REVIEW ARTICLE

Carbon Quantum Dots: Properties, Synthetic Methods, Applications in Pharmaceutical and Pollutant Analysis

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ABSTRACT

Introduction: The nanostructured form of carbon known as carbon quantum dots has shown promise in a wide range of fields, including bioimaging, optoelectronics, bio-sensing drug delivery systems, photovoltaics, and photocatalysis. They stand out from the crowd thanks to exceptional conductivity, low toxicity, and great photochemical and thermal stability.

Objectives: This article provides a concise overview of the last decade's worth of study into the use of carbon quantum dots (QDs) like CDs, GQDs, and PDs in the creation of a fluorescence imaging bio-sensing system for the early detection of cancer.

Methods: Recent research in the field of Carbon QD (CQD) in the last 20 years was collected, sorted for their application in analysis and summarized.

Results and conclusion: Most recent research on the CQDs has focused on their fluorescence characteristics and photocatalytic properties. The authors offer a glimpse into the future in an effort to help researchers overcome obstacles and dive further into this exciting topic.

Keywords: Carbon quantum dots, Pollutant analysis, Analysis of pollutant by chromatographic technique, Nanoparticle in pollutant analysis.

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INTRODUCTION

Carbon nanomaterials with a new, quasi-spherical shape have been discovered; they are simply highly bright and photoluminescent carbon quantum dots. These are mostly made of graphite, which has carbon atoms hybridized in sp^2 or sp^3 and is typically fewer than 10 nanometers in size.[1] The population growth that is connected with it and the manufacturing of synthetic substances in the food, textile, and dyeing industries has led to an increase in discharges. If left untreated, these compounds would produce vast volumes of trash. The appropriate disposal of hazardous waste is crucial since it directly impacts humans, animals, and the marine environment.[2] Carbon quantum dots (CQDs) have been the attention of extensive study because of their unusual properties and enormous potential for technical applications, especially in biomedicine. There has been a lot of interest in CQDs recently because of their exciting electrochemical, chemical, and excitation-dependent luminescence properties, as seen in Figure 1. Succession of extraordinary discoveries discovered recently in the field has controlled to number of ground-breaking developments. As an outcome, scientists set out to learn more about quantum dots' fluorescence properties, which ultimately resulted in the creation of a novel category of fluorescent carbon nanomaterials. The name "carbon quantum dots" was coined by Zuo and coworkers after they successfully tested a synthetic method to produce CQDs by strong fluorescence emission via surface passivation.[3] Top-down and bottom-up synthetic methods are the two primary options for making CQDs. Polymerization and carbonization reactions are at the heart of the bottom-up strategy for converting carbon-containing macromolecules into CQDs, while chemical, physical, and electrochemical degradation of carbon-containing macromolecules is at the heart of the top-down strategy. Oxidized CQDs have several hydroxyl and carboxyl groups on their surface. Manufacturing process used to make the CQDs determines the oxygen content, which is between 5 and 50% by weight.[4,5] This enables simple chemical modification with great water solubility, surface functionalization, surface passivation, fluorescence tuning, and physical property modification by using a variety of organic,

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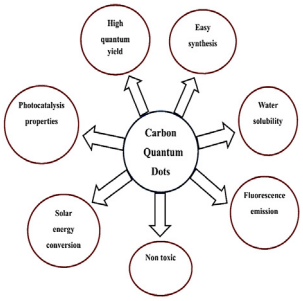

Figure 1: Carbon quantum dot's properties

inorganic, polymeric, or biological moieties. Different isotropic forms and adjustable surface functionality are features of CQDs. These characteristics set them apart from other carbon nanostructures including carbon nanotubes, nanodiamonds, fullerenes, and graphene sheets. Other characteristics of CQDs include quick and affordable synthetic preparations with a variety of applications, like bioimaging,[6] biosensing,[7] drug delivery,[8] tumor invasive biomarker detection, electrochemical biosensing[9] and in food samples detection.[10] Strong and controllable fluorescence has made semiconductor quantum dots a mainstay in biological research for years. CQDs can be employed in place of these semiconductor quantum dots. One major drawback of this technique is the employment of potentially harmful heavy metals in the creation of carbon quantum dots. Heavy metals are normally not employed in clinical trials because it has been demonstrated that they are exceedingly harmful at low quantities. CQDs, on the other hand, have many advantages, including low toxicity, a hydrophilic surface, non-flashing fluorescence, resistance to photobleaching, ease of passivation, chemical stability, and favorable cell compatibility.[11] As a result, CQDs are at the lead of extensive research projects to create eco-friendly, non-toxic substitutes with desirable qualities in response to environmental and biosecurity concerns.

