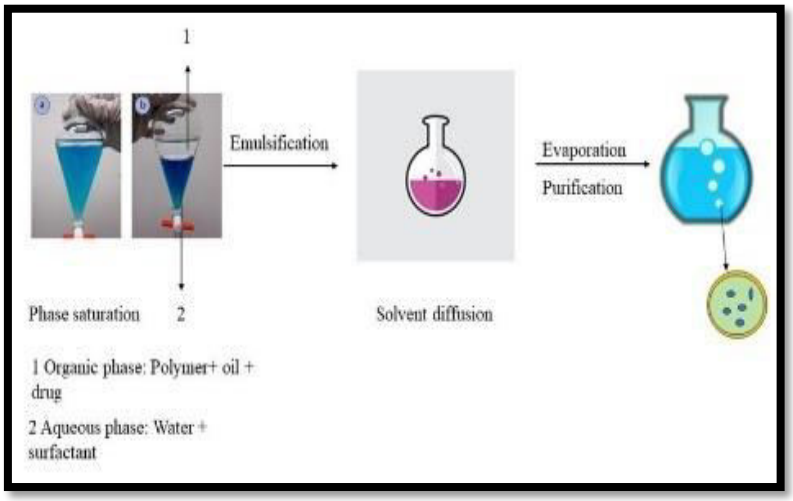

Figure 5. Development of Drug-Loaded Chitosan Nanoparticles Using Emulsification–Solvent Diffusion Method for Controlled Release(Wang et al., 2016)

Ionic gelation method: Chitosan nanoparticles (CNPs) are formed through the process of ionic crosslinking, as shown in Figure 6. The ionic compound is composed of a cationic amine group and an anionic polyanion, specifically tripolyphosphate (TPP) (Yanat and Schroën, 2021). Chitosan was converted into a cationic liquid by simply immersing it into a solution that was diluted with acetic acid, while TPP was converted into anionic solutions by diffusing in water (Zhao et al., 2018). The TPP solution was incrementally added to the cationic chitosan solution, drop by drop. CNPs were rapidly generated using mechanical agitation at room temperature. Modulating the quantity of chitosan and crosslinking agent, along with the pH level of the solution, can impact the physicochemical characteristics of the resulting nanoparticles, including their particle size and surface charge (Mahalingam and Krishnamoorthy, 2015). Bavel et al. (2023) utilized sub-100 nm CNPs as a precursor for developing novel biopolymer-based viral surrogates for water-related purposes. The CNPs were synthesised using ionic gelation utilising low molecular weight chitosan (deacetylation 75–85%) and tripolyphosphate as a crosslinker. This process involved severe homogenisation to reduce the size and improve the uniformity of the particles. The CNPs were then purified by passing them through 0.1 µm polyether sulfone syringe filters (Van Bavel et al., 2023).

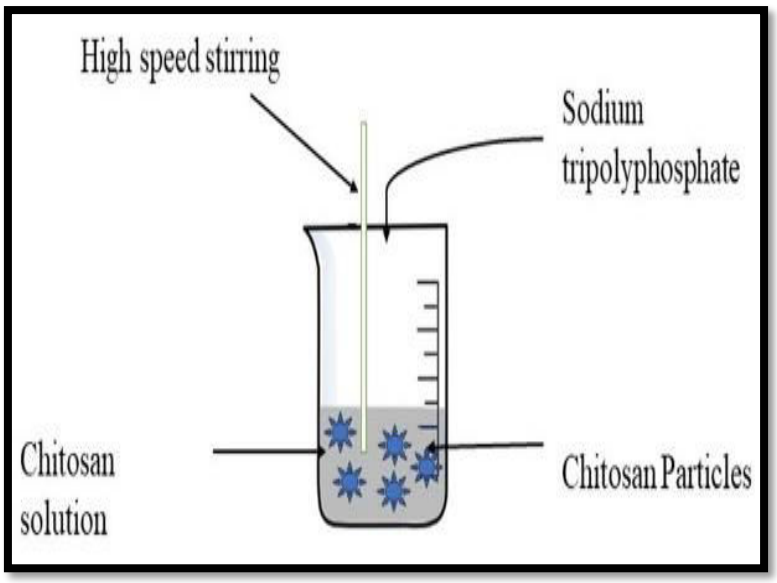

Figure 6. Diagram illustrating the formation of chitosan nanoparticles through ionic gelation with tripolyphosphate under high-speed stirring conditions (Mahalingam and Krishnamoorthy, 2015)

