Nitrogen-Doped Carbon Quantum Dots: Green Synthesis, Drug Loading and Biomedical Applications

Ankita Ashokrao Kambale[1*], Dr. Bharat Vijaykumar Jain[2]

[1,] Research Scholar, Department of Pharmaceutics, MGSM Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda, Maharashtra, India.

[2]Professor, Department of Pharmaceutics, MGSM Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda, Maharashtra, India.

Corresponding Author

Ankita Ashokrao Kambale[1],

[1,] Research Scholar, Department of Pharmaceutics, MGSM Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda, Maharashtra, India.

Mail Id. ankitanakul2023@gmail.com

ABSTRACT:

Nanotechnology continues to redefine strategies in drug delivery, diagnostics, and therapeutic engineering, with carbon quantum dots (CQDs) emerging as a versatile class of nanomaterials. Owing to their ultrasmall size, high aqueous solubility, low inherent toxicity, and tunable photoluminescence, CQDs have attracted considerable interest for biomedical use. Recent advances indicate that nitrogen doping significantly alters their electronic structure and surface chemistry, leading to improved fluorescence efficiency, enhanced electron transfer, and superior drug loading capability. This review critically examines nitrogen-doped carbon quantum dots (N-CQDs) with a focus on green synthesis approaches employing renewable precursors such as plant-derived materials and biomolecules, offering sustainable and biocompatible alternatives to conventional methods. Key synthesis parameters, doping mechanisms, and their influence on physicochemical properties are systematically discussed. In addition, the review evaluates drug loading interactions, stimuli-responsive release behavior, and the performance of N-CQDs in targeted delivery systems. Emerging applications in bioimaging, cancer therapy, antimicrobial activity, and biosensing are analyzed with emphasis on functional advantages and current limitations. Despite promising laboratory-scale outcomes, challenges related to large-scale production, reproducibility, and long-term safety remain significant barriers to clinical translation. Overall, N-CQDs represent a promising multifunctional platform, although further quantitative validation and regulatory alignment are required to advance their role in precision nanomedicine.

Keywords: Carbon quantum dots; Nitrogen-doped CQDs; Green synthesis; Drug delivery; Bioimaging; Nanomedicine; Biosensing; Nanocarriers

How to cite this article: Kambale AA, Jain BV. Nitrogen-doped carbon quantum dots: green synthesis, drug loading and biomedical applications. Int J Drug Deliv Technol. 2026;16(73s): 159-171. DOI: 10.25258/ijddt.16.73s.17

1. Introduction

1.1 Nanotechnology in Modern Medicine

Nanotechnology has become integral to contemporary biomedical science, offering innovative approaches for diagnosis, drug delivery, and therapeutic intervention. Nanoscale systems enable precise control over physicochemical properties, allowing improved solubility, stability, and bioavailability of therapeutic agents. In particular, nanocarrier-based delivery systems have demonstrated the ability to enhance site-specific targeting while minimizing off-target toxicity, which is especially relevant in the management of complex disorders such as cancer and chronic diseases [1].

Beyond therapeutics, nanomaterials play a crucial role in diagnostics due to their high surface-to-volume ratio and tunable functional properties. These features facilitate sensitive detection of biomolecules, enabling early-stage disease identification and real-time monitoring. Materials such as quantum dots, metallic nanoparticles, and nanosensors have been widely explored in imaging and biosensing platforms, contributing to improved diagnostic accuracy and speed [2]. Among these, carbon-based nanomaterials have gained increasing attention because of their

favorable safety profile and versatile surface chemistry.

1.2 Carbon Quantum Dots (CQDs)

Carbon quantum dots (CQDs) represent a distinct class of carbon-based nanomaterials characterized by particle sizes typically below 10 nm and unique optical behavior, particularly excitation-dependent photoluminescence [3]. Structurally, CQDs consist of a carbonaceous core that may exhibit graphitic or amorphous features, surrounded by abundant surface functional groups such as hydroxyl, carboxyl, and carbonyl moieties. These surface groups not only impart excellent aqueous dispersibility but also provide reactive sites for further functionalization, which is essential for biomedical applications [4].

Compared with conventional semiconductor quantum dots, CQDs offer notable advantages, including lower toxicity, improved biocompatibility, and reduced environmental concerns due to the absence of heavy metals [5]. These attributes make them promising candidates for applications in bioimaging, drug delivery, and sensing. However, limitations such as moderate quantum yield and variability in optical performance have driven efforts to modify their structure for enhanced functionality.