Optical Properties

By gradually altering their size, shape, and surface functionalities, CQDs can emit light across the spectrum, from ultraviolet to near-infrared. They also exhibit tunable fluorescence and efficient multiphoton upconversion and downconversion, two of their most remarkable and unique features. Similar to how surfaces can be doped, surfaces can be functionalized based on size, shape, QCE, surface effect, and edge effect.[12]

Absorbance

CQDs typically absorb light from the visible range to the UV range (260–320 nm) (400–700 nm). Since CQDs are photon-collecting devices, the highest absorption occurs at short wavelengths. The highest peak for the SP^2-conjugated carbon transition is attributed to the transition at around 230 nm, whereas the n-p transition is connected to hybridization to shoulder heteroatoms at approximately 300 nm. In fact, surface passivation or modification processes can change the absorption property of CQDs.[13] Using the hydrothermal approach, Jiang and his colleagues were able to successfully make CQDs that glow green, red, and blue by employing 3 isomers of phenylenediamines.[14] It was discovered that the absorption slowly turned red. Furthermore, it has been demonstrated that heteroatom doping is one of the effective techniques to alter the absorption pattern of CQDs. According to Zhao and colleagues' research, the absorption band of CQDs shifts towards the visible spectrum between 550 and 595 nm when heteroatoms like S and N are doped into them.[15]

Photoluminescence

The main distinguishing characteristic of CQDs is their tunable photoluminescence, which gives them a large spectrum range and extraordinarily deep emission peaks, ranging from the NIR to the UV. Excitation-dependent luminescence spectra is another title for this important phenomenon. Given the size of nanoparticles and QCE, the excitation wavelength utilized to excite CQDs can control the emission color.[16] When CQDs are surface passivated for high quantum efficiency, the energy states associated with surface defects provide the quantum efficiency (PL) attribute.[17] Numerous other studies have demonstrated that it is possible to minimize the flaws responsible for various energy levels by altering the CQD surface with a single emission wavelength.[18] One of the most remarkable characteristics of CQD that makes it useful for long-term real-time imaging is non-blinking PL, which aids in monitoring a single molecule while also possessing the quality of photostability. When compared to organic fluorophores, which photobleach in just 0.5 hours, laser-ablated PL-CQDs have an intensity that is just 4.5% lower after four hours. CQDs are sensitive to pH, which has been demonstrated in numerous studies and has an impact on their photostability.

- *Chemical luminescence*

The process of chemical luminescence (CL) occurs when a chemical reaction activates CQDs. The CL properties of EQDs were first seen when CRDs were found to coexist with different oxidants like $KMnO_4$ and cerium. Exposure to oxidants like cerium and KNO_4 causes CQDs to produce holes, as seen by the paramagnetic electron. This mechanism boosts the hole population in CQDs and accelerates electron-hole annihilation, leading to increased CL emission. Since the redox reaction in CQDs creates many electron holes and accelerates their annihilation, energy is released in the form of CL emission. CL intensity is determined by the quantity and frequency of chemical reactions.[19] Two reactions happen at once in one solution in the conventional CQD-CL mechanism. Electron injection is a method for transferring electrons into the excited energy level of CQDs, while hole injection is used to remove electrons from the ground level. CL results from the injection of electrons that are then moved from excited to lower energy levels. The discovery of this process was made by Mitra and colleagues who found that CQDs produce a high and intense CL upon contact with a very alkaline NaOH solution. This is because CQDs can donate electrons to oxygen atoms that are currently in solution, leading to the production of superoxide anion radicals, and because NaOH accelerates the reduction

of groups on the surface of CQDs. Thus, the interaction between electrons produced by chemical reduction events and the cavities produced by heat reactions results in strong and intense luminescence. The usage of CQDs is now constrained by a difficult redox process and CQD coupling, despite the fact that they have a great deal of promise for photocatalysis and can act as electron acceptors and donors.[20]

