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REVIEW

Symmetry and Scale: The Precise Engineering of Chitosan-Based Polyhedral for the Delivery of Therapeutic Materials at the Nanoscale

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ABSTRACT

Preparation of chitosan-based drug delivery carriers requires converting linear polysaccharide chains into individual 3D objects. By building on the natural structural properties of chitin-based polymers, in addition to control the geometry of organically derived raw material from feedstock to submicron polyhedral or spherical dimensions. This geometric change is governed by a surface area-to-volume ratio that maximizes the exposure of the therapeutic payload to the external environment.

The approach centres on the development of such carriers using ion-complexation and emulsification methodologies, which involve electrostatic cross-linking of ion-binding pairs to define an impenetrable boundary separating a liquid from a solid phase. Critical geometric factors, namely particle radius (size) and internal fill (loading efficiency), were optimized. A relatively low porosity was introduced by tuning the crosslinking density, which dictates the flow rate of the enclosing agents from the central region towards the periphery.

The resulting configurations exhibit a degree of ordering in their packing and distribution, which is suitable for the spatial positioning of active agents within the defined geometric framework with accuracy. Targeted delivery depends on the direction and homing of nanoparticles towards specific biological targets. Using a sustained-release curve, the system maximizes bioavailability-density at the target site while minimizing volumetric dispersion in regions other than the systemic circulation.

Keywords: Geometry, Chitin-based, Methodologies, Nanoparticles, Drug dilevery

1. Introduction to chitosan-based nanoparticles

1.1. Principles of structural engineering in nanomedicine and targeted delivery

This shift in nanomedicine engineering involves moving from a focus on chemistry (mass) to design (structure). Crucial design considerations include size control, as nanomaterials (approximately 5×10^{-9} m) have a large surface area-to-volume ratio [1]. Engineers have exploited this property to increase the density of functional groups (bonds) on the particle surface, thereby increasing its affinity for specific cells [2]. Surface engineering such as coating nanoparticles with polymers like polyethylene glycol (PEG), protects the particles from recognition by the immune system (stealth). Encapsulation agents, such as antibodies or peptides, also enable active targeting. Nanocarriers (smart carriers) can be designed to modify their shape or release drugs in the presence of specific environmental stimuli such as changes in pH (tumor acidosis), temperature, or magnetic fields [3]. The biocompatibility and degradability that can

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be used are materials (fats, polymers, or metals) with predictable degradability rates that allow for the safe disposal of the (scaffold) or (carrier) [4].

There are many engineering application in medicine, one of the most important is pharmacokinetics (targeted drug delivery) where the engineers design nano-carriers such as liposomes, polymer micelles and dendrimers for entrapping toxic drugs. Three fundamental problems are solved in this feat of engineering: (1) **solubility**, to facilitate the transport of a drug through the blood if it is unusually hydrophobic (2**) protection**, to shield fragile molecules (as with messenger RNA in COVID-19 vaccines) from enzymatic degradation. (Placement) Taking advantage of the enhanced permeability and retention (EPR) effect, wherein nanomaterials tend to accumulate in the porous vasculature of tumors [5]. Nanomaterials and imaging allow for construction of novel optical and magnetic functionality particles early detection of disease [6]. Quantrum dots (semiconductor nanocrystals, which emit at distinct wavebands of light for high resolution cellular imaging) and supermagnetic iron oxide nanoparticles are developed as contrast agents to improve sensitivity MRI findings [7]. Such is the case of nanosensors added to microfluidic chips able to identify biomarkers (such as cancer proteins) in a single drop of blood. In the field of regenerative medicine, particularly tissue engineering, nanomaterials pose as ECM-like scaffolds [8].

Nanomedicine represents a revolutionary advancement in healthcare, utilizing nanoscale materials and technologies to diagnose, manage, and prevent diseases [9]. This rapidly advancing field takes advantage of the unique properties of nanoparticles to enhance the effectiveness of drug delivery systems. Notably, nanoparticles made from biocompatible and biodegradable materials such as chitosan are at the forefront, primarily due to their capacity to improve drug stability, bioavailability, and targeted delivery [10].

(CNPs) are a specific type of nanocarrier recognized for their beneficial characteristics, including low toxicity, biodegradability, and compatibility with biological systems. Obtained from chitin through deacetylation, chitosan's natural polymer origins contribute to these important attributes [11]. Its cationic nature allows it to interact with negatively charged biomolecules like DNA and proteins, facilitating encapsulation and enhancing therapeutic efficacy. This interaction is particularly advantageous for improving drug absorption across various biological barriers. A major advantage of nanomedicine is its ability to enable targeted drug delivery [12]. By designing nanoparticles that deliver specific therapeutic agents directly to affected tissues or cells while minimizing exposure to healthy ones, side effects can be significantly reduced. This precision is especially critical in cancer treatment, where conventional therapies often cause collateral damage to healthy tissues. Researchers have demonstrated that CNPs can effectively carry a variety of drugs intended for localized treatment applications, including ocular drug delivery, pulmonary therapies, and gene therapy [13].

Moreover, nanoparticle-based systems allow for controlled release profiles that further improve therapeutic outcomes. These systems can be designed to release drugs at specific rates or in response to defined stimuli such as pH changes or enzymatic activities within targeted environments like tumors or inflamed tissues [14]. This level of precision closely resembles natural physiological processes compared to traditional drug administration methods.

The versatility of CNPs extends beyond cancer treatment; they are also being explored for immunotherapy and vaccine development due to their potential as carriers that enhance immune responses by effectively delivering antigens. Their flexibility also applies to oral drug delivery applications, where they can help overcome gastrointestinal barriers that often limit the bioavailability of therapeutic agents [15].

As research in nanomedicine progresses, there is a strong focus on improving synthesis techniques for CNPs to further enhance their performance. Various methods, such as ionic gelation or emulsion techniques, are being utilized not only for encapsulating therapeutic agents but also for improving essential physicochemical properties necessary for effective drug delivery systems, including stability and scalability [16].

1.2. Importance of drug delivery systems

The development of effective drug delivery systems (DDS) is crucial for enhancing therapeutic efficacy and minimizing adverse effects. DDS are designed to transport drugs safely and efficiently to specific target areas. Among various methodologies, chitosan-based nanoparticles (CNPs) have gained attention as promising carriers due to their biodegradability, biocompatibility, and low toxicity [17].

CNPs significantly improve the stability and bioavailability of drugs by encapsulating them, protecting them from degradation and allowing for tailored release profiles based on therapeutic needs. They can be engineered to respond to changes in pH or temperature, enabling controlled release at specific locations and rates. Another advantage of CNPs is their ability for targeted delivery. By modifying their surface properties with targeting ligands or

antibodies, these nanoparticles can preferentially bind to certain cell types or tissues. This targeted approach enhances drug effectiveness by increasing local concentrations at disease sites while reducing systemic exposure and side effects [18]. Recent advancements highlight the versatility of chitosan nanoparticles across various administration routes, including oral, nasal, pulmonary, and ocular pathways. Their mucoadhesive properties allow for prolonged retention on mucosal surfaces, improving absorption, while their positive charge promotes cellular uptake, making them valuable for non-parenteral applications where patient adherence is critical [19].