Reverse micellar method: Chitosan nanoparticles are produced by the reverse micellar process; in this method nanoparticles are formed inside the water-based nucleus of reverse micellar droplets. Subsequently, crosslinking is achieved through the utilisation of glutaraldehyde. Reverse micelles are formed by combining a surfactant with an organic solvent. Then, an aqueous chitosan solution is added to prevent cloudiness (Hembram et al., 2016). The transparent solution then undergoes crosslinking with continuous agitation, ensuring the bonding of the unbound amine group of chitosan with glutaraldehyde. After overnight stirring to complete the crosslinking process, the organic solvent is evaporated under low pressure to remove it. Any excess surfactant is precipitated with a suitable salt and then removed by centrifugation. Finally, the resulting NPs suspension is dialyzed before lyophilisation, resulting in chitosan NPs with a size of less than one hundred micron and significant monodispersed (Hembram et al., 2016),(Abdelgawadet al., 2017). Orellano et al., (2020) in his study employed chitosan crosslinking reaction within the radial cores of reverse micelles (RMs) to investigate the impact of the micellar interface on the production of CNPs. They also evaluated both benzyl-n hexadecyltrimethylammonium chloride (BHDC) and sodium 1,4-bis-2-ethylhexylsulfosuccinate (AOT RMs) due to the significant disparities in their interfacial water entrapment structure (Orellano et al., 2020).

Nanoprecipitation method: O Fessi's batch was the prior to developing the nana particles method, which is sometime referred to as liquid ejection or interfacial deposition (Hamedi et al., 2018).This technique involves slowly incorporation of the oil phase to the aqueous phase while stirring gently to create nanoparticles, in a colloidal

suspension shown in Figure 7. One of the benefits of this method is its ability to produce nanoparticles quickly and easily, as they are generated immediately in a single step. The process is greatly affected by critical parameters such as the pace at which the organic phase is injected, the agitation of the aqueous phase, and the ratio of the oil phase to the aqueous phase. Maan et al., (2024) synthesised a nano-formulation containing chlorpyrifos pesticide using chitosan and guar-gum. They used nano-precipitation methods to control the release of the pesticide in water (Maan et al., 2024).

Grafted chitosan: Chemical alteration of chitosan networks has been explored to enhance or bestow new qualities to chitosan. Incorporate tiny molecules or polymer branches to the spin of the chitosan is a common way to change it, as is quaternizing the amino groups. Chitosan chains have three reactive sites that are suitable for chemical modification (Wang, Xue and Mao, 2020). These sites are acetyl amino and glycoside linkages, as well as C_3-OH, C_6-OH, and C_2-NH_2 bonds as shown in figure 4. There are several methods of modification. Examples include sulfonation, quaternarization, carboxymethylation, and N- and O-hydroxyalkylation. Various graft copolymerization's of chitosan with compounds such as lactic acid, oleic acid, lauric acid, polyacrylic acid, vinyl pyrrolidone, 3-O-dodecyl-D-glucose, and N-isopropylacrylamide etc, have been introduced and assessed as useful biomedical materials (Almeida et al., 2022),(Kumar et al., 2020),(Canale-Salazar et al., 2020).The researcher Yu et al., (2007) created a copolymer by combining poly(L-lysine) with chitosan (PLL-g-Chi). They then tested the effectiveness of this copolymer in attaching plasmid DNA and introducing genes into HEK 293T cells. The copolymer exhibited superior to pristine chitosan, with gene delivery efficiency dependent on the copolymer composition (Yu et al., 2007). A galactose-grafted chitosan copolymer (GC) coats polystyrene, enhancing hepatocyte adhesion and spheroid formation through a unique relationship between GC molecules and hepatocytes. PEG-grafted chitosan nanoparticles were prepared, demonstrating efficient gene delivery without toxicity in neuronal cells. Additionally, a copolymer of quaternized chitosan with PEG showed enhanced solubility and biocompatibility compared to quaternized chitosan alone, with reduced cytotoxicity (Luo et al., 2022). In another study, Zhang et al. (2008) used the ionic gelation method to make G-g-chitosan nanoparticles, which have better insulin binding properties: they were grafted with polyethylene glycol. Set side by side to the G-g-chitosan suspension and the authorised insulin solution, the nasal absorption of insulin significantly improved, influenced by the molecular weight of chitosan and PEG polymer, as well as the degree of substitution (Zhang et al., 2008).