- *Electrochemical luminescence*

The electrochemically induced electrons and the holes they produce drive CQDs to higher energy levels, where electrochemiluminescence (ECL), which occurs when the CQDs relax to the emission ground state form, releases energy, has also been examined.[21] The process of luminescence is assumed to involve the excitation of electrons at the surface, which then relax to a lower energy state and release light. On the other hand, shorter wavelength luminescence in CQDs is attributable to core energy levels rather than surface states with higher energy separation.[22] These issues will be at the forefront of future conversations. Low oxidation state CQDs (r-CQDs) and high oxidation state CQDs (o-CQDs) are used to study the effects of CQD configuration, shape, and surface structure on photoluminescence (PL) and ECL. The carbonization-extraction method and the carbonization-oxidation method are both used to create these CQDs.[23] Electrode surface o-CQDs/KS2O8 dispersion was found to be responsible for electrochemical reactions. "Loose shell" of oxygen-containing groups on o-CQDs generates oxidants, which are o-CQD radicals. When $S_2O_8^{-2}$ accepts an electron from an anionic o-CQD, it generates SO_4 radical, which is then expelled. At 1.10 V, the beginning of the ECL wave, and at 1.30 V, the peak of the cyclic voltammogram shows oxidation (CVs). As a result, there is a strong correlation between o-CQD oxidation and ECL emission. On the basis of CQDs, a current density-dependent light-emitting diode (LED) was created. Depending on the voltage applied, the same sample generates various ECLs that emit light in the blue-to-white spectrum (ECL).[24] Low- and highly-oxidized CQDs, called r-CQDs and o-CQDs, respectively, were investigated using a carbonation extraction method and a carbonation-oxidation procedure to appreciate how composition, morphology, and surface structure of CQDs affect PC and ELC in certain applications.[25,26]

- *Up-conversion photoluminescence*

CQDs also have the ability to up-convert photoluminescence (UCPL), which occurs when 2 or more longer-wavelength photons are activated simultaneously through absorption. This trait causes luminescence to be emitted at a wavelength shorter than the excitation wavelength. This captivating optical characteristic, which extends from the visible to near-infrared, has a variety of uses in photocatalysis for cell imaging and two-photon luminescence microscopy.[27] The first visible emission from CQDs was achieved by Cao and colleagues employing three components, namely a 5 nm wavelength, a two-photon excitation mechanism in near-infrared, or 800 nm, and a femtosecond pulsed laser ablation.[28] Later investigations noticed UCPL emissions from CQDs created using various methods. For instance, Li and his coworkers found that sonication-produced CQDs exhibit both normal and UCPL properties.[29] UCPL is thought to develop from regular fluorescence in this second light, which is created when excitation light is diffracted and has a wavelength that coexists with the first. To prevent this from happening, a long tube can be attached to the fluorescence spectrophotometer. Only with a femtosecond pulsed laser can you see the conventional fluorescence known as UCPL, which is not a multiphoton phenomena.[30] Shen and colleagues, on the other hand, asserted that the upconverted luminescence in CQDs cannot be sufficiently described by the multiphoton process. Therefore, they created GQDs using graphene oxide (GO), which were subsequently passivated using polyethylene glycol.[31,32]

Photoinduced electron transfer properties

One of the most recent initiatives in research has concentrated on CQDs for photoinduced charge separation, electron transfer processes, and photoresponse, with applications ranging from B in light energy conversion to other closely related applications. Extensive research into the development of CQDs is ongoing. Wang and coworkers propose that CQDs are both electron acceptors and donors, which would account for the presence of electron acceptors like dinitro toluene and nitrotoluene. They effectively quench nitrotoluene and dinitrotoluene, as well as other electron donors like N,N-diethylaniline. Fluorescence intensity measurements and lifetime quenching tests reveal that nitrotoluene and dinitrotoluene have different CQD electron-accepting properties. The researchers claim that excited-state disruption in redox processes brought on by doped metals, whose primary function is to emit strong and intense fluorescence, could be the explanation for distinct quenching patterns for effective PL in CQDs.[33]