Additionally, chitosan-based systems support combination therapy strategies by encapsulating multiple therapeutic agents within a single nanoparticle, facilitating synergistic effects that enhance treatment outcomes, especially in addressing drug resistance in cancer therapies [20]. Despite these benefits, challenges in formulating effective CNPs remain, particularly in achieving optimal drug loading efficiency. Many existing systems struggle with low encapsulation efficiency, limiting clinical practicality. Ongoing research aims to refine synthesis methods and formulation strategies to enhance loading capacity and controlled release [21].

Moreover, thorough long-term safety assessments are vital before widesprea clinical application of CNPs. Preclinical studies must investigate potential immune reactions and systemic toxicity risks to ensure patient safety. Ultimately, chitosan-based nanoparticles present significant opportunities for improving drug delivery, therapeutic effectiveness, and reducing side effects associated with conventional treatments [22].

1.3. Properties of chitosan

Chitosan, derived from the deacetylation of chitin, is highly regarded for its wide array of properties that make it an essential component in drug delivery systems. One of its key attributes is biocompatibility, which allows it to be easily integrated into various therapeutic formulations without causing adverse reactions in biological systems. This quality ensures that nanoparticles made from chitosan can interact safely with body tissues. Furthermore, chitosan is biodegradable, allowing it to break down naturally within the body and reducing the risks of accumulation and toxicity that are often associated with synthetic polymers [23].

Another important characteristic of chitosan is its cationic nature, resulting from the presence of amino groups in its molecular structure. This positive charge provides CNPs with remarkable mucoadhesive properties, greatly enhancing their interactions with mucosal membranes and promoting prolonged retention at targeted sites. These attributes are particularly beneficial in oral drug delivery applications where sustained release and specific localization are crucial for achieving therapeutic effectiveness [24].

Chitosan demonstrates excellent encapsulation efficiency due to its capacity to form nanoparticles through various innovative synthesis methods, such as ionic gelation and emulsion techniques. The inherent physicochemical properties of chitosan facilitate the encapsulation of a wide range of bioactive compounds, especially hydrophilic drugs that typically face challenges in traditional delivery systems due to solubility issues. As a result, CNPs can significantly improve the solubility and stability of therapeutic agents while addressing degradation concerns [25].

The surface properties of these nanoparticles can be easily modified through chemical alterations aimed at enhancing targeting capabilities or optimizing drug release profiles. Such modifications enable the engineering of CNPs with specific surface charges or ligands that promote binding to designated cells or tissues. This adaptability in design makes them suitable for various therapeutic applications, including cancer treatment and management of localized diseases [26].

Moreover, one notable feature of (CNPs) is their pH-sensitive behavior, which stems from their polyelectrolyte characteristics due to the amino groups. In acidic environments—like those found in gastrointestinal tracts or tumor microenvironments—these nanoparticles can undergo rapid swelling or de-swelling transitions that facilitate controlled release of encapsulated drugs in response to local pH changes. This ability ensures that treatments are precisely adjusted according to specific physiological conditions, optimizing both timing and dosage [27].

Additionally, chitosan possesses inherent antibacterial properties that provide further advantages as a drug carrier by protecting against microbial contamination during the formulation and application phases. This aspect not only enhances the safety profile of drug delivery systems utilizing CNPs but also broadens their applicability beyond conventional pharmaceuticals to include areas such as wound healing and infection management [28].

2. Synthesis methods for drug-loaded nanoparticles

2.1. Ionic gelation technique

2.1.1. Mechanism of ionic gelation

Ionic gelation is a widely used method for creating (CNPs), primarily due to its simplicity and efficiency.

Table 1. Principles of structural engineering in nanomedicine and targeted delivery.

Parameter	Chitosan Nanoparticle Delivery	Conventional Delivery	Significance	References
Drug Bioavailability	High	Moderate to Low	Improved drug absorption	[29]
Release Kinetics	Controlled	Rapid	Reduced side effects, sustained therapeutic effect	[30]
Targeting Efficiency	Enhanced	Non-specific	Increased drug delivery to the tumor site	[31]
Systemic Toxicity	Reduced	Higher	Enhanced safety profile	[32]
Biodegradability	High	Variable	Eco-friendly, reduced long-term effects	[33]
Stability of Formulation	Improved	Prone to degradation	Extended shelf life	[34]
Encapsulation of Various Drugs	Yes	Limited	Versatile drug delivery system	[35]
Controlled Drug Release	Yes	No	Maintained therapeutic concentration over time	[30]
Clinical Translation	Expanding	Established	Emerging technology with potential	[11]

This technique relies on the electrostatic interactions between the amino groups of chitosan, a polycationic polymer, and negatively charged polyanions like tripolyphosphate (TPP) [36]. When these components are combined in an aqueous solution, they interact through ionic bonds, leading to the formation of gels. This process aids in the creation of nanoparticles by encouraging the aggregation of these oppositely charged particles [37].

The ionotropic gelation method starts with dissolving chitosan in an acidic environment, producing a soluble form of the biopolymer. The solubility of chitosan, which is significantly affected by its degree of deacetylation, influences its interaction with polyanions during nanoparticle synthesis. Once a uniform chitosan solution is achieved, TPP is carefully added dropwise while stirring, ensuring an even distribution of TPP throughout the solution. When TPP is not in intimate contact with chitosan, the crosslinking of TPP was initiated and subsequently created a 3D network that encapsulates drugs within a polymer matrix. A mechanism of electrostatic attractions between TPP phosphate group with the amino group on chitosan backbone, as well as ensuring good stability and integrity during particle formation and drug-loaded process [38].

The particle size, shape and entrapment efficiency are dependent on the pH value, chitosan/TPP concentration ratio, as well as stirring velocity. Hence, the higher TPP solution concentration and crosslinking density are correlated but can result in larger particle size if one is not careful. Conversely, not enough TPP can form a poor and fragmented nanoparticle [39].

The ion gelation method is moreover a key contributor in managing the drug release behavior of such nanoparticles as well with a vital role upon their entry to medical applications. The profiles of release are influenced by multiple parameters, such as the size, the charge and the hydrophilicity or hydrophobicity on their surface conferred by chemical modifications during synthesis. Generally, d smaller particles have higher diffusivity than the larger ones due to larger surface area per volume [40].