Evaluation of chitin and chitosan: The categorisation of biopolymer into chitin or chitosan is determined primarily by the extent of deacetylation (DD), which indicates the ratio of D-glucosamine to the amino acid N- -units within the polymeric structure.

This distinction is pivotal, particularly in the realm of modified nanocomposites involving chitosan. Analysis of synthetic altered chitosan generate from chitin often involves chromatographic and spectroscopic techniques (Kumirska et al., 2010). For instance, Attenuated total reflectance, Fourier-transform infrared spectroscopy (ATR-FTIR) serves to identify functional groups present and assess the degree of interaction among constituent components. Moreover, X-ray diffraction analysis (XRD) is instrumental is probing the crystal structure of nanoparticles through the detection of diffraction peaks (Basit et al., 2008). Techniques like transmission electron microscopy (TEM) and scanning electron microscopy (SEM) offer valuable insights into the properties of minute samples, revealing structural and morphological feature via the illumination of specimens with accelerated electron beams (Inkson, 2016). Additionally, the quantification of zeta potential plays a crucial role in evaluating the electrostatic forces governing particles interactions. This measurement typically conducted using specialized zeta sizer equipment, provides essential data on the extent of repulsion and attraction between particles, informing the design and optimization of nanocomposite formulation (Dubey et al., 2020).

Diverse Applications of Chitosan a natural polymer in Drug Delivery

In recent research, chitosan biopolymers have emerged as promising carriers for drugs, therapeutic proteins, and genes, utilising various preparation methods with varying effectiveness and constraints (Bernkop-Schnürch and Dünnhaupt, 2012). The inherent cationic properties of chitosan, attributed to its primary amino groups, confer numerous advantagesregulated pharmacological dispersion, cohesiveness, in creation of gel, mutagenesis, enhanced permeation and efflux mechanism inhibition thus rendering it valuable in drug release systems (Felt, Buri and Gurny, 1998). Park et al., (2012) have investigated specific chitosan-based for delivering low molecular weight drugs (Park et al., 2010), while Werle et al., (2010) have focused on synthesising and characterising thiolates chitosan, demonstrating its potential for oral drug delivery across rang of chemical categories,encompassing peptides and substrates for efflux pumps.The practical uses of chitosan and its derivatives are briefly succinctly outline below (Werle and Bernkop-Schnürch, 2010).

Table 1: Alternative Formulations Beyond Chitosan Nanoparticles

Formulation	Description	Examples study	Ref.
Tablet	Oral dosage form using chitosan for controlled release; made via wet granulation or direct compression.	Bhagwat et al.: AAm-g-CS copolymers (15–30% grafting) improved swelling, pH-independent solubility; propranolol HCl SR tablets matched commercial profiles ($f_2 \approx 90$).	(J. et al., 2013),(Millottiet al., 2014),(Hejazi and Amiji, 2003),(Bhagwat et al., 2020)

Film	Rapidly dissolving films for oral, buccal, ocular, or topical delivery; made by solution casting.	Wenling et al.: Catechol–chitosan formed CSCT–Ag films with ~8 nm Ag NPs; improved strength, barrier properties, and antibacterial activity.	(Karki et al., 2016),(Huang, Liu and Chen, 2017), (Cao et al., 2020)
Microsphere	Free-flowing powders for controlled, targeted delivery; made via crosslinking or spray drying	Diana et al.: Genipin-crosslinked ~4 µm microspheres loaded AMP peptide; >3 log kill of H. pylori.	(Sahil et al., 2011),(Luo et al., 2019),(Fonseca et al., 2022)
Hydrogel	3D networks with tunable release; physically or chemically crosslinked	Pamela et al.: Chitosan–hyaluronic acid hydrogels improved adhesion, sustained antimicrobial release, aided wound healing in dermatitis.	(Neufeld and Bianco-Peled, 2017),(Garcia et al., 2025)
Bead	Spherical particles made by dropping chitosan into NaOH; properties depend on concentration and pH.	Amara et al.: AOGO–chitosan–PVA beads removed Cu(II) more effectively; confirmed via FTIR and SEM.	(Gericke, Trygg and Fardim, 2013),(Keshvardoostchokamiet al., 2021), (Nasir et al., 2022)
Micelle	Self-assembled colloids with hydrophilic/hydrophobic domains for drug delivery.	Amara et al.: Oleic acid–chitosan micelles (60–100 nm) loaded moxifloxacin/rifampicin; >100 h release, 2× C_{max} in rats.	(Cagel et al., 2017), (Zlotnikov et al., 2023)