Biological Properties

Stable CQDs and high PL probes have made notable strides in development. For potential applications in living cells and tissues, CQD's biocompatibility remains a challenge. Recent CQD cytotoxicity tests have been conducted. Graphite rods were refluxed in HNO_3 for 12 hours while CQDs were produced using the arc discharge method for the cytotoxicity assay. The lethal concentration of CQD was determined to be 0.4 mg per mL.[34] MTT assay demonstrated that even at high concentrations, PEI samples were not harmful to HT-29 cells; however, PEI-CQDs are more toxic to cells than PPEI-EI-CQDs due to higher concentration of EI units in PEI.[28] PEI has a higher number of EI units, Also, even at concentrations as low as 50 mg mL^{-1}. Furthermore, it was shown that even at concentrations as low as 50 mg/mL^{-1}, free PAA in non-aqueous solution is toxic to cells. At the same concentrations, it was demonstrated that both PAA-CQDs and free PAA were found to be lethal to cells after a 24-hour exposure, but less so after a four-hour exposure.[35] Additionally, PEG and PPEI-EI can be functionalized for *in-vivo* bioimaging and biosensing even at high concentrations. These can be utilized if very toxic substances like PAA are still necessary for the CQD functionalization. The cell viability assay was utilized

to determine the cell toxicity of N-doped CQDs (N-CQDs). For 24 hours, HepG2 cells are cultivated with N-CQDs and CQDs. It turned out that CQDs were less harmful than CQDs. Results showed significant levels of cell viability even at high doses, indicating the N-doped CQDs were both safe and highly compatible with cells.[36]

Method of Synthesis

Numerous techniques for creating CQDs have been devised since their discovery. For the goal of synthesizing CQDs, there are commonly two different synthesis techniques: the top-down method and the bottom-up method. Conversely, CQDs are formed through a sequence of polymerization and carbonization processes in the bottom-up process. The top-down approach primarily deals with physical, chemical, or electrochemical destruction, degradation, or dispersion of carbonaceous macromolecules, examples of which are graphite, nanodiamonds, and activated carbon in nano-sized CQDs. These CQDs are made from small carbonaceous molecules including citric acid, glucose, and sucrose.

Top-down approaches

- *Laser ablation*

Laser ablation is used for manufacturing a wide range of nanocomposites that have the property and morphology to get easily regulated.[6,28] The target molecules' surfaces should be exposed to a high-energy laser pulse in order to create these CQDs, which should then be further forced into a high-temperature, high-pressure thermodynamic condition. The target molecules rapidly vaporize and transfer to plasma, where they condense into nanoparticles. Li and his colleagues demonstrated a highly easy, direct, and uncomplicated method for building CQDs utilizing laser irradiation. This approach allows for the dispersion of carbon nanoparticles in various solvents in this case.[29] The proposed CQDs' PL was predictable, observable, and tunable. Hu and his coworkers found that altering the CQD surface with the application of a suitable organic solvent allows for fine-tuning of the PL properties of created CQDs.[37] It was ultimately determined that the size of CQD can be controlled by adjusting the width of a laser pulse. This will ultimately affect how quickly and severely CQD manifests. More CQDs of varying sizes can be manufactured in one go than is possible with batch processing. This opened up more possibilities for industrial-scale manufacture of CQDs. In vitro imaging of human cell lines was performed using CQDs. The CQDs were produced by varying the time interval between two femtosecond laser pulses. CQDs generated via double-pulse ablation often have smaller mean sizes than those generated *via* single-pulse ablation, which is advantageous because it allows for the creation of more functional groups on the surface of the CQDs, which can be used in analysis and sensing applications.

- *Chemical ablation*

A type of technique that makes use of potent oxidizing acids is chemical ablation. The nanocarbonaceous materials created by these acids' charring of the small organic molecules are then controlled and oxidized into small sheets.[38] CQDs may be produced in large quantities without complicated equipment. However, there are various drawbacks to the treatment, including B. serious problems and traumatic experiences. Peng and his associates demonstrated a straightforward method to create colored CQDs by dehydrating carbohydrates with strong sulfuric acid. This carbonaceous material was then divided into individual CQDs using nitric acid, which were subsequently further passivated using amine-terminated chemicals. CQD luminescence has always required surface passivation. Nitric acid can be repeatedly exposed to the reactants or starting material to vary the emission wavelength of CQDs because this depends on how long they have been exposed to the acid.[37]

