

REVIEW ARTICLE



Fluorescent carbon dots: Emerging nanomaterials for real-time glucose sensing and diabetes management

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ABSTRACT

Fluorescent carbon dots (CDs) have emerged as promising nanomaterials for real-time glucose sensing and diabetes management due to their unique optical properties, high biocompatibility, and cost-effective synthesis. This review provides a comprehensive overview of CDs-based fluorescence glucose sensors, highlighting their potential to revolutionize non-invasive and continuous glucose monitoring. We have discussed the synthesis and characterization of CDs, emphasizing top-down and bottom-up approaches that enable tunable fluorescence and high quantum yields. The fluorescence sensing mechanisms, including enhancement, quenching, Förster resonance energy transfer (FRET), and ratiometric detection, are discussed for their sensitivity and selectivity in detecting glucose in biological fluids such as serum, saliva, and urine. Applications of CD-based sensors are examined across in vitro assays, in vivo continuous monitoring, and point-of-care devices. Despite significant progress, challenges such as selectivity against interfering biomolecules, photostability, and long-term biocompatibility persist. Future research should integrate CDs with wearable technologies, IoT platforms, and advanced material modifications to enhance specificity and scalability.

KEY WORDS

Carbon Dots;
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Introduction

Monitoring blood glucose levels and dietary glucose intake is crucial for preventing or delaying the onset of diabetes and its associated complications, including heart disease, blindness, vascular and kidney disorders, as well as various neurological problems [1-3]. Therefore, there is a significant need to develop analytical techniques that can selectively and accurately measure glucose in blood and food for both basic biological research and the food industry. A wide range of traditional analytical methods have been used for glucose detection, such as electrochemical analysis, colorimetric assays, high-performance liquid chromatography (HPLC), near-infrared spectroscopy, and mass spectrometry [4-7]. Although these methods provide important advantages for glucose measurement, they are often limited by lengthy procedures, complex sample preparation, and sophisticated equipment. In contrast, fluorescent analysis presents a promising alternative due to its straightforward operation and high sensitivity.

Fluorescence-based glucose sensing has become a promising method for non-invasive diabetes management, overcoming the limitations of traditional invasive techniques [8]. Recent progress in fluorescent nanomaterials, such as carbon dots, quantum dots, and nanoparticles, provides potential alternatives for glucose monitoring [9]. Conventional glucometers, which rely on invasive sampling and electrochemical detection, cause discomfort, offer intermittent data, and can be affected by interfering substances like uric acid and ascorbic acid [10]. These challenges have driven the development of noninvasive or minimally invasive sensing technologies, with fluorescence-based approaches standing out because of their high sensitivity, quick response times, and suitability for compact, point-of-care devices [11]. Continuous glucose monitoring and real-time data collection are key benefits of non-invasive techniques [12]. The goal of these advancements is to reduce the pain, inconvenience, and cost linked to traditional glucose testing, thereby potentially

enhancing diabetes management for the increasing number of affected individuals worldwide.

Carbon dots (CDs), a type of carbon-based nanomaterial usually smaller than 10 nm, have attracted significant interest because of their unique optical properties, including adjustable fluorescence, high quantum yield, and excellent photostability [13,14]. Unlike traditional fluorescent materials, CDs provide benefits such as low toxicity, high biocompatibility, and affordable production, making them suitable for biomedical applications like biosensing, bioimaging, and drug delivery [15]. Recent developments have shown the potential of CDs for continuous glucose monitoring in various biological fluids, such as blood serum, saliva, and urine [16]. Continuous glucose monitors (CGMs) are being improved for non-invasive, wearable use, with new technologies examining different bodily fluids to improve comfort and usability [17]. Lanthanide-doped CDs have demonstrated particular promise in detecting glucose and pH levels within clinically relevant concentration ranges [18]. These advances emphasize the potential of CDs for both in vitro and in vivo glucose monitoring, including applications in non-invasive detection in fluids like saliva and tears [15].

Although promising progress has been made, CD-based fluorescence glucose sensors still face several hurdles that limit their widespread use in clinics. Selectivity remains a major challenge because interfering biomolecules like ascorbic acid and uric acid can impact fluorescence signals in complex biological samples [19]. Also, the photostability of CDs under extended exposure and their long-term safety in living organisms need more study to ensure consistent performance [13]. Hence, researchers are focused on improving CD properties for particular medical uses and exploring their role in theranostics [20,21]. Additionally, combining CDs with other nanomaterials or technologies, such as wearable devices or IoT platforms, has not been thoroughly explored.