Chitosan based Nanoparticle

Nanoparticles, typically defined as fragments with dimensions less than 100 nanometres, have distinct physical and chemical properties due to their tiny size and large surface area-to-volume ratio, making them extremely effective in various scientific and industrial applications, including drug delivery, imaging, and material science (Boholm and Arvidsson, 2016). Nano-particles of chitosan with tripolyphosphate exhibit a high quality capacity for insulin association, characterised by high positive charge and rapid release kinetics, making them promise for nasal drug delivery (Sarmento et al., 2007). Insulin loading on polyelectrolyte complex nanoparticles of chitosan and alginate significantly enhances intestinal absorption, resulting in improved hypoglycaemic effect and insulinemia levels compared to oral insulin solution or physical mixtures. Nanoparticle consisting of chitosan modified and linked with several galactose residues (Gal-m-CS) demonstrate stability in aqueous environments and high affinity to HepG2 cells, suggesting potential for liver-targeted drug/gene delivery (Ko et al., 2002).

Quaternization

In an living system study, conducted by Hamman et al. (2002) to explored the impact of quaternization level of N-trimethyl chitosan chloride (TMC) on the nasal absorption of [14C]-mannitol in rats (Hamman, Stander and Kotzé, 2002). Their studies revealed that a quaternization level of 48% for TMC yielded maximal incorporation, with no significant enhancement noted at elevated quaternization levels. The initial augmentation in charge density due to quaternization was succeeded by steric effects, elucidating this observation. Another study evaluated the influence of quaternization degree on the enhancement of ofloxacin absorption through rabbit corneal epithelial cells in vitro. Chitosan variants with different molecular weights and quaternization degrees were examined, demonstrating that polymers with intermediate quaternization degrees notably enhanced permeability irrespective of polymer molecular weight. These findings were further validated in vitro using rabbit eyes. TMC was observed to enhance the intestinal permeation of the peptide medication Buse Relin by transiently opening the paracellular pathway. The effectiveness of TMC was validated through both in vitro studies using Caco-2 cell single layers and in vivo experiments conducted in rats. Furthermore, the impact of the degree of quaternization of N-trimethyl chitosan TMC on their adhesive properties and their ability to enhance penetration across buccal mucosa was investigated. The mucoadhesive characteristics were found on the degree of quaternization, and trimethylation significantly improved polymer penetration, especially in pH 6.4 buffer solutions (Di Colo et al., 2004)

Modification with metal-materials

Metal nanoparticles, such as zinc oxide (ZnO), titanium dioxide (TiO_2), montmorillonite, and iron oxide, have attracted interest in therapeutic uses, especially in cancer treatment, owing to their capacity to improve drug absorption, regulate release rates, and target specific sites within the body(Wawrzyńczak, Chudzińska and Feliczak-Guzik, 2024) . ZnO nanoparticles, encapsulated with cationic chitosan, have been utilized to synthesize doxorubicin-loaded ZnO quantum dots, with the particles demonstrating considerable drug-loading efficiency and regulated release profiles. Additionally, chitosan/ZnO nanoparticles demonstrated antimicrobial and UV protection abilities when applied to cotton fabrics, with increased activity at higher nanoparticle concentrations (Rajan and Raj, 2013). A titanium-based titania nano-tube array accompanied by hydrophilic chitosan grids has been investigated as a carrier for indomethacin, exhibiting improved drug release profiles with extended-release characteristics. Furthermore, carboxymethyl chitosan/MMT nanoparticles loaded with isoniazid showed improved cell viability in human lymphocytes, indicating good cytocompatibility (Shu, Zhu and Song, 2001).