1.3 Significance of Nitrogen Doping

Heteroatom doping has emerged as an effective strategy to tailor the physicochemical properties of CQDs, with nitrogen being one of the most extensively studied dopants. Incorporation of nitrogen atoms into the carbon framework alters the electronic distribution and surface chemistry, leading to improved functional performance.

Nitrogen doping introduces additional energy states within the carbon matrix, which enhances radiative recombination processes and results in increased fluorescence intensity and quantum yield. This improvement is particularly advantageous for imaging and sensing applications [6]. Furthermore, nitrogen-containing functional groups enhance electron transfer kinetics, supporting applications in catalysis and biosensing.

From a drug delivery perspective, nitrogen doping increases the density of active surface sites, facilitating stronger interactions with therapeutic molecules through electrostatic attraction, hydrogen bonding, and π–π interactions. As a result, nitrogen-doped CQDs (N-CQDs) often demonstrate superior drug loading capacity and functional versatility compared to their undoped counterparts [7]. Despite these advantages, systematic evaluation and standardization of doping strategies remain areas requiring further investigation.

1.4 Role of Green Synthesis Approaches

The growing emphasis on sustainability has led to the development of green synthesis strategies for nanomaterials, including CQDs. These approaches utilize renewable and non-toxic precursors such as plant extracts, fruit waste, and other biomass-derived materials, reducing reliance on hazardous chemicals and energy-intensive processes [8].

Biogenic precursors are particularly attractive due to their natural abundance, low cost, and inherent composition of organic molecules that can act as both carbon and nitrogen sources. Techniques such as hydrothermal and microwave-assisted synthesis are commonly employed, offering relatively simple procedures and improved energy efficiency.

Compared to traditional chemical routes, green synthesis methods can enhance the biocompatibility and environmental safety of CQDs, which is critical for biomedical applications. However, challenges such as batch-to-batch variability, limited control over particle size, and reproducibility issues still persist, highlighting the need for process optimization and standardization [9].

1.5 Aim and Scope of the Review

This review aims to provide a critical and structured overview of nitrogen-doped carbon quantum dots, with emphasis on green synthesis strategies, structure–property relationships, and biomedical applications. Particular attention is given to drug loading mechanisms, controlled release behavior, and the functional performance of N-CQDs in areas such as bioimaging, cancer therapy, antimicrobial activity, and biosensing. In addition, current limitations, research gaps, and challenges associated with scalability, reproducibility, and clinical translation are discussed to outline future research directions.

2. Structure and Physicochemical Properties of Nitrogen-Doped Carbon Quantum Dots:

A detailed understanding of the structural and physicochemical properties of nitrogen-doped carbon quantum dots (N-CQDs) is essential for assessing their performance in biomedical applications. These characteristics govern their optical behavior, surface reactivity, and interaction with biological systems, thereby influencing their efficiency as nanocarriers and imaging agents.

2.1 Structural Characteristics-

Nitrogen-doped carbon quantum dots are composed of a nanoscale carbon core surrounded by a variety of surface functional groups. The core is primarily formed by sp^2-hybridized carbon atoms arranged in graphitic or partially amorphous domains, which

provide structural stability and contribute significantly to electronic transitions within the material [4]. These transitions play a crucial role in determining fluorescence behavior and charge transfer properties.

The introduction of nitrogen atoms into the carbon framework occurs either within the lattice or on the surface, resulting in different nitrogen configurations such as pyridinic, pyrrolic, and graphitic nitrogen. Each of these configurations influences the electronic density and energy levels differently, thereby modulating the optical and chemical properties of N-CQDs [6].

Typically, N-CQDs possess particle sizes in the range of 2–10 nm, placing them within the quantum confinement regime. At this nanoscale, discrete energy levels are formed, leading to size-dependent optical properties. Moreover, their small size facilitates efficient cellular uptake and penetration across biological barriers, enhancing their suitability for drug delivery and imaging applications [3].

2.2 Optical Properties-

N-CQDs exhibit remarkable optical properties, which are among their most attractive features for biomedical use. These nanomaterials display strong photoluminescence, primarily arising from radiative recombination of electron–hole pairs within the carbon core as well as from surface defect states. Nitrogen doping introduces additional energy levels that enhance radiative recombination, resulting in increased fluorescence intensity and improved quantum yield [7].

The fluorescence emitted by N-CQDs is typically bright, stable, and resistant to photobleaching, which provides a significant advantage over conventional organic dyes. This stability enables prolonged imaging and real-time monitoring in biological environments without significant signal loss [5].

A notable feature of N-CQDs is excitation-dependent emission, where the emission wavelength varies with the excitation wavelength. This phenomenon is attributed to heterogeneous surface states and multiple emissive centers within the nanostructure. Such tunable emission properties allow N-CQDs to be utilized in multicolor imaging, multiplexed detection, and advanced sensing applications [13].