Furthermore, when utilized for drug delivery, achieving suitable zeta potential values is essential for maintaining stability in suspension; typically, values above +30 mV provide strong colloidal stability due to electrostatic repulsion among particles. Additionally, the choice of drug affects encapsulation efficiency; drugs with functional groups that can interact favorably with either chitosan or TPP are generally loaded more efficiently because of enhanced binding interactions [41].

Recent studies have shown that variations in sonication time during nanoparticle synthesis can also affect physical characteristics such as size distribution and stability. For example, optimizing sonication durations can lead to more uniform formulations and reduce the tendency for agglomeration in dispersions [42].

In summary, ionic gelation is an effective strategy for producing biodegradable nanoparticles with controlled release properties, making them suitable for a range of therapeutic applications, including cancer treatment and targeted antibiotic delivery systems, while addressing toxicity issues often linked with traditional therapies [43].

2.1.2. Advantages and limitations

(CNPs) are considered as a promising candidate for drug delivery system owing to its biocompatible and biodegradable properties. Chitosan, a natural polymer obtained from chitin is less toxic and human body compatible; thus suitable for pharmaceutical

Table 2. Advantages and limitations& challenges.

Category	Advantages	Limitations & Challenges
Biocompatibility	Exceptional biocompatibility, biodegradability, and low toxicity; derived from natural chitin.	Potential toxicity concerns when using complex cross-linking agents to improve stability.
Drug Protection	Protects therapeutic agents (proteins, peptides) from enzymatic degradation; improves solubility.	Achieving optimal loading capacity for larger molecules or specific release kinetics remains difficult.
Targeting & Adhesion	Strong **mucoadhesive properties**; prolongs residence time at mucosal sites (e.g., GI tract).	Stability in various physiological conditions over long periods is not always guaranteed.
Surface Engineering	Highly versatile for chemical modifications to tailor surface charge and specific targeting.	Sensitivity to synthesis variables (pH, temperature); leads to fluctuations in particle size and morphology.
Release Kinetics	Enables tailored release profiles through methods like ionic gelation.	**pH-dependent solubility:** Limited responsiveness in non-neutral environments, affecting release in acidic/basic tissues.
Clinical Readiness	Promising *in vitro* results observed against various disease models.	Regulatory barriers; requires comprehensive *in vivo* pharmacokinetic assessments and long-term safety evaluations.

applications. By using different nanoparticle formation methods such as ionic gelation, the encapsulation of therapeutic agents including proteins, peptides, and hydrophobic drugs can be well realized leading to improved solubility and bioavailability of the drug protecting it from enzymatic degradation [44].

The mucoadhesive properties of chitosan enable it to bind with specific mucosal tissues promoting a prolonged residence at predetermined sites within the gastrointestinal tract or other mucosal regions and hence enhance therapeutic efficiency. In addition, chitosan nanoparticles can be designed for particular biomedical applications by chemical modifications leading to charge or surface change.

However, challenges exist in the development of (CNPs) for drug delivery. Synthetic changes can cause fluctuation on particle size or morphology which is strongly controlled by variables, such as temperature and the concentrations of reagent. These discrepancies can influence the drug-release kinetics and efficacy. Additionally, ionic gelation yields sturdiest particles is not guaranteed to be stable over a long period of time in physiological conditions [45].

Chitosan has a limited pH responsiveness and a change in its solubility and ionization can be induced at different pH, importantly drug release behavior in non- neutral environment would be influence. Thus, alternative methods may be necessary for effective release of drugs into acidic- or basic-habituated tissues [30].

Moreover, achieving optimal loading capacity remains difficult, particularly with larger molecules or those requiring specific release kinetics. Enhancements to loading efficiency might necessitate complex formulations or cross-linking agents, potentially raising toxicity concerns.

Although encouraging in vitro results have been observed against various disease models, comprehensive in vivo assessments are still needed to evaluate pharmacokinetics and therapeutic effectiveness before clinical approval. Regulatory barriers related to biocompatibility and long-term safety evaluations also pose challenges to the clinical application of chitosan-based nanoparticles [46].

2.2. Emulsion techniques

2.2.1. Types of emulsion techniques

Emulsion methodologies are crucial in the production of (CNPs), particularly for drug loading applications. This emulsion process involves creating a heterogeneous mixture where one liquid is suspended in another that does not mix with it. Different types of emulsions can be classified based on which phase is dispersed and the type of emulsifiers used [48].

A common method is the water-in-oil (W/O) emulsion technique, where an aqueous phase containing chitosan or therapeutic agents is suspended in an oil phase. This technique helps encapsulate hydrophilic drugs, allowing for controlled release profiles due to the surrounding oil matrix. Conversely, an oil-in-water (O/W) nanoparticles emulsion can also be utilized, dispersing oil droplets in a water-based solution. These emulsions are especially advantageous for incorporating hydrophobic drugs into formulations enhanced with water-soluble polymers like chitosan. Another approach is miniemulsion techniques, which stabilize small droplets using surfactants or co-surfactants to prevent coalescence [49]. Miniemulsions typically yield NPs within the 50-500 nm size range, making them suitable for applications requiring high surface area and effective drug loading capabilities. The stability and characteristics of miniemulsions are significantly influenced by the choice of surfactant and processing conditions such