Exploring Alternative Formulations Beyond Chitosan Nanoparticles

In addition to chitosan nanoparticles, various other formulations utilising chitosan as a key component have been developed for medication delivery and biomedical applications. These include chitosan microspheres, films, scaffolds, and coatings, each presenting distinct benefits in drug encapsulation, release timing, and tissue compatibility.

Chitosan-Based Drug Delivery Methods

Since chitosan microparticles reduce size of drug particles and exhibit mucoadhesive qualities, they have been used in a variety of ways. Chitosan-DNA microparticles, developed by researchers Dastan and Turan, demonstrated prolonged DNA release and possible cell line transfer. In simulated fluids, a different group developed chitosan-DNA microparticles for mucosal vaccination. Chua et al. developed chitosan-based microparticles that release luteinising hormone to administer vaccines. The ability of these particles to successfully carry hormones has expanded their utility in enhancing protection against bacteria, viruses, and tumour antigens (Noshirvani et al., 2017),(Dastan and Turan, 2004).

Oral Drug-Delivery

Oral drug delivery is widely regarded as the simplest, most convenient, and effective method for treating chronic diseases (Ensign, Cone and Hanes, 2012). It offers enhanced patient comfort, improves compliance, and allows for flexibility in accommodating various formulations. The extensive surface area of the gastrointestinal tract's mucosa layer facilitates efficient drug absorption, making it the preferred route of administration (Hua, 2020). Through the development of new formulations, drug administration can be precisely targeted to specific sites, improving both local and systemic absorption while minimising premature drug degradation. However, oral administration has its challenges, including the need for drugs to withstand the diverse conditions of the gastrointestinal tract, such as varying pH levels and degrading enzymes. Physiological factors, such as arterial perfusion, nourishment accessibility, and the tiny absorption windows of specific medicines, may impede the absorption of orally administered medications(Mansi et al., 2012).

Buccal drug delivery

The buccal mucosa offers high bioavailability and avoids first-pass metabolism, making it an attractive route for drug delivery. However, barriers such as mucosal properties and enzymatic activity limit its efficacy. Mucoadhesive polymers like chitosan can enhance drug delivery by adhering to the mucosa, improving absorption without causing irreversible damage. Chitosan-based formulations have shown promise in treating oral candidiasis, with drug delivery systems like chitosan-coated microspheres demonstrating effective local antifungal activity. Additionally, chitosan-based films

loaded with antifungal agents like miconazole nitrate have exhibited improved adhesiveness and dissolution rates (Rençber et al., 2016). Chitosan-based gels containing penetration enhancers have been developed for delivering drugs like celecoxib, showing favourable retention properties for the chemoprevention of tumours in the buccal cavity (Cid et al., 2012). Insulin delivery via buccal route has also been explored using chitosan nanoparticles and electrospun scaffolds, demonstrating enhanced permeability and bioactivity (Othman et al., 2021). Furthermore, a novel hydrogel which included lidocaine showed prolonged adhesion and sustained admistration of the drug, offering the potential for periodontal drug delivery (Samiraninezhad et al., 2023).

Pulmonary drug delivery

The pulmonary route offers a rapid onset of action and avoids pre-systemic metabolism, making it favourable for systemic drug delivery (Warnken, Smyth and Williams, 2016). Microparticles and nanoparticles serve as efficient delivery mechanism for this route, with microparticles targeting the upper lungs and nanoparticles targeting the lower lungs (Abdelaziz et al., 2018). Chitosan-coated microcapsules of dapsone were developed to treat pneumonia, overcoming issues of hepatic metabolism and unwanted side effects (Cé et al., 2019),(Sarath Chandran et al., 2023). Additionally, chitosan nanoparticles of itraconazole showed enhanced deposition in the respiratory tract, while chitosan-based formulations of rifampicin and protionamide exhibited sustained release and improved efficacy for tuberculosis treatment (Ni et al., 2018).