2.3 Surface Chemistry-

The surface chemistry of N-CQDs is characterized by the presence of various functional groups, which significantly influence their dispersibility, stability, and interaction with biomolecules. Common functional groups include amino (–NH_2), hydroxyl (–OH), and carboxyl (–COOH) moieties.

Amino groups, largely introduced through nitrogen doping, enhance the overall reactivity of N-CQDs and provide active sites for binding negatively charged drugs and biomolecules. These groups facilitate electrostatic interactions and improve drug loading efficiency [14]. Hydroxyl groups contribute to hydrophilicity and ensure good dispersion of N-CQDs in aqueous media, which is essential for biological applications. They also participate in hydrogen bonding interactions, stabilizing drug–nanocarrier complexes [15].

Carboxyl groups serve as important sites for chemical conjugation and surface modification. They enable covalent attachment of targeting ligands, therapeutic agents, or polymers, thereby enhancing the specificity and functionality of N-CQDs. Overall, the presence of these functional groups allows for easy functionalization and customization of N-CQDs for diverse biomedical applications [16].

2.4 Advantages in Biomedical Applications-

The unique combination of structural and physicochemical properties makes N-CQDs highly advantageous for biomedical applications. One of their most significant benefits is high biocompatibility. Being carbon-based and free from toxic heavy metals, N-CQDs exhibit low cytotoxicity and are generally safe for both in vitro and in vivo applications [5]. Their superior fluorescence characteristics enable high-resolution imaging of cells and tissues, making them highly effective in bioimaging and diagnostic applications. The ability to tune emission wavelengths further enhances their utility in multiplexed imaging systems [13].

In addition, N-CQDs demonstrate excellent chemical and photostability under physiological conditions. This ensures consistent performance during drug delivery and imaging processes, even in complex biological environments. Their ease of surface functionalization further allows the development of targeted and multifunctional nanoplatforms, integrating therapeutic and diagnostic capabilities within a single system.

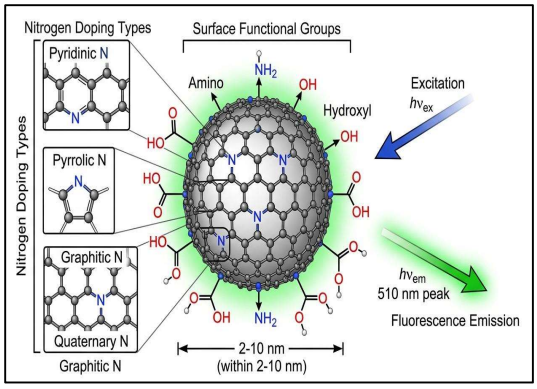

Figure 1: Schematic representation of nitrogen-doped carbon quantum dots (N-CQDs) illustrating the carbon core structure, nitrogen doping (pyridinic, pyrrolic, and graphitic forms), surface functional groups (–NH_2, –OH, –COOH), and excitation-dependent photoluminescence behavior.

3. Green Synthesis of Nitrogen-Doped Carbon Quantum Dots:

Green synthesis has emerged as a promising approach for the preparation of nitrogen-doped carbon quantum dots (N-CQDs), offering an environmentally sustainable alternative to conventional chemical methods. This approach emphasizes the use of non-toxic reagents, renewable resources, and energy-efficient processes, making it highly suitable for biomedical applications.

3.1 Concept of Green Nanotechnology-

Green nanotechnology focuses on designing nanomaterials through eco-friendly and sustainable processes that minimize environmental impact and health hazards. In the context of N-CQDs, green synthesis involves the use of natural precursors and mild reaction conditions to reduce the generation of toxic by-products [17].

Eco-friendly synthesis not only reduces the use of hazardous chemicals but also enhances the biocompatibility of the resulting nanomaterials. This is particularly important in biomedical applications, where toxicity and safety are critical concerns. Additionally, the use of sustainable materials such as plant-derived compounds and biomolecules aligns with the principles of green chemistry, promoting resource efficiency and environmental protection [18].

3.2 Natural Precursors Used for Synthesis-

A wide range of natural precursors has been explored for the green synthesis of N-CQDs. These precursors are typically rich in carbon and may also contain nitrogen, which facilitates in situ doping during synthesis. Plant extracts are commonly used due to their abundance of organic compounds such as polyphenols, carbohydrates, and proteins. These biomolecules act as both carbon sources and stabilizing agents during nanoparticle formation [19].