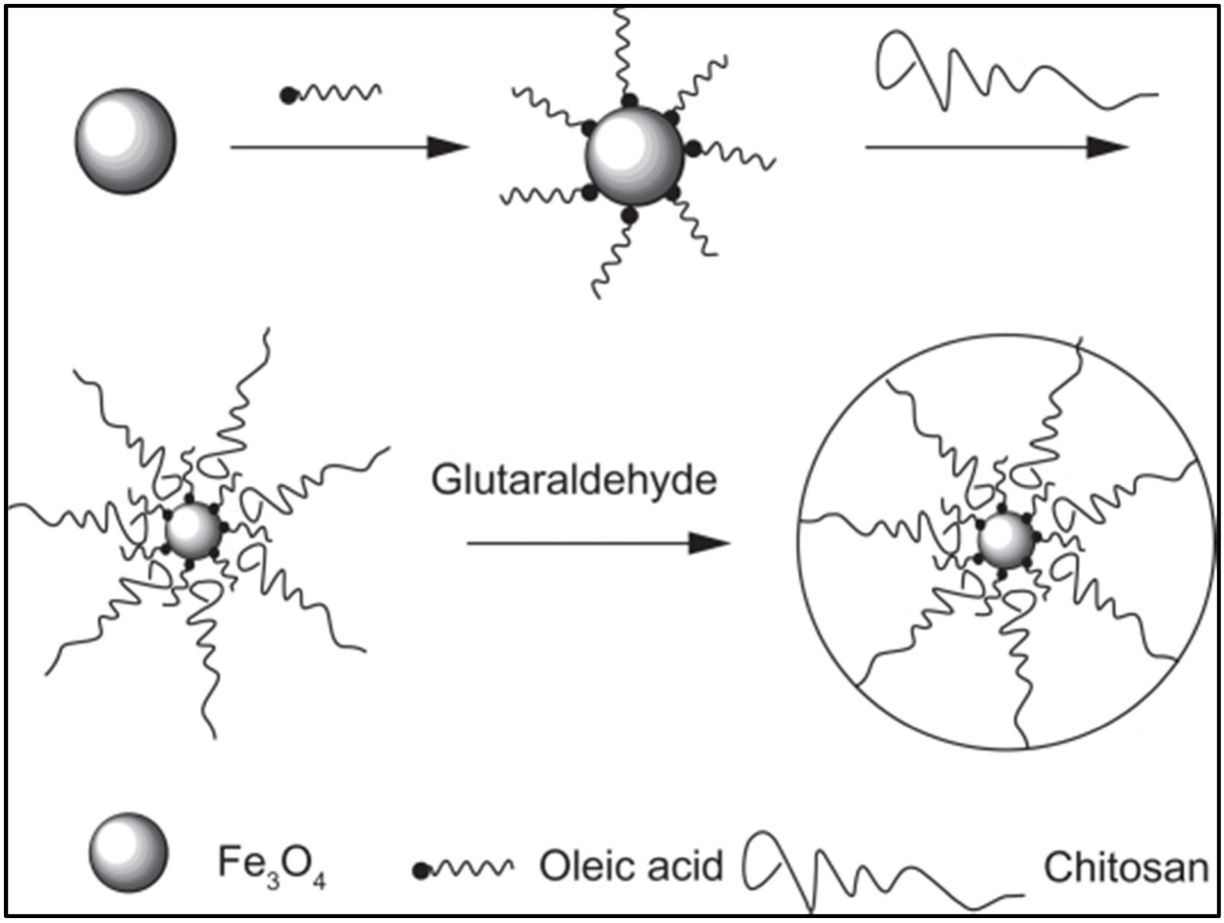

Fig. 1. Representation of Fe_3O_4 -(CNPs). (Wang et al., 2011) [47].

as stirring speed and duration. Gas-in-water-in-oil (G/W/O) double emulsions represent a more complex technique that facilitates the creation of porous structures within (CNPs). In this method, gas bubbles are introduced into an aqueous chitosan solution before its emulsification in an oil phase. This innovative strategy not only enhances porosity but also greatly increases drug loading capacities due to the larger internal surface areas available for adsorption or encapsulation [50].

Membrane emulsification presents a more energy-efficient alternative compared to traditional methods like ultrasonic emulsification or high-pressure homogenization. By using specially designed membranes with specific pore sizes, this method allows for controlled droplet formation while reducing energy consumption during particle synthesis. Membrane emulsification can produce uniform particles with narrow size distributions, essential for predicting drug release behaviors [51].

The effectiveness of these emulsion techniques is further influenced by several factors, including surfactant concentration, stirring velocity, temperature, and the molecular weight of chitosan used in the synthesis process. Additionally, incorporating cross-linkers during nanoparticle fabrication can enhance mechanical stability while controlling drug release kinetics from the final product [52].

2.2.2. Impact on particle characteristics

Emulsion methodologies play a crucial role in creating (CNPs) for drug delivery, significantly affecting their physical properties. The emulsification technique chosen impacts the size, shape, and encapsulation efficiency of NPs, typically ranging from 50 to 500 nm. This size range enhances drug bioavailability and cellular uptake due to a higher surface area-to-volume ratio [48].

The mechanical properties of NPs can be tailored by incorporating different materials during the emulsion process. For instance, hybrid systems combining chitosan with silica improve mechanical stability and modify drug release profiles. Silicate presence influences therapeutic release from the polymer matrix,

often resulting in prolonged release rates compared to pure chitosan [53].

Several factors affect the morphology of (CNPs) during synthesis, including emulsifier type and concentration, pH, and ionic strength of the aqueous phase. Adjusting these parameters allows for changes in particle shapes from spherical to irregular, which is critical for biological interactions. Spherical particles tend to distribute more uniformly in blood circulation than irregularly shaped ones [54].

Porosity also plays a key role in determining drug loading capacity and release kinetics. Research indicates that porous chitosan micr-oarticles achieve greater drug loading efficiencies due to increased surface area for adsorption or encapsulation, supporting gradual and controlled release profiles [50].

Temperature variations and cross-linking conditions are significant in influencing nanoparticle characteristics. Changes in temperature can affect emulsion viscosity and droplet behavior, while cross-linking agents like tripolyphosphate(TPP) induce gelation, impacting both particle morphology and drug release dynamics [55].

Optimizing these synthesis conditions aims to produce NPs with desirable physical traits and optimal therapeutic profiles for specific applications, such as targeted delivery or pH-responsive mechanisms for cancer therapies. Utilizing natural polymers like chitosan enhances biocompatibility and reduces toxicity concerns associated with synthetic polymers. Chitosan's biodegradability ensures non-toxic degradation products, making it an ideal candidate for sustainable drug delivery platforms [56].

3. Optimization parameters in nanoparticle development

3.1. Particle size optimization

The optimization of particle size is a crucial element in formulating (CNPs) for drug delivery, as it significantly influences the behavior, stability, and efficacy of these nanocarriers. The ionic gelation technique is a widely used method for producing (CNPs), with various factors intricately affecting the resulting particle size [25].

Key factors include the concentrations of chitosan and tripolyphosphate (TPP), the pH levels during synthesis, and operational parameters such as stirring speed and duration [57].

Chitosan concentration plays a critical role in determining the final particle size. Higher concentrations typically lead to larger NPs due to increased interactions among polymer chains, which can cause aggregation [58]. Conversely, lower concentrations may produce smaller NPs but could compromise mechanical stability or decrease encapsulation efficiency. Research suggests that there exists an optimal range for chitosan concentration; for instance, concentrations below 2.5 mg/mL might impede proper nanoparticle formation due to excessive cross-linking with TPP, whereas exceeding this optimal threshold could result in larger aggregates instead of distinct NPs [59].

The concentration of TPP is equally vital in controlling particle dimensions through ionic gelation. As TPP levels increase relative to chitosan, the density of interactions rises, enhancing cross-linking effects and leading to varying nanoparticle sizes. Even minor adjustments in TPP concentration can produce significant changes; one study demonstrated that increasing TPP could shift mean diameters from around 152 nm to approximately 393 nm depending on specific experimental conditions. The pH during synthesis also holds considerable importance. Chitosan's solubility depends on its protonation state in acidic environments; thus, adjusting pH can affect charge interactions between chitosan and TPP molecules. The ionic strength associated with different pH levels greatly influences how these compounds interact during nanoparticle formation, ultimately impacting their final dimensions [60].