Topical and transdermal drug delivery

The transdermal route offers advantages over oral administration due to the skin's large surface area and avoidance of first-pass metabolism. However, the stratum corneum presents a barrier to drug permeation (Singh Malik, Mital and Kaur, 2016). Topical dosage forms like ointments and creams are not optimal for transdermal delivery, whereas bio adhesive gels and patches, often containing chitosan, are suitable. Nanogels incorporating chitosan nanoparticles show sustained drug permeation and enhanced anti-inflammatory effects (Panonnummal et al., 2021). Microemulsions and microspheres with chitosan exhibit effective drug release and muco-adhesion for transdermal delivery (Ariful Islam et al., 2015). Crosslinked chitosan films loaded with zidovudine showed improved drug flux, while chitosan-based transdermal patches enhance drug permeability. These formulations offer promising strategies for transdermal drug delivery (Algin-Yapar and Önal, 2014),(Klecker et al., 1987)

Nasal drug delivery

The nasal route has gained prominence for systemic drug delivery due to advantages like well-vascularized mucosa and circumvention of first-pass metabolism (Feridooni, Hotchkiss and Agu, 2016). Challenges include short residence time and limited

formulation volume. Strategies to enhance drug bioavailability include improving residence time, nasal absorption, and modifying drug structure (Kashyap and Shukla, 2019). Mucoadhesive hydrogels containing chitosan and other polymers showed increased adhesion to nasal mucosa. Chitosan nanoparticles loaded with drugs like leuprolide and sumatriptan succinate demonstrated enhanced drug permeation across the nasal mucosa (Jha and Mayanovic, 2023). Novel biodegradable capsules made of chitosan and poly (L-aspartic acid) exhibited strong mucoadhesive capability and cytocompatibility, enabling improved systemic bioavailability of drugs like olanzapine (Vlachopoulos et al., 2022).

Ocular drug delivery

Eye is a small complicated multi-compartmental organ. Its morphology, physiology, and biochemistry make it extraordinarily resistant to toxic compounds. Pharmaceutical experts find ophthalmic drug delivery to be one of the most attractive one on one hand, as well as a difficult task on another hand (Wadhwa et al., 2009). Chitosan has gained a great deal of interest as a mucoadhesive polymer for the administration of ocular drugs due to its absorption- enhancing effect. It is hypothesised that Chitosan's capacity to transiently open the tight junction improves drug bioavailability. While cohesion, is facilitated by the electrostatic between positively charged chitosan with ionized mucin; it extends corneal contact time (Nagpal, Singh and Mishra, 2010). The following are key dosage forms and compositions of drugs and polymers utilised across for diverse drug delivery routes Table 2.

Table 2: Pharmaceutical dosage forms and formulations in conjunction with polymers utilized in diverse drug delivery pathways

Routes of drug delivery	Dosage form	Polymers	Drug (s)	Ref
Oral	▪ Composite and particulate composite ▪ Nanocomposite ▪ Beads ▪ Nanoparticles	▪ Chitosan and Boswellia gum resin ▪ Chitosan-poly(acrylamide)/ Zn ▪ Chitosan and alginate ▪ Chitosan-modifed PLGA	▪ Aceclofenac ▪ Ofloxacin ▪ Insulin ▪ Tolbutamide	(Jana, Laha and Maiti, 2015) (Pathania et al., 2016) (Tahtat et al., 2013) (Shi et al., 2018)

Buccal	▪ Films ▪ Gels ▪ Nanoparticles	▪ Chitosan, pectin, HPMC, chitosan–pectin and chitosan–HPMC ▪ Chitosan ▪ Chitosan, DMEC and thiolated DMEC	▪ Miconazole nitrate ▪ Celecoxib ▪ Insulin	(Tejada et al., 2017) (Cid et al., 2012) (Al-Nemrawi et al., 2019)
Nasal route	▪ Nanoparticles ▪ Mucoadhesive hydrogels	▪ Chitosan ▪ Chitosan, PVP and Carbopol	▪ Cyclosporine A ▪ Acyclovir	(Das, Gupta and Nath, 2012) (Alsarra et al., 2009)
Skin and transdermal delivery	▪ Nanogels ▪ Microspheres	▪ Chitosan, egg albumin and carbopol 940 ▪ Chitosan	▪ AceclofenacPolyphenol from olive leaf extract	(Ziegler-Borowska et al., 2016)