Fruit peels, including those of orange, banana, and lemon, are also widely utilized as cost-effective and renewable carbon sources. These waste materials not only reduce environmental burden but also provide a sustainable route for nanomaterial synthesis [20]. Herbal materials, such as medicinal plant extracts, offer additional advantages due to their inherent bioactive compounds, which may enhance the functional properties of N-CQDs.

Amino acids, such as glycine and urea, are frequently employed as nitrogen-rich precursors. They facilitate efficient nitrogen doping, improving the optical and chemical properties of the synthesized CQDs [21].

3.3 Green Synthesis Methods-

Several green synthesis techniques have been developed for the preparation of N-CQDs, each with distinct mechanisms, advantages, and limitations.

3.3.1 Hydrothermal Synthesis-

Hydrothermal synthesis is one of the most widely used methods, involving the treatment of natural precursors in a sealed autoclave at elevated temperatures and pressures. Under these conditions, carbonization and nitrogen incorporation occur simultaneously, leading to the formation of N-CQDs.

The reaction mechanism typically involves dehydration, polymerization, and carbonization of organic molecules, followed by nucleation and growth of quantum dots [22].

Advantages:

Simple and cost-effective

High yield and good control over particle size

Suitable for a wide range of precursors

Limitations:

Requires longer reaction time

Limited scalability due to batch processing

3.3.2 Microwave-Assisted Synthesis-

Microwave-assisted synthesis utilizes microwave irradiation to rapidly heat the reaction mixture,

significantly reducing synthesis time. The uniform heating promotes efficient carbonization and doping.

The mechanism involves rapid molecular motion and localized heating, leading to quick nucleation and formation of N-CQDs [23].

Advantages:

Rapid synthesis (minutes instead of hours)

Energy-efficient

Uniform particle distribution

Limitations:

Limited control over reaction parameters

Requires specialized equipment

3.3.3 Solvothermal Synthesis-

Solvothermal synthesis is similar to hydrothermal synthesis but uses organic solvents instead of water. This method allows better control over particle morphology and surface properties.

The reaction mechanism involves solvent-mediated carbonization and nucleation processes under controlled temperature and pressure conditions [24].

Advantages:

Better control over size and surface functionality

Enhanced optical properties

Limitations:

Use of organic solvents may reduce eco-friendliness

More complex purification process

Each method has advantages and limitations depending on synthesis conditions.

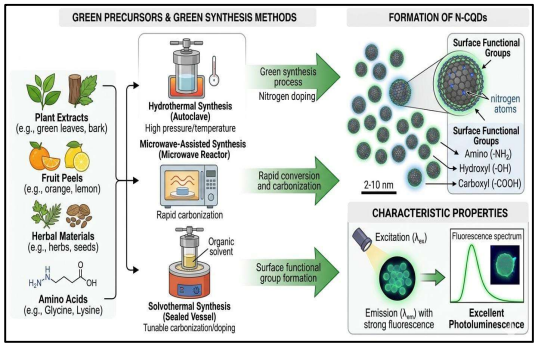

Figure 2: Schematic representation of the green synthesis of nitrogen-doped carbon quantum dots (N-CQDs) using natural precursors such as plant extracts, fruit waste, and amino acids through hydrothermal, microwave-assisted, and solvothermal methods.

3.4 Factors Affecting Synthesis-

The properties of N-CQDs synthesized through green methods are highly influenced by several reaction parameters:

Temperature:

Higher temperatures promote efficient carbonization and improved crystallinity. However, excessive temperatures may lead to particle aggregation or loss of functional groups [25].

Reaction Time:

Longer reaction times allow complete carbonization and growth of nanoparticles, but may also increase particle size and reduce fluorescence efficiency.

Precursor Concentration:

The concentration of the starting material affects nucleation and growth processes. Higher concentrations generally lead to larger particle sizes and increased aggregation.

pH:

The pH of the reaction medium influences the surface charge, functional groups, and stability of N-CQDs. Controlled pH conditions are essential for obtaining uniform and stable nanoparticles [10].

Table 1: Factors Affecting Performance of N-CQDs

Factor	Effect on Property	Impact on Application
Temperature	Controls carbonization	Affects fluorescence
pH	Alters surface charge	Influences stability
Precursor type	Determines doping level	Impacts drug loading
Reaction time	Controls particle size	Affects bioavailability

Table 2: Green Synthesis Methods and Their Characteristics

Method	Principle	Advantages	Limitations
Hydrothermal	High temperature & pressure	Simple, high yield	Time-consuming, batch process
Microwave-assisted	Microwave irradiation heating	Rapid, energy-efficient	Limited control, equipment needed
Solvothermal	Organic solvent-based synthesis	Better control, improved properties	Uses solvents, complex purification

3.5 Drug Loading and Drug Delivery Applications:

Nitrogen-doped carbon quantum dots (N-CQDs) have emerged as highly promising nanocarriers for drug delivery due to their unique structural features, tunable surface chemistry, and excellent biocompatibility. Their nanoscale size and abundant functional groups enable efficient drug loading and controlled release, making them suitable for advanced therapeutic applications [1, 2, 15].