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This review offers a comprehensive overview of CDs-based fluorescence glucose sensors. It covers the optical properties of CDs that make them suitable for glucose detection, followed by an examination of fluorescence sensing mechanisms, including quenching, enhancement, and ratiometric detection. Additionally, we explore the various applications of these sensors in *in vitro* assays, *in vivo* monitoring, and point-of-care devices, emphasizing their potential for noninvasive and continuous glucose monitoring. Finally, the review discusses current challenges, such as selectivity issues, photostability, and biocompatibility concerns, and presents future perspectives to improve real-world diabetes management.

Carbon Dots: Synthesis and Characterization

Synthesis methods

Carbon dots (CDs) are generally synthesized through either top-down or bottom-up approaches [22]. Top-down methods include arc-discharge, laser ablation, and electrochemical exfoliation, while bottom-up techniques involve hydrothermal/solvothermal treatment, microwave irradiation, and thermal decomposition (Figure 1) [23,24]. The most commonly used techniques for producing fluorescent CDs with controlled size and surface chemistry are electrochemical exfoliation, hydrothermal treatment, and solvothermal reactions.

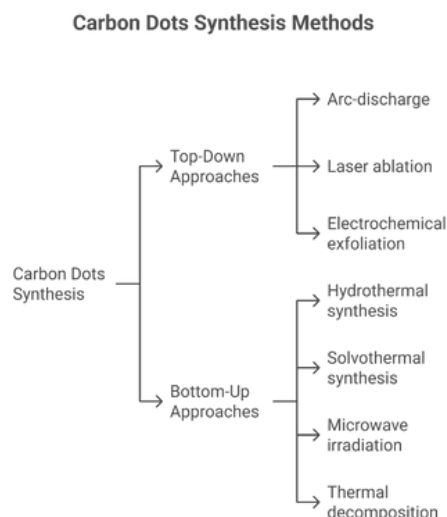


Figure 1. Different synthesis approaches for CDs.

Electrochemical exfoliation is a flexible method for producing CDs with adjustable properties. This approach offers several benefits, such as fast and large-scale production, simple equipment, low cost, and high yield of individual layers [25]. Using graphite rods as electrodes in different electrolytes, CDs with sizes from 2 to 6 nm can be created [26]. The electrolyte composition greatly impacts the characteristics of the resulting CDs. Water-based electrolytes can produce CDs with narrow fluorescence spectra (FWHM \approx 10 nm) and UV emission, while ionic liquid-water mixtures enable size control by changing water enerate both graphene quantum dots and graphene oxide quantum dots with tunable oxygen functional groups [26]. These CDs usually display excitation-dependent emission in the UV-visible range and quantum yields around 10% [26,28].

Hydrothermal synthesis is a flexible method for creating CDs with high quantum yields and various uses. This one-pot process usually employs organic precursors like citric acid and polyethyleneimine, producing CDs with efficient up- and down-converted photoluminescence [28, 29]. The resulting CDs show excellent water stability, pH sensitivity, and potential for cellular imaging. Biomass-based routes further lower costs and boost biocompatibility since they offer a sustainable, affordable alternative for CD production while maintaining desirable features such as uniform size and heteroatom doping options [30]. Recent progress has increased CD yield from biomass-derived carbons through gentle oxidation techniques, reaching yields of up to 76.9 wt% with excellent quantum yields [31].

Solvothermal synthesis is similar to the hydrothermal approach but uses organic solvents (e.g., DMF, ethanol, acetic acid) at high temperature and autogenous pressure (150–250 °C) [32]. Being able to control reaction conditions, such as solvent choice and temperature, allows for the production of CDs with specific size, shape, and surface chemistry, which improves their performance in fluorescence-based sensors. For example, Ma et al. reported N-doped multicolor CDs made in a single step from citric acid and urea, with quantum yields of up to 15.89% [33]. The fluorescence mechanism relies on factors like C=O content, pyrrolic N levels, and the degree of graphitization.

Characterization

Characterization of CDs provides insights into their physical, chemical, and optical properties. CDs are commonly characterized using various spectroscopic and microscopic techniques, including Ultraviolet-visible (UV-Vis) spectroscopy, fluorescence, Fourier-transform infrared spectroscopy (FTIR), X-ray photoelectron spectroscopy (XPS), Raman spectroscopy, and Transmission electron microscopy (TEM) (Figure 2) [34].