Chitosan Nanocarriers for Topical Therapy of Atopic Dermatitis

Atopic dermatitis is a long-lasting inflammatory condition characterized by a compromised skin barrier, which is indicated by increased trans epidermal water loss and altered lipid composition, alongside a state of active and persistent immune response(Chaudhary et al., 2024). To effectively address this disease, topical carriers must navigate several physiological challenges: they need to adhere tightly to the stratum corneum, resist rapid clearance, and deliver therapeutic agents to the deeper layers of the epidermis while avoiding irritation. Chitosan, with its inherent mucoadhesive and biocompatible properties, serves as an outstanding scaffold for these nanocarriers(Guo et al., 2024). To enhance skin partitioning and prolong residence time, chitosan chains can undergo chemical modifications with hydrophobic groups, such as linoleic or oleic acid, thereby optimizing their affinity for the lipid-rich stratum corneum(Akhtar, Verma and Pathak, 2015). The thiolation process of chitosan improves adhesion by forming disulfide bonds with keratinocyte surface proteins(Lin et al., 2020). In contrast, quaternization introduces pH-sensitive swelling and controlled release in the mildly acidic microenvironment found in irritated skin. Composite systems incorporating lipids or in situ–gelling polymers, such as chitosan–lipid nano emulsions or patch-forming gels, effectively combine occlusive hydration with prolonged drug release, creating a multifaceted approach for barrier repair and anti-inflammatory delivery(Oh et al., 2024). Following these design principles, Yu et al. created tacrolimus-loaded chitosan nanoparticles (TAC@CNPs) through a two-step nanoprecipitation/electrostatic-assembly method. Enhanced TAC@CNPs containing tacrolimus-maintained stability up to 3 wt%, retained their structural integrity under physiological conditions for a minimum of four weeks, and facilitated a sustained release of the drug. In vitro, TAC@CNPs enabled percutaneous delivery and exhibited

non-toxicity to HaCaT keratinocytes—demonstrating antiproliferative activity comparable to tacrolimus dissolved in organic solvent. In a mouse model of oxazolone-induced AD, a TAC@CNP formulation containing one-tenth of the tacrolimus concentration found in commercial Protopic® Ointment demonstrated comparable anti-inflammatory efficacy. This study demonstrates that cationic chitosan nanocarriers can markedly improve topical delivery and reduce dosing thresholds for calcineurin inhibitors in atopic dermatitis(Lee et al., 2024).

The evaluation of these chitosan systems in preclinical stages is performed using both in vitro and in vivo models. Franz diffusion cells utilizing human or pig epidermis facilitate the quantification of cumulative drug flux and the assessment of barrier repair by measuring trans epidermal water loss(Shakolaet al., 2023). Monitoring involves the suppression of primary pro-inflammatory cytokines (IL-4 and IL-13) and the restoration of epidermal thickness in reconstructed skin or ex vivo biopsies(Pérez-Salas et al., 2023). Valentino et al. encapsulated resveratrol within TPP-crosslinked chitosan nanoparticles (120–500 nm, +13–19 mV, 80 % EE) and integrated them into a 4 % HA hydrogel. The HA matrix preserved NP integrity for four weeks at both 4 °C and 25 °C, demonstrating a delayed release profile (15 % versus 45 % at 1 hour, approximately 80 % by day 5). In vitro studies on TNF-α/IFN-γ–stimulated HaCaT cells demonstrated that pretreatment with Res@gels for 6–24 hours resulted in reduced ROS levels and downregulation of IL-4, IL-6, IL-13, IL-25, IL-33, and TSLP, highlighting the effectiveness of CS–HA hydrogels as sustained antioxidant and anti-inflammatory treatments for AD(Conte et al., 2023).