Stirring techniques are also crucial, affecting micromixing dynamics throughout synthesis and thereby influencing particle size distribution. High-speed stirring generates shear forces that promote homogenization but may unintentionally lead to larger particles if not carefully monitored [61].

Temperature variations during formulation steps additionally influence reaction kinetics and thermodynamics, resulting in differences in molecular arrangement that affect final size characteristics. Cooler temperatures generally increase viscosity, potentially slowing down particle formation rates and leading to larger aggregates [62].

To ensure accurate evaluations post-synthesis, characterization methods such as dynamic light scattering (DLS) and scanning electron microscopy (SEM) are routinely employed to assess hydrodynamic diameters along with polydispersity indices (PDI). Favorable formulations usually exhibit low PDI values, indicative of narrow size distributions—features that are beneficial for controlled drug release profiles [63].

3.2. Encapsulation efficiency improvement strategies

Encapsulation efficiency is crucial in develo tripolyphosphate (TPP) ping (CNPs) for drug

Table 3. Tripolyphosphate (TPP): Average particle size of (CNPs) prepared at different concentrations [64].

Particle Size Optimization Mechanisms	Limitations	Advantages	Category
Using natural cross-linkers to stabilize the matrix without increasing biological toxicity.	Regulatory barriers regarding long-term safety evaluations.	Biocompatible, biodegradable, and low toxicity.	**Biological**
Precise control of the: solvent pH during synthesis to influence the degree of ionization and hydrodynamic diameter.	Limited pH responsiveness; solubility issues in non-neutral environments.	Mucoadhesive; enhances drug solubility and bioavailability.	**Functional**
Fine-tuning the concentrations of reagents and temperature to prevent particle aggregation and maintain uniform morphology.	Instability over long periods in physiological conditions.	Can be modified for specific surface charges or ligands.	**Physical**
Adjusting the chitosan to-stabilizer ratio (e.g., TPP) to ensure efficient entrapment while maintaining a nanometric scale.	Difficult to achieve optimal loading for large molecules.	Capable of encapsulating proteins and hydrophobic drugs.	**Loading**

delivery, significantly affecting therapeutic effectiveness. Various strategies have been explored to enhance this efficiency by modifying the physicochemical properties of both chitosan and the encapsulated drug [65].

One effective approach is altering chitosan's molecular weight and degree of deacetylation. Higher molecular weight chitosan correlates with improved encapsulation efficiencies due to increased viscosity, facilitating better drug entrapment. Studies indicate that medium molecular weight chitosan can achieve encapsulation efficiencies between 27.4% and 88.6%, depending on formulation conditions and drug characteristics [66].

The ionic gelation method also enhances encapsulation through electrostatic interactions between positively charged chitosan and negatively charged crosslinkers like tripolyphosphate (TPP). By adjusting TPP concentrations during nanoparticle assembly, researchers can fine-tune particle size and surface charge, impacting drug loading. For instance, quaternized aminated (CNPs) demonstrated a significant increase in curcumin encapsulation efficiency, reaching up to 94.4% [67].

Incorporating additives such as surfactants or stabilizers during production can further improve drug loading and stability. Surfactants enhance solubility and dispersion, reducing agglomeration and promoting even drug distribution within the polymer matrix. Additionally, using hydrophilic polymers like polyethylene glycol (PEG) alongside chitosan has shown promise in increasing encapsulation rates while maintaining controlled release profiles. Hybrid systems combining different NPs offer another strategy to boost encapsulation efficiency. For example, integrating magnetic nanoparticles into chitosan formulations aids targeted delivery and modifies drug release dynamics via external magnetic fields or environmental pH changes [68].

Optimizing preparation techniques is vital for achieving high loading efficiencies without compromising drug stability or release kinetics. Microfluidics technology allows precise control over particle size and distribution, leading to superior encapsulation outcomes [69].

Post-synthesis modifications, such as surface functionalization, enable targeted drug-na NPs noparticle interactions that improve retention and release profiles. Understanding the molecular dynamics between chitosan matrices and drugs, including hydrophilicity/hydrophobicity ratios, is essential for enhancing loading capabilities and therapeutic efficacy while minimizing side effects from traditional formulations [70].

3.3. Controlled release profiles analysis

CNPs are of paramount importance in improving drug delivery systems, especially in therapeutic settings. The mechanisms that govern the release are influenced by various factors, including the physicochemical properties of both the encapsulated drug and the chitosan matrix, as well as the environmental conditions present during administration. Numerous studies have shown that CNPs typically exhibit a biphasic release profile, characterized by an initial rapid release followed by a slower, sustained phase. This early burst effect is often associated with drugs that are adsorbed onto the surface of the NPs s or located within their outer layers, dissolving quickly upon contact with an aqueous environment [71].

The efficiency of encapsulation and the subsequent release kinetics depend on variables such as particle size, cross-linking density, and pH levels. Research indicates that smaller NPs s tend to have a larger surface area relative to their volume, which enhances the dissolution rate of the encapsulated agents. The pH-sensitive nature of chitosan plays a vital role in controlling drug release rates drugs encapsulated within (CNPs) may demonstrate different release profiles under varying pH conditions often in acidic or