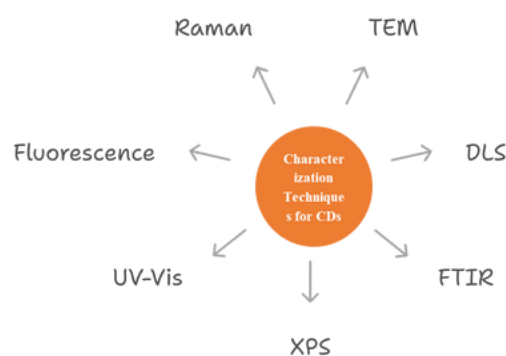


Figure 2. Characterization techniques for CDs.

TEM provides detailed images of carbon dots' morphology and size, showing their generally spherical shape and narrow size distribution. TEM also offers insights into the degree of crystallinity within the carbon core by resolving lattice fringes. Dynamic light scattering (DLS), on the other hand, measures the hydrodynamic diameter of dispersed particles, allowing assessment of their size distribution in solution and indicating colloidal stability. Surface functional groups are identified by FTIR, which detects characteristic vibrational modes such as hydroxyl, carbonyl, and amine bands, reflecting the chemical groups present on the surface of CDs. Additionally, XPS quantifies the elemental composition of the

surface and differentiates bonding states. UV-Vis absorption spectroscopy probes electronic transitions within the carbon dots, highlighting π - π^* and n - π^* transitions that correspond to conjugated double bonds and surface defects. Fluorescence spectroscopy characterizes their emission behavior, showing how the fluorescence peak position and intensity change with excitation wavelength, as well as measuring overall quantum yield and excited-state lifetimes. Finally, Raman spectroscopy evaluates the balance of sp^2 versus sp^3 hybridized carbon by analyzing the D and G bands, with the relative intensities of these peaks serving as a metric of defect density and graphitization within the carbon framework.

Sensing Mechanisms

Carbon dots (CDs) have become a powerful platform for fluorescence-based glucose sensing, taking advantage of their adjustable photoluminescence, high quantum yield, and excellent biocompatibility. These features allow CDs to detect glucose with high sensitivity and selectivity, making them promising for non-invasive, real-time monitoring in diabetes management. The fluorescence sensing mechanisms mainly depend on the interaction of CDs with glucose or its byproducts, such as hydrogen peroxide (H_2O_2) produced during enzymatic oxidation by glucose oxidase (GOx) [35].

Fluorescence-based mechanisms

Fluorescence-based sensing mechanisms utilize the optical properties of CDs to detect glucose by observing changes in fluorescence intensity, wavelength, or emission ratios. Figure 3 shows all the fluorescence-based mechanisms reported for glucose sensing. These mechanisms are very sensitive and suitable for use in biological fluids, making them promising for non-invasive glucose monitoring.

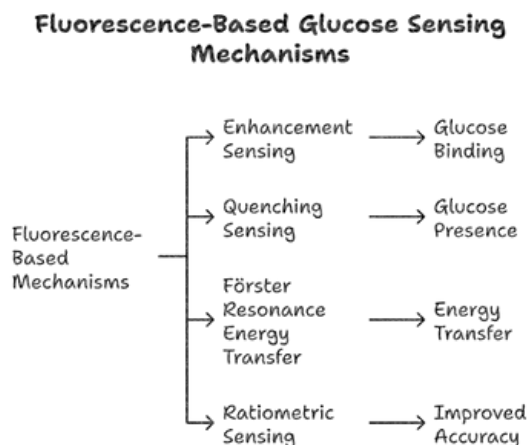


Figure 3. Fluorescence-based mechanism for glucose sensing.

Enhancement (Turn-on) sensing

In turn-on fluorescence sensing, the presence of glucose or its byproducts increases the fluorescence intensity of CDs. This mechanism often involves the interaction of glucose with functionalized CDs, which changes their electronic structure or surface chemistry to enhance radiative recombination or reduce non-radiative decay pathways. For example, CDs functionalized with specific groups, such as phenyl boronic salt (PBS), can show increased photoluminescence upon glucose binding, providing a positive signal for detection [36].

Functionalized CDs, especially those with boronic acid groups, display enhanced fluorescence when binding glucose, enabling sensitive detection [37, 38]. This turn-on fluorescence mechanism involves glucose-triggered assembly of CDs, which restricts non-radiative emission pathways [38]. Additionally, CDs combined with manganese dioxide nanosheets have been used in a glucose oxidase-coupled assay, where hydrogen peroxide produced from glucose oxidation activates fluorescence recovery [39]. These methods demonstrate high sensitivity, wide linear ranges, and suitability for biological samples, making them promising for diabetes management and biosensing applications.