Drug Loading Mechanisms-

The drug loading capability of N-CQDs is primarily governed by non-covalent interactions between the nanocarrier surface and drug molecules. These interactions allow efficient loading without altering the chemical structure of the drug.

One of the most important mechanisms is π–π stacking interaction, which occurs between the aromatic rings of drug molecules and the graphitic domains of the carbon core. This interaction is particularly significant for hydrophobic drugs such as anticancer agents, as it enhances drug loading capacity and stability within the nanocarrier system [3, 15]. Hydrogen bonding also plays a crucial role in drug loading. Functional groups present on the surface of N-CQDs, such as hydroxyl and amino groups, can form hydrogen bonds with polar drug molecules. This interaction contributes to stable drug attachment and controlled release behavior [10, 13].

Another key mechanism is electrostatic interaction, which occurs between oppositely charged functional groups on N-CQDs and drug molecules. For example, positively charged amino groups on N-CQDs can interact with negatively charged drug molecules, facilitating efficient loading and retention [12]. The combination of these interactions enables high drug loading efficiency and stability of the Nano carrier system.

Controlled Drug Release-

One of the major advantages of N-CQDs in drug delivery is their ability to provide controlled and stimuli-responsive drug release. This ensures that the drug is released at the desired site and time, improving therapeutic efficacy while minimizing side effects.

pH-responsive release is widely utilized in cancer therapy. Tumor microenvironments are typically more acidic than normal tissues, and N-CQDs can be engineered to release drugs preferentially under acidic conditions. This targeted release enhances drug accumulation at tumor sites and reduces systemic toxicity [2, 16].

Redox-responsive release is based on differences in redox potential between intracellular and extracellular environments. In particular, high concentrations of glutathione (GSH) in cancer cells can trigger the release of drugs from N-CQDs by breaking redox-sensitive linkages [15].

Enzyme-triggered release involves the use of specific enzymes that are overexpressed in certain disease conditions. These enzymes can degrade surface linkages or modify the nanocarrier structure, leading to site-specific drug release. This approach provides an additional level of targeting and precision in drug delivery systems [16].

Advantages of CQDs as Drug Carriers-

N-CQDs offer several advantages that make them highly suitable as drug delivery platforms. Their high surface area allows the attachment of a large number of drug molecules, increasing loading capacity and therapeutic efficiency [10, 12]. The presence of multiple functional groups further enhances their ability to interact with different types of drugs. N-CQDs also contribute to improved bioavailability of drugs by enhancing solubility and stability, particularly for poorly water-soluble compounds. This results in better absorption and therapeutic performance [1, 2].

Another significant advantage is targeted delivery. Through surface modification with ligands such as antibodies or peptides, N-CQDs can be directed toward specific cells or tissues, improving treatment specificity and reducing off-target effects. Finally, N-

CQDs exhibit reduced toxicity compared to conventional nanocarriers, as they are primarily composed of carbon and lack heavy metals. Their biocompatibility and biodegradability make them safer for clinical applications [5, 15].

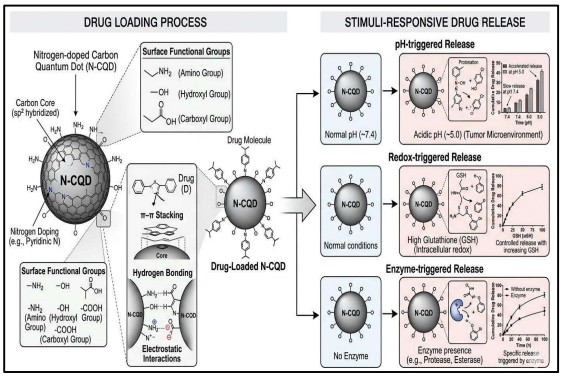

Figure 3: Schematic illustration of drug loading and stimuli-responsive drug release mechanisms using nitrogen-doped carbon quantum dots (N-CQDs), highlighting π–π stacking, hydrogen bonding, electrostatic interactions, and pH-, redox-, and enzyme-triggered release pathways.