Ultimately, the effectiveness has been validated in animal models—typically NC/Nga mice or those with oxazolone-induced dermatitis—where treatment outcomes include diminished lesion severity, reduced scratching behavior, and histological resolution of epidermal hyperplasia(Huang et al., 2024). In a similar vein, Xia et al. developed a multifunctional hydrogel by encapsulating tetramethylpyrazine (TMP) within liposomes and applying a surface coating of sodium alginate–chitosan to create a T-Lip-AC hydrogel. The system exhibited significant TMP entrapment (approximately 75%), sustained release via skin and dialysis membranes, and CS-mediated antibacterial properties that inhibited bacterial colonization. In vitro, T-Lip-AC demonstrated comparable efficiency to free TMP in scavenging DPPH and H_2O_2 radicals. In a DNCB-induced AD mouse model, it accelerated wound healing, reduced scratching activity and epidermal hyperplasia, normalized splenomegaly, enhanced SOD activity, and lowered MDA levels when compared to TMP or liposomes alone. The findings underscore the potential of alginate–chitosan–liposome hydrogels for concurrent transdermal delivery, antimicrobial defense, and antioxidant/anti-inflammatory treatment in AD(Xia et al., 2024). Integrating these design and assessment methodologies allows for the formulation of chitosan nanocarriers that can effectively and safely deliver anti-inflammatory agents for the topical management of atopic dermatitis.

Conclusion

The integration of chemical adaptability and biological safety of chitosan underpins its extensive use in various drug delivery systems, including oral, buccal, nasal, pulmonary, ocular, and transdermal applications. Through the strategic selection of modification and formulation techniques, chitosan systems can achieve controlled release, precise tissue targeting, and reduced dosing frequency. The promising preclinical results in atopic dermatitis—employing mucoadhesive, pH-sensitive, and occlusive chitosan nanocarriers—highlight its potential for dermatological applications. Upcoming obstacles will involve the need to standardize production processes, ensure long-term stability, and navigate regulatory pathways. Advancing multifunctional chitosan composites and rigorous in vivo validation will be crucial for translating these promising nanocarriers into effective and safe treatments for complex diseases.

Future Aspects

Leveraging its established safety profile and diverse chemical properties, upcoming chitosan platforms for atopic dermatitis (AD) will evolve into fully "smart" and barrier-responsive systems. By integrating sensor components that react to local pH variations or inflammatory biomarkers, these carriers can deliver calcineurin inhibitors or biologics precisely when and where they are required. Innovations in 3D bioprinting will enable the creation of patient-specific chitosan hydrogel patches that precisely match lesion geometry, incorporating occlusion, hydration, and extended drug release capabilities. The co-encapsulation of probiotics or microbiome-stabilizing peptides within chitosan nanocarriers presents a synergistic approach, enhancing the microbial barrier of the skin while simultaneously delivering anti-inflammatory actives. Simultaneously, the development of thiolated–quaternized chitosan derivatives is expected to enhance adhesion strength and facilitate penetration into the hyperkeratotic stratum corneum associated with chronic AD, which may lead to a reduction in dosing frequency and systemic exposure. In addition to its applications in dermatology, chitosan's properties such as biodegradability, biocompatibility, and recognized safety enable its utilization across various fields including food, cosmetics, water treatment, agriculture, and biomedical engineering. Through the modulation of properties such as mucoadhesion, antimicrobial action, pH responsiveness, and surface charge, researchers have developed a variety of delivery vehicles, including nanoparticles, emulsions, micelles, microcapsules, and hydrogels. This review establishes the theoretical basis for upcoming advancements in modified chitosan systems, highlighting non-invasive administration methods and advanced formulation techniques. Adopting these innovative platforms requires a collaborative approach across various fields, extensive GMP-compliant production of chitosan derivatives, and rigorous, well-supported clinical trials to deliver personalized, minimally invasive treatments that effectively restore, protect, and stabilize atopic skin.

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Abbreviations: So HST: School of Health Sciences and Technology; UPES: University of Petroleum and Technology; PLGA: Poly (lactic-co-glycolic acid); FTIR: Fourier transform infrared; XRD: X-Ray diffraction analysis; TEM: Transmission electron microscopy; SEM: Scanning electron microscopy; NP: Nanoparticles; BHDC: benzyl-n hexadecyltrimethylammonium chloride; AOT RMs; Sodium 1,4-bis-2-ethylhexylsulfosuccinate; CS; Chitosan; MNPs; Metal nanoparticles; TPP; Tripolyphosphate; RMs: Reverse micelles; DD: Deacetylation; TMC: N-trimethyl chitosan chloride; ZNO: Zinc oxide; TiO_2: Titanium dioxide; MMT: Montmorillonite; HPMC: Hydroxypropyl methylcellulose.

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