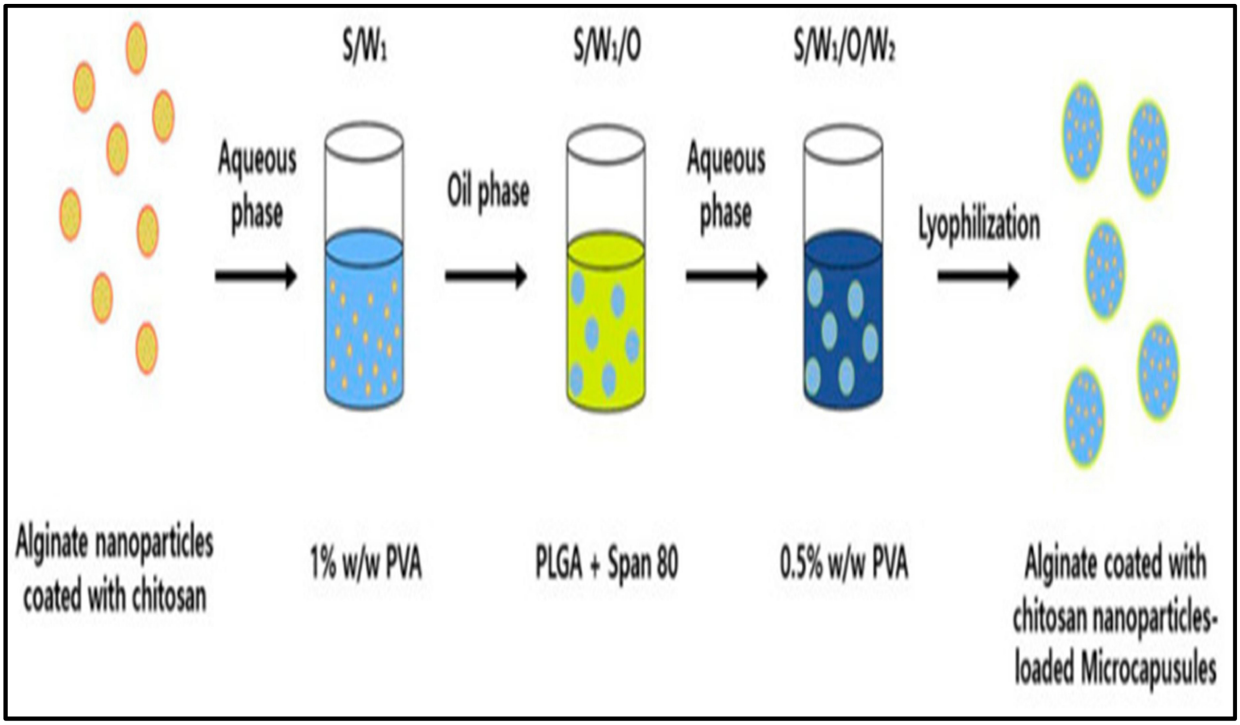

Fig. 2. Illustration of the encapsulation of metoprolol tartrate (MET)-loaded alginate coated with (CNPs) into poly (DL-lactide-co-glycolide) (PLGA) microcapsules.

alkaline environments found in biological systems [72].

A relevant case study involving rifampicin-loaded CNPs showed that these NPs s achieved better delivery efficiency at an alkaline pH (pH 8) compared to acidic (pH 4) or neutral (pH 7) conditions. This finding suggests that customizing CNP formulations could provide significant advantages for specific therapeutic applications where precise localized drug delivery is essential [73].

Mathematical modeling is a key tool for evaluating and predicting drug release kinetics from CNPs. Commonly used models include zero-order kinetics, first-order kinetics, the Higuchi diffusion model, and the Korsmeyer-Peppas model. By comparing these kinetic models with experimental data from in vitro drug release studies, researchers can gain valuable insights into how changes to CNP formulations impact their performance. For example, increasing the molecular weight of chitosan or adjusting its deacetylation degree can enhance its adhesion to mucosal surfaces, thereby improving bioavailability and prolonging retention times within targeted tissues [74].

Additionally, cross-linking agents like tripolyphosphate (TPP) can be added during the synthesis of NPs s to optimize the mechanical strength and permeability of chitosan matrices. Such modifications enable controlled adjustments in drug release rates tailored to therapeutic needs, ensuring optimized pharmacokinetics while minimizing side effects [75].

Recent research also highlights the importance of external stimuli, such as ultrasound or magnetic fields, which can further refine release profiles from CNPs when combined with innovative material strategies. These approaches create opportunities for improved targeted delivery while managing systemic exposure [76].

In summary, analyzing controlled release profiles is vital for developing effective drug delivery systems using (CNPs). By understanding and manipulating the various factors affecting encapsulation efficiency and drug diffusion dynamics across different environments, researchers can significantly improve patient outcomes through more personalized therapeutic strategies [73].

4. In vitro evaluation methods for drug release

Carbon nanoparticles (CNPs) are crucial for understanding the kinetics and mechanisms of action that influence therapeutic efficacy. These methods evaluate drug release efficiency under controlled conditions that mimic physiological environments, using a variety of experimental setups to gain in-depth

insights into the performance of carbon nanoparticles [77].

The static diffusion method is commonly used, where drug-infused CNPs are immersed in a dissolution medium. Samples taken at specified intervals allow quantification of released drug concentrations, often analyzed using high-performance liquid chromatography (HPLC) or UV-Vis spectrophotometry. This technique helps construct cumulative drug release profiles, revealing key characteristics such as initial burst release and sustained release phases [78].

Dynamic systems like flow-through cells or rotating paddle devices provide a more accurate representation of physiological fluid dynamics. In these setups, continuous flow conditions impact drug release rates by altering diffusion gradients, enabling examination of how variables like shear stress influence release behavior from CNPs [79].

Chitosan's pH-sensitive nature adds complexity to drug release investigations. Its solubility in acidic environments means that pH shifts can alter swelling and change drug discharge rates. Analyzing release across various pH levels predicts CNPs functionality in different biological contexts, including gastrointestinal fluids or tumor microenvironments [80].

Temperature fluctuations are also significant, as they affect both polymer behavior and drug solubility. Conducting experiments at physiological temperatures (approximately 37 ˚C) is essential for generating relevant data. Mathematical modeling enriches understanding by analyzing kinetic data from experiments. Models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas help characterize mechanisms governing drug diffusion rates [81].

Factors influencing encapsulation efficiency are vital since they correlate with therapeutic efficacy. Higher encapsulation rates often lead to improved bioavailability and prolonged therapeutic effects.

Advanced imaging techniques, like confocal laser scanning microscopy or transmission electron microscopy, visualize structural changes in CNPs during dissolution, providing insights into morphological alterations associated with drug release. Cytotoxicity assays, such as the MTT assay, assess whether released drugs maintain efficacy without harming healthy cells, establishing safety margins for different drug concentrations. Integrating these methodologies effectively characterizes the performance of (CNPs) in controlled drug delivery systems [82].

5. Therapeutic applications of (CNPs)

5.1. Cancer treatment applications

(CNPs) have gained recognition as an effective method for the precise delivery of anticancer agents, addressing the limitations of traditional cancer treatments that often exhibit insufficient efficacy and significant side effects. A notable advantage of CNPs in oncology is their ability to encapsulate a variety of therapeutic compounds, including small molecules like doxorubicin, proteins, peptides, and nucleic acids such as siRNA. This versatility enables the development of customized formulations aimed at specific types of cancer cells and distinct tumor microenvironments [10].

The enhanced permeability and retention (EPR) effect is another important characteristic leveraged by (CNPs). Tumors typically have leaky blood vessels and impaired lymphatic drainage, which leads to a higher concentration of NPs s in tumor tissues compared to normal tissues. Studies have shown that CNPs not only improve drug solubility but also significantly enhance uptake by cancer cells, thereby increasing therapeutic effectiveness. For instance, doxorubicin encapsulated within (CNPs) has demonstrated reduced systemic toxicity while displaying greater cytotoxicity against breast cancer cells compared to its un-encapsulated counterpart [83].

To further increase specificity toward cancerous cells, targeting ligands can be attached to the surface of (CNPs). These modifications allow CNPs to target specific receptors that are overexpressed in certain tumors. An example of this is folate receptors, commonly found on the surface of various cancers such as ovarian and breast cancers. By designing (CNPs) with folate groups, researchers have successfully enhanced drug delivery specifically to these tumor types while reducing unintended effects.