Biomedical Applications of Nitrogen-Doped Carbon Quantum Dots:

Nitrogen-doped carbon quantum dots (N-CQDs) have emerged as versatile nanomaterials due to their unique optical properties, excellent biocompatibility, and tunable surface chemistry. These features enable their application across multiple biomedical fields, including bioimaging, drug delivery, cancer therapy, antimicrobial activity, and biosensing [10, 12, 15].

Bio imaging Applications-

N-CQDs are extensively used in bioimaging owing to their strong and stable fluorescence properties. Unlike traditional fluorophores, they exhibit high resistance to photobleaching and improved photostability, allowing prolonged imaging in biological systems [5, 13].

In fluorescence imaging, N-CQDs emit bright and tunable light under different excitation wavelengths, making them suitable for multicolor imaging and tracking biological processes at the cellular level [12, 25].

In cell imaging, their small size (2–10 nm) and hydrophilic surface groups enable efficient cellular uptake. Once internalized, they can localize in specific cellular regions, allowing real-time visualization of cell morphology and intracellular processes with minimal cytotoxicity [14, 15].

Drug Delivery Systems-

N-CQDs have demonstrated significant potential as drug delivery carriers, especially in anticancer therapy. Their high surface area and abundant functional groups facilitate efficient drug loading and controlled release [1, 2].

For instance, anticancer drugs such as doxorubicin can be loaded onto N-CQDs through π–π interactions and hydrogen bonding. These drug-loaded nanocarriers exhibit enhanced accumulation in tumor tissues and improved therapeutic outcomes [16].

Additionally, surface modification of N-CQDs with targeting ligands allows selective delivery to cancer cells, minimizing off-target effects and reducing systemic toxicity. This targeted approach significantly improves treatment efficiency [2, 15].

Anticancer Applications-

N-CQDs contribute to cancer therapy through multiple mechanisms. One major mechanism is reactive oxygen species (ROS) generation, where N-CQDs induce oxidative stress in cancer cells, leading to damage of cellular components such as DNA and proteins [16].

They also promote apoptosis induction, activating programmed cell death pathways that selectively eliminate cancer cells while sparing normal cells [15]. Furthermore, N-CQDs can be engineered for tumor targeting through surface functionalization with ligands such as antibodies or peptides, enabling selective binding and enhanced therapeutic precision [12].

Antibacterial Applications-

N-CQDs exhibit strong antibacterial activity through multiple mechanisms. One of the primary mechanisms is membrane damage, where interaction with bacterial cell membranes disrupts their structure, leading to leakage of intracellular contents [9].

Additionally, N-CQDs induce oxidative stress mechanisms by generating reactive oxygen species, which damage bacterial DNA and proteins, ultimately resulting in cell death [20]. These combined effects make N-CQDs effective against a broad spectrum of microorganisms while maintaining low toxicity toward human cells.

Bio sensing Applications-

N-CQDs have gained importance in biosensing due to their excellent optical and electronic properties. In biomolecule detection, they can interact selectively

with analytes such as glucose, proteins, metal ions, and nucleic acids. These interactions result in measurable changes in fluorescence intensity, enabling sensitive detection [25].

In disease diagnostics, N-CQDs-based sensors provide rapid, accurate, and low-cost detection of disease biomarkers. Their high sensitivity and fast response make them suitable for point-of-care diagnostic systems [12].

Table 3: Recent Biomedical Applications of Nitrogen-Doped Carbon Quantum Dots

Application Area	Mechanism/Function	Example Use	Key Advantage
Bioimaging	Fluorescence emission	Cell imaging	High photostability
Drug Delivery	Drug loading & release	Anticancer therapy	Targeted delivery
Anticancer	ROS generation, apoptosis	Tumor treatment	Selective cytotoxicity
Antibacterial	Membrane damage, ROS	Bacterial inhibition	Broad-spectrum activity
Biosensing	Fluorescence detection	Biomarker detection	High sensitivity

Toxicity and Biocompatibility:

The successful application of nitrogen-doped carbon quantum dots (N-CQDs) in biomedical fields largely depends on their safety profile. Evaluating their toxicity and biocompatibility through both in vitro and in vivo studies is essential to ensure their suitability for clinical use. Due to their carbon-based composition and absence of heavy metals, N-CQDs are generally considered less toxic compared to conventional semiconductor quantum dots; however, their biological interactions must be carefully assessed [25].

In Vitro Toxicity Studies-

In vitro cytotoxicity studies provide initial insights into the safety of N-CQDs at the cellular level. These studies are typically conducted using various cell lines, including cancer cells and normal human cells, to evaluate cell viability, proliferation, and potential toxic effects.