Quenching (Turn-off) sensing

Quenching, or turn-off sensing, is a common mechanism where the fluorescence of CDs decreases in the presence of glucose. This usually happens through the production of H_2O_2 from the enzymatic oxidation of glucose by GOx, which interacts with CDs to quench their fluorescence via static or dynamic processes. Static quenching involves forming a nonfluorescent ground-state complex, while dynamic quenching results from collisional interactions [40]. For example, CDs made from gelatin in the presence of Fe(II) show linear fluorescence quenching with H_2O_2 , enabling glucose detection in the range of 0.05–100 μM [41]. The production of H_2O_2 from glucose oxidation by glucose oxidase causes fluorescence quenching of C-dots with Fe^{2+} , which is then used to detect glucose. In another study, Abraham et al. developed boron-doped CDs and GOx-modified bovine serum albumin-gold nanoclusters, achieving a detection limit of 0.03 mM for glucose [42]. The generation of H_2O_2 quenched the red fluorescence of the probe upon adding glucose via a static quenching mechanism.

Forster resonance energy transfer (FRET) sensing

Forster resonance energy transfer (FRET)-based probes use CDs as energy donors and molecular or nanoparticle acceptors whose absorption overlaps with CD emission. CDs have been used as energy donors in FRET-based glucose sensing systems. They have been linked with glucose oxidase (GOx) and other molecules to create sensitive probes. When glucose is present, GOx catalyzes its oxidation, producing H_2O_2 , which interrupts the FRET process and causes fluorescence recovery [35, 43]. These FRET-based systems have proven effective in detecting glucose in aqueous samples and blood, with some showing minimal interference from temperature, pH, and common ions.

Ratiometric sensing

Ratiometric fluorescence sensing measures the ratio of fluorescence intensities at two different emission wavelengths, providing a self-referencing signal that improves accuracy and reduces sensitivity to external factors such as probe concentration variations or fluctuations in the light source [44]. Recent studies have developed dual-emission nanosensors for glucose detection by combining CDs with other fluorophores. Zhai et al. [45], used CDs with m-dihydroxybenzene, achieving a detection limit of 0.35 μM . Hong et al. [46] combined gold nanoclusters and graphene quantum dots, reaching a lower detection limit of 0.18 μM . These ratiometric methods enable self-calibration, reducing susceptibility to external influences and allowing sensitive glucose detection in complex biological samples like serum.

Applications in Glucose Monitoring

CDs-based glucose sensors have been demonstrated across three principal application contexts: in vitro analysis of

biofluids, in vivo continuous monitoring via implantable devices, and point-of-care/real-time testing using portable or smartphone-based platforms.

In vitro sensing

In vitro glucose sensing with CDs focuses on detecting glucose in biological fluids such as human serum, saliva, and urine. These methods utilize the fluorescence properties of CDs to achieve high sensitivity and selectivity, often surpassing conventional enzymatic assays in terms of detection limits and ease of use.

Thiol-functionalized CDs have shown high sensitivity, with a detection limit of 0.03 μM in human serum, and excellent selectivity for glucose over other saccharides [47]. Non-enzymatic methods using CDs and boronic acid derivatives have demonstrated linear responses in the 1–30 mM range for glucose detection in blood serum [48]. CD-based glucose sensors frequently rely on enzymatic reactions involving glucose oxidase (GOx) to generate hydrogen peroxide (H_2O_2), which causes changes in fluorescence or chemiluminescence [49, 50]. For example, GQDs functionalized with hemin have achieved a detection limit of 0.1 μM for glucose in human serum [51]. Likewise, a GQD-based fluorescent biosensor combined with GOx and horseradish peroxidase reached a detection limit of 0.08 μM for glucose [49]. These sensors hold promise for clinical use, providing high sensitivity and specificity in glucose monitoring.

In vivo sensing

In vivo glucose sensing using CDs is a critical advancement for CGM, enabling real-time tracking of glucose levels in physiological environments. CDs have emerged as promising materials for in vivo sensing and biomedical applications. Their advantages include low toxicity, high photostability, and biocompatibility [52, 53]. CDs, particularly those with near-infrared emission, offer deep tissue penetration and reduced photodamage, making them suitable for tumor diagnostics and treatments. In glucose monitoring, cyclodextrin-based CDs improve the sensitivity, selectivity, and biocompatibility of sensors [54]. Doped-CDs further enhance these properties and enable diverse applications such as bioimaging, photothermal therapy, and biosensing [53]. Furthermore, CDs have been incorporated into electrochemical and photochemical sensors for in vivo biological monitoring, addressing challenges like detection limits and long-term stability [55].

Point-of-care and real-time monitoring

Point-of-care (POC) and real-time monitoring devices are essential for making glucose testing accessible, rapid, and user-friendly. CDs' fluorescence properties and compatibility with miniaturized platforms make them ideal for developing portable and smartphone-based glucose sensors.