Additionally, innovative formulations that combine CNPs with magnetic materials have been explored to improve targeting accuracy. By integrating superparamagnetic iron oxide NPs s into chitosan microspheres, scientists have developed a dual-responsive drug delivery system capable of achieving localized release prompted by external magnetic fields or internal pH changes within the tumor environment. This approach not only supports precise targeting but also enables rapid release profiles suitable for urgent therapeutic interventions [84].

Recent studies have underscored the potential of CNPs for delivering siRNA targeting anti-apoptotic genes such as Bcl-2, which is frequently overexpressed in various cancer types. The use of chitosan-based carriers has resulted in improved gene silencing efficiency and promotion of apoptosis in treated tumors, representing a promising pathway for integrating gene therapy with traditional chemotherapeutics [85].

Moreover, clinical trials involving CNPs have produced encouraging results across multiple cancer types. For example, formulations using thiolated

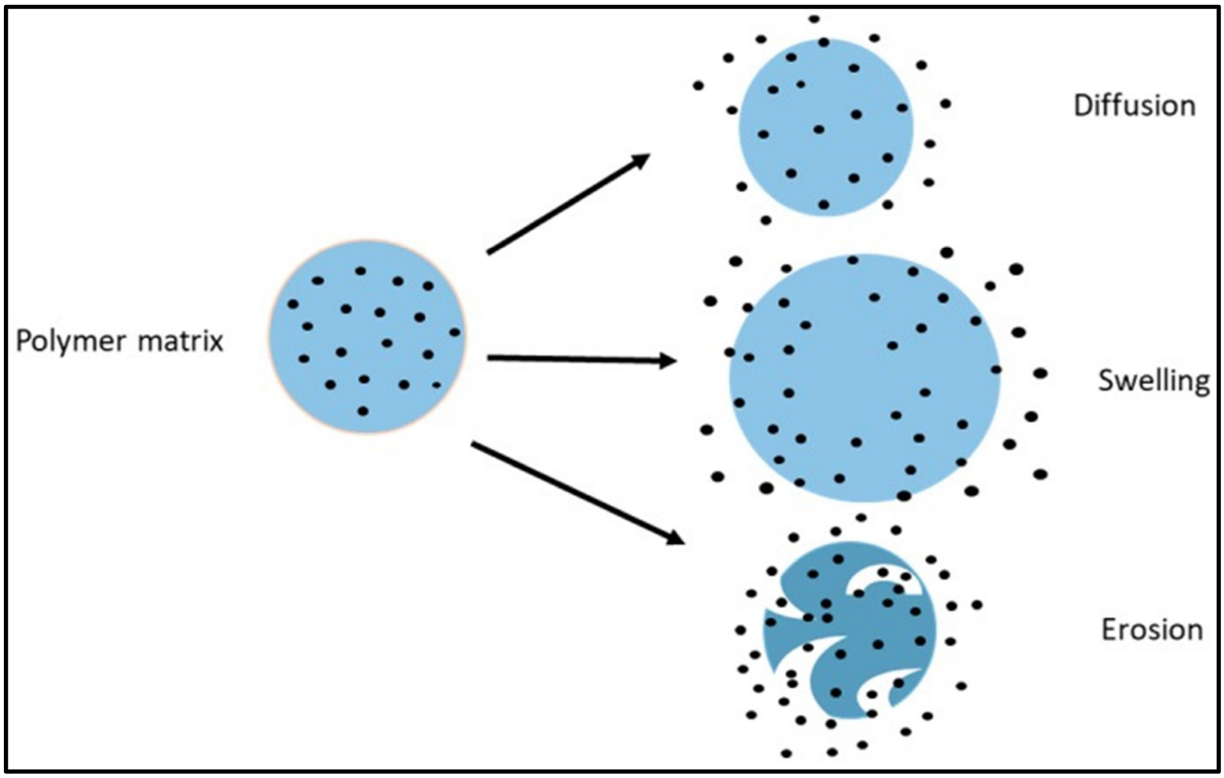

Fig. 3. Representing the possible mechanisms of drug release by diffusion, swelling and erosion of polymer (chitosan) matrix.

chitosan as a carrier for 5-fluorouracil (5-FU) have shown increased cellular uptake and cytotoxicity against triple-negative breast cancer cells compared to treatments with the free drug. The combination of sustained release properties with targeted delivery leads to superior therapeutic outcomes while reducing systemic side effects typically associated with conventional chemotherapy protocols.

In conclusion, (CNPs) represent a groundbreaking strategy to address many challenges posed by current anticancer therapies through their multifunctional capabilities—enhancing drug solubility, stability, targeted delivery, and controlled release profiles tailored specifically for various malignancies.

5.2. Targeted delivery mechanisms in therapeutics

The mechanisms of targeted drug delivery using (CNPs) have attracted significant attention due to their ability to enhance the effectiveness of anticancer therapies while reducing side effects. Chitosan, a non-toxic and biodegradable polysaccharide derived from chitin, is an excellent candidate for creating NPs that can specifically deliver drugs to tumor sites. Its unique properties, such as mucoadhesiveness, low toxicity, and ease of modification, support the development of NPs tailored for specific therapeutic needs.

One of the most effective methods for achieving precise drug delivery involves modifying the surface of (CNPs) with ligands that selectively bind to receptors overexpressed on cancer cells [20]. A key example is folate receptors (FRs), which are abundant in various cancers, including breast and ovarian cancer. By attaching folate to (CNPs), researchers have significantly improved the uptake of anticancer agents like doxorubicin in tumors expressing folate receptors. This approach not only increases drug concentration at targeted sites but also reduces the off-target effects typically associated with conventional chemotherapy [86].

In addition to ligand-targeting strategies, pH-sensitive release mechanisms have been incorporated into the design of chitosan-based NPs. Tumor microenvironments generally exhibit more acidic conditions compared to normal tissues. By engineering (CNPs) to dissolve or release their drug payload more effectively in these acidic environments, researchers can ensure that a higher concentration of medication is available exactly where it is most needed—at the tumor site itself. This pH-triggered release strategy can lead to prolonged therapeutic effects while minimizing systemic toxicity [30].