Most studies report that N-CQDs exhibit low cytotoxicity at moderate concentrations, maintaining high cell viability even after prolonged exposure. This is largely attributed to their small size, hydrophilic surface, and functional groups such as –OH and –COOH, which enhance compatibility with biological systems [26].

However, at higher concentrations, some degree of cytotoxicity has been observed, primarily due to oxidative stress or disruption of cellular processes. Therefore, dose optimization is critical to ensure safe application. In addition, surface functionalization and synthesis methods can significantly influence cytotoxicity, highlighting the importance of controlled fabrication processes [27].

In Vivo Studies-

In vivo studies using animal models are essential for understanding the systemic behavior and long-term safety of N-CQDs. These studies evaluate parameters such as biodistribution, organ accumulation, immune response, and overall toxicity.

Experimental findings indicate that N-CQDs generally exhibit good biocompatibility and minimal toxicity in animal models when administered at appropriate doses. They are well tolerated, with no significant adverse effects observed in major organs such as the liver, kidneys, and lungs [28].

Furthermore, N-CQDs demonstrate favorable circulation behavior and limited immune response, making them suitable for biomedical applications such as imaging and drug delivery. However, long-term studies are still required to fully assess their chronic toxicity and potential accumulation in tissues [29].

Bio distribution and Clearance-

Understanding the bio distribution and clearance of N-CQDs is crucial for evaluating their safety and effectiveness. After administration, N-CQDs are typically distributed throughout the body via the bloodstream and can accumulate in specific organs depending on their size, surface charge, and functionalization.

Studies have shown that N-CQDs are primarily cleared through renal pathways due to their small size, which allows them to pass through the glomerular filtration system. This rapid clearance reduces the risk of long-term accumulation and toxicity [30].

In some cases, partial accumulation in organs such as the liver and spleen has been reported, particularly

for larger or surface-modified particles. Therefore, optimizing particle size and surface properties is essential to ensure efficient elimination and minimize potential toxicity [31].

Critical Analysis and Quantitative Comparison

Despite rapid progress in the development of nitrogen-doped carbon quantum dots (N-CQDs), a closer evaluation of the literature reveals several limitations that restrict their translational potential. Most published studies emphasize synthesis optimization and proof-of-concept demonstrations, while comparatively fewer investigations provide quantitative benchmarking against established nanocarriers. This lack of standardized comparison makes it difficult to assess the true clinical advantage of N-CQDs.

One of the most frequently reported benefits of N-CQDs is enhanced photoluminescence. However, the reported quantum yield values typically range between 20–60%, which remain lower than those of conventional semiconductor quantum dots such as CdSe-based systems (often exceeding 80%). Although N-CQDs offer superior biocompatibility, this trade-off between optical performance and safety must be carefully considered when selecting materials for imaging applications.

Similarly, in drug delivery studies, N-CQDs demonstrate promising loading efficiencies (commonly 60–85%) and controlled release behavior under stimuli-responsive conditions. However, many reports rely on model drugs and simplified in vitro systems, limiting the relevance of these findings to complex physiological environments. Comparative data with clinically approved carriers such as liposomes or polymeric nanoparticles are rarely provided, creating a gap in performance validation.

Another critical issue lies in reproducibility. Variations in precursor selection, synthesis conditions, and doping strategies often lead to inconsistent particle size, surface chemistry, and functional properties. This lack of uniformity presents a major barrier for large-scale production and regulatory approval. Green synthesis approaches, although environmentally favorable, further contribute to variability due to the complex composition of natural precursors.

Toxicological evaluation also remains insufficient. While most studies report low cytotoxicity in short-term assays, comprehensive investigations involving long-term exposure, immunogenicity, and biodistribution are limited. Without such data, the safety profile of N-CQDs cannot be conclusively established for clinical applications.

Overall, N-CQDs represent a promising multifunctional nanoplatform; however, their advancement beyond laboratory-scale research requires systematic standardization, quantitative comparison with existing systems, and rigorous biological evaluation. Addressing these gaps will be essential to bridge the transition from experimental studies to real-world biomedical applications.

Table 4: Quantitative Comparison of N-CQDs with Other Nanocarriers

Parameter	**N-CQDs**	**Liposomes**	**Polymeric NPs**	**Metal QDs**
Particle Size (nm)	2–10	50–200	100–300	5–20
Quantum Yield (%)	20–60	Not applicable	Not applicable	70–90
Drug Loading (%)	60–85	30–70	50–80	40–65
Toxicity	Low	Very low	Moderate	High
Biocompatibility	High	Excellent	Good	Limited
Clinical Approval	No	Yes	Partial	No

Challenges and Limitations:

Despite their promising potential, N-CQDs face several challenges that must be addressed before widespread clinical application.