CDs have been integrated into portable glucose sensors that enable quick testing in various environments. For instance, CDs-based nanopapers have been created for colorimetric glucose detection, providing visual results without the need for complicated equipment [13]. Moreover, CD-based microfluidic technologies have shown promise for glucose detection in settings with limited resources, offering benefits such as centrifugal liquid handling and compatibility with standard CD players [56]. Cyclodextrins have been added to glucose monitoring systems, enhancing sensitivity, selectivity, and biocompatibility through host-guest interactions [54]. Paper-based microfluidic devices (μPADs) combined with various

nanomaterials, including CDs, have demonstrated improved sensitivity and selectivity for detecting glucose in bodily fluids like saliva, tears, and urine [57].

Moreover, CDs can be incorporated into various sensing mechanisms, including single-probe, ratiometric, and visual detection methods [13]. The integration of CDs with other materials, such as metals and metal oxides, can further enhance sensor performance [16]. CGM technologies utilizing CDs have the potential to improve diabetes management by providing continuous, real-time glucose data, reducing hypoglycemia incidence, and decreasing glycemic variability [58].

Challenges and Future Directions

Despite their considerable promise, CD-based glucose sensors encounter several ongoing challenges. These include interference from competing molecules, such as ascorbic acid and uric acid in biological samples, which reduces selectivity [19]. Photobleaching and loss of catalytic activity during continuous use also undermine long-term stability [59]. While CDs are generally regarded as low-toxicity, comprehensive biocompatibility studies are still limited [19]. To tackle these issues, researchers are exploring various strategies. For example, cyclodextrins can enhance sensitivity, selectivity, and biocompatibility through host-guest interactions [54]. Enzymatic cascade systems, such as combining catalase with glucose oxidase, can improve photostability and decrease cytotoxicity by quickly breaking down hydrogen peroxide [59].

Recent research highlights significant advancements in non-invasive glucose monitoring technologies for diabetes management. Various approaches are being explored, including sensors for analyzing tears, sweat, and interstitial fluid [60]. Promising developments include smart tattoos, microneedle patches, and flexible bioelectronics capable of detecting multiple biomarkers [61]. Integration of these sensors with artificial intelligence and IoT platforms could enable real-time data transmission and personalized analytics [62]. However, challenges remain in maintaining sensor accuracy, ensuring user compliance, and addressing data privacy concerns. The iontophoresis-based electrochemical-enzymatic glucose sensing method shows potential, though the relationship between interstitial fluid and blood glucose levels requires further investigation [60]. Despite these hurdles, non-invasive glucose monitoring technologies are poised to revolutionize diabetes care, offering painless, continuous monitoring solutions that could significantly improve patient outcomes and quality of life.

The commercialization and mass production of CD-based glucose sensors will need reproducible, scalable, and cost-effective manufacturing methods, preferably using environmentally friendly precursors and minimal purification steps, combined with standardized device fabrication processes. Additionally, improving specificity and sensitivity through advanced material modifications, such as heteroatom co-doping, surface molecular imprinting, or combining with plasmonic nanoparticles, will be crucial for reaching ultra-low detection limits (<100 nM) and reducing false positives caused by interfering biomolecules.

Conclusions

CDs represent a groundbreaking advance in glucose monitoring, providing a promising solution for managing diabetes, a condition affecting millions worldwide. Their exceptional fluorescence, biocompatibility, and affordability

make them well-suited for developing sensitive and potentially non-invasive sensors. This review emphasizes how CDs enable accurate glucose detection in biological fluids such as serum, saliva, and urine through mechanisms like fluorescence quenching, enhancement, and ratiometric sensing. Their uses range from in vitro diagnostics to implantable devices for continuous monitoring and portable, smartphone-based systems for rapid testing, addressing the limitations of traditional invasive methods. These capabilities could revolutionize diabetes care by increasing accessibility, reducing discomfort, and enabling real-time monitoring.

Despite their potential, challenges such as interference from biomolecules, sensor stability, and biocompatibility remain. Future research should aim to develop non-invasive sensors for biofluids like saliva or tears, improve specificity through material modifications, and integrate CDs with IoT and AI for smart, real-time monitoring. Scaling up production and creating cost-effective, user-friendly devices will be essential for widespread adoption. By overcoming these hurdles, CDs could transform glucose monitoring, making it seamless and patient-friendly. Ongoing innovation in material design and technology integration will bridge current gaps, paving the way for CD-based sensors to become a key part of diabetes management, ultimately enhancing patient outcomes and quality of life.

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