Another innovative approach being explored involves magnetic targeting using (CNPs). By

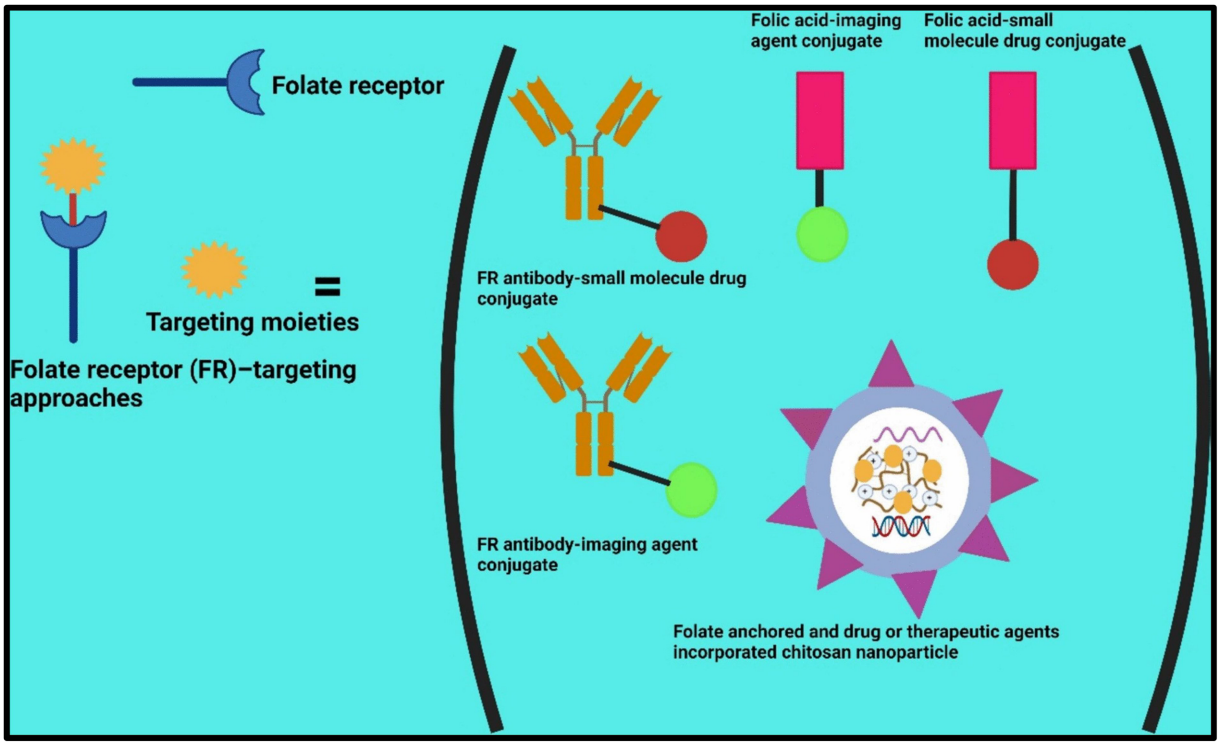

Fig. 4. Illustration demonstrating the method of conjugating folate receptor antibody or folic acid (FA) with small drug molecules or imaging agents; or anchoring FA into the chitosan (FA-chitosan conjugate) and anticancer drug incorporated NPs.

incorporating magnetic materials into the NPs formulation, it becomes possible to direct these carriers precisely to specific tumor locations using external magnetic fields. This method not only ensures localized delivery but also enhances treatment efficacy by concentrating anticancer agents directly at malignant sites [87].

Furthermore, encapsulating small interfering RNA (siRNA) within (CNPs) offers a novel approach for gene therapy aimed at silencing oncogenes associated with cancer progression. Advanced formulations that combine siRNA with components such as gold-coated superparamagnetic iron oxide nanoparticles (Au-SPIONs) have shown promising results in preclinical studies by improving stability and facilitating targeted delivery through external magnetic guidance [88].

The versatility of chitosan as a nano-carrier extends beyond simple passive targeting; it enables active targeting strategies that dynamically respond to physiological signals, such as temperature or enzymatic activity typical of tumors. This potential can be harnessed through advanced engineering techniques that create stimuli-responsive systems capable of delivering drugs precisely based on environmental triggers [89].

As research continues to refine these targeted delivery systems utilizing chitosan-based formulations, significant challenges such as ensuring long-term stability and minimizing possible immunogenic responses remain critical issues that require further investigation. However, with ongoing advancements in nanotechnology and biopolymer science, there is considerable potential for enhancing treatment modalities across various cancer types through sophisticated drug delivery mechanisms involving (CNPs) [90].

6. Conclusion and future directions in research and development

The investigation into (CNPs) for drug delivery has revealed significant potential, particularly in enhancing targeted and effective treatment options. Chitosan's versatility as a biopolymer allows for numerous functionalization possibilities, enabling the customization of drug delivery systems tailored to specific therapeutic goals. Future research should focus on addressing current challenges, such as nanoparticle aggregation and suboptimal encapsulation efficiency, by employing advanced synthesis techniques and innovative formulations. Notably, the combination of (CNPs) with magnetic targeting and responsive elements could facilitate precise drug release mechanisms that adapt to physiological changes.

A comprehensive assessment of the safety profiles associated with these NPs in clinical settings remains crucial. While initial studies have provided insights into their toxicity and biocompatibility, thorough validation through extensive clinical trials is essential to evaluate long-term effects and effectiveness in human subjects. As new formulations emerge, addressing safety concerns will be critical for obtaining regulatory approval and ensuring broad implementation in therapeutic applications.

Collaborative strategies that integrate (CNPs) with other biomaterials are rapidly gaining traction. The combination of different polymers or the incorporation of inorganic components could result in hybrid systems that enhance both stability and functional performance. Such collaborations may not only improve encapsulation efficiency but also expand the range of drugs that can be effectively delivered using this platform.

The emergence of theranostic—an innovative blend of diagnostics and therapeutics—represents an exciting avenue for future research involving (CNPs). By leveraging their unique properties to co-deliver imaging agents alongside therapeutic compounds, researchers could pave the way for next-generation treatments that provide real-time insights into treatment efficacy while concurrently addressing disease progression.

Moreover, advancements in nanotechnology are leading to new methodologies such as electro spraying, which could enhance particle size uniformity and reduce production costs while improving scalability for commercial applications. Exploring the implications of these techniques concerning chitosan-based NPs could open up pathways for more efficient manufacturing processes.

Finally, there is a pressing need to investigate various routes of administration beyond oral delivery systems—such as intranasal or pulmonary methods—which could leverage chitosan's mucoadhesive properties to significantly improve drug absorption at targeted sites. Addressing these multifaceted aspects will not only refine existing formulations but may also expand their applicability across diverse fields including oncology, neurology, and immunotherapy.

As we enter this new era of personalized medicine, where treatments are tailored to individual patient profiles, there exists a wealth of opportunities for researchers to continuously innovate within the realm of chitosan nanoparticle technology. This dynamic environment requires interdisciplinary collaboration that integrates materials science, engineering principles, pharmacology, and clinical practice to fully harness the immense potential of this adaptable carrier system.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this study. The research was conducted independently, and no financial, personal, or professional relationships influenced the study design, data collection, analysis, or interpretation related to Symmetry and scale: The precise engineering of chitosan-based polyhedra for the delivery of therapeutic materials at the nanoscale.

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