One major limitation is large-scale synthesis. Although laboratory-scale production is well established, scaling up the synthesis process while maintaining uniform size, quality, and functional properties remains challenging [32]. Stability issues also pose a concern, as N-CQDs may undergo aggregation or changes in optical properties under certain environmental conditions, affecting their performance in biomedical applications.

Although generally considered safe, toxicity concerns still exist, particularly regarding long-term exposure, accumulation in tissues, and interactions with biological systems. More comprehensive studies are needed to fully understand these effects [33].

Additionally, regulatory barriers present a significant challenge. The lack of standardized protocols for toxicity evaluation, quality control, and clinical

testing makes it difficult to obtain regulatory approval for nanomaterial-based therapies [34].

Future Perspectives:

The future of N-CQDs in nanomedicine is highly promising, with ongoing research focusing on expanding their applications and improving their performance. One key area is the development of advanced nanomedicine applications, including targeted drug delivery systems, theranostic platforms, and real-time disease monitoring. These applications aim to combine therapeutic and diagnostic functions within a single nanoplatform [35].

The design of multifunctional quantum dots is another important direction. By integrating multiple functionalities such as imaging, drug delivery, and sensing, N-CQDs can provide more efficient and personalized treatment options. The clinical translation potential of N-CQDs depends on overcoming current challenges related to safety, scalability, and regulatory approval. Continued research and collaboration between scientists, clinicians, and regulatory bodies will be essential for successful translation into clinical practice [36].

Furthermore, the integration of N-CQDs with personalized medicine approaches holds great promise. By tailoring nanocarrier systems based on individual patient characteristics, it is possible to achieve more precise and effective treatments with reduced side effects.

Comparison of N-CQDs with Other Nanocarriers-

Table 5: Comparative analysis of nitrogen-doped carbon quantum dots (N-CQDs) with conventional nanocarriers highlighting their features, advantages, limitations, and biomedical applications.

Nanocarrier Type	Key Features	Advantages	Limitations	Biomedical Applications
N-CQDs	Carbon-based, nanoscale (2–10 nm), fluorescent, surface-functionalized	High biocompatibility, strong fluorescence, easy functionalization, green synthesis possible	Limited large-scale production, long-term toxicity data lacking	Bioimaging, drug delivery, biosensing, cancer therapy
Liposomes	Phospholipid vesicles with bilayer structure	Excellent biocompatibility, clinically approved, suitable for hydrophilic & hydrophobic drugs	Stability issues, drug leakage, short shelf life	Drug delivery, vaccines, gene therapy
Polymeric Nanoparticles	Biodegradable polymer-based carriers	Controlled drug release, tunable properties, good stability	Complex synthesis, possible polymer toxicity	Sustained drug delivery, targeted therapy
Dendrimers	Highly branched, well-defined structure	High drug loading capacity, precise functionalization	Expensive synthesis, potential cytotoxicity	Gene delivery, targeted drug delivery
Metal Nanoparticles (e.g., Au, QDs)	Metallic or semiconductor-based	Strong optical properties, useful in imaging and therapy	Toxicity concerns, accumulation in tissues	Imaging, photothermal therapy, diagnostics

Conclusion:

Nitrogen-doped carbon quantum dots (N-CQDs) have emerged as a versatile and promising class of nanomaterials with significant potential in modern biomedical applications. Their unique physicochemical properties, including nanoscale size, strong and tunable photoluminescence, high surface area, and rich surface functionality, make them highly suitable for applications such as bioimaging, drug delivery, biosensing, and cancer therapy. The incorporation of nitrogen into the carbon framework further enhances their optical performance, electron transfer capability, and drug loading efficiency, thereby improving their overall functionality. A key advantage of N-CQDs lies in the development of green synthesis approaches, which utilize eco-

friendly, cost-effective, and sustainable precursors such as plant extracts, fruit waste, and biomolecules. These methods not only reduce environmental impact but also enhance the biocompatibility and safety of the synthesized nanomaterials, making them more suitable for clinical applications. Despite these advantages, certain challenges remain, including large-scale production, long-term toxicity evaluation, and regulatory approval. Addressing these issues will be crucial for the successful translation of N-CQDs from laboratory research to real-world medical applications. Looking ahead, continued advancements in synthesis techniques, surface engineering, and multifunctional design are expected to further expand the scope of N-CQDs. Their integration into targeted drug delivery systems and personalized medicine holds great promise for improving therapeutic outcomes. Overall, N-CQDs represent a powerful platform in nanomedicine, with the potential to contribute significantly to the future of healthcare and advanced diagnostic technologies.

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