- *Electrochemical carbonization*

CQDs are frequently produced via electrochemical carbonization under normal pressure and temperature conditions. This process makes it simple to generate a large number of CQDs from bulk carbon precursors, making it a method of choice since it makes it simple to produce CQDs of the desired size by altering PL of the CQDs.[39] This technique was developed by Zhang and his colleagues to produce CQDs.[40] The working electrode and the secondary electrode were both made of Pt foils. The reference electrode was a calomel electrode connected to a Luggin capillary that could be fully adjusted. Electrochemical carbonization process worked well to transform the alcohols into CQDs. The volumes and levels of graphitization of these CQDs expand along with application possibilities. Without the need for laborious cleaning and passivation procedures, resulting amorphous-core CQDs exhibited excellent excitation- and size-dependent PL properties. Remember that these CQDs can achieve quantum yields (QYs) of up to 15.9%. Several small molecular alcohols that are nontoxic to human cancer cells can be used to create CQDs.[41]

- *Ultrasonic synthesis*

Ultrasound creates positive and negative pressures in liquids, which cause miniature vacuum bubbles to form and burst. Deagglomeration, severe hydrodynamic shear forces, and acceleration of the liquid jets are all possible outcomes of cavitation in these bubbles. Because of this, the ultrasonic waves immense energy can reduce large carbon molecules to microscopic CQDs.[42] By sonicating D-fructose (carbon addition) and PEG, CQDs were produced (surface passivation). CQDs are more capable than fluorescent probes when the target analyte is present during synthesis. The produced CQDs were around 2.5 nm in size, which allowed for examination with a portable fluorine spectrometer. Dang and his coworkers used ultrasound and an oligomeric polyamide resin to make CQDs.[43]

Bottom-up approaches

- *Hydrothermal method*

HTC, or hydrothermal carbonization, is one of the most popular methods for transforming a wide range of basic materials into novel carbonaceous nanomaterials. Its inherent non-toxicity and low resistance to photofading are just two of

its many advantages. It produces CQDs that are both uniform in size and extremely brilliant.[44] In the standard method, organic molecules are first dissolved in a solvent before being transferred to a stainless steel reactor lined with Teflon. A few hours of melting the reaction's starting components at a moderately high temperature produces CQDs with a particle size of > 10 nm. When compared to fluorescent dyes, CQDs have maximum quantum yields of up to 80%, according to research by Zhu and his colleagues.[45] CQDs are frequently produced using organic solvent extraction and solvothermal carbonization. Chemicals that donate carbon are frequently heated before being extracted and concentrated in high-boiling organic solvents. By carbonizing carbohydrates, Bhunia et al. were able to create CQDs with sizes of less than 10 nm that were both hydrophobic and hydrophilic. Octadecylamine and octadecene were mixed with different amounts of carbohydrates, then heated at 70 to 300°C for 10 to 30 minutes to create hydrophobic ones. Hydrophilic carbohydrates can be made by heating an aqueous solution of carbohydrates across a wide pH range.[46]

- *Microwave-assisted pyrolysis*

When organic molecules are then microwave irradiated, CQDs can be made fast and easily. Under microwave irradiation, CQDs were synthesized in under a minute using diethylene glycol (DEG) as the reaction media and sugar as the carbon source. Transparent and easily dispersed in water, these DEG Stabilized CQDs (DEG-CQDs) are a great addition to water-based applications. As the excitation wavelength was widened (360 nm excitation), the PL's intensity dropped after reaching a maximum. PL peak did not alter audibly between 320 and 380 nm, though. These DEG-CQDs also demonstrated low cytotoxicity and were readily absorbed by C6 glioma cells, indicating the possibility of their usage in bioimaging.[47] Less than five minutes were spent microwaving these CQDs with lysine. The carbonization technique was used to produce lysine-based CQDs. The outcomes demonstrated that they can be utilized safely for biological imaging of cell medium due to their demonstrated exceptional non-toxicity and biocompatibility. The correct monomer selection and reaction management are essential for the creation of highly soluble and high-performance PL-CQDs during microwave treatment.[48] The primary amine molecules supplied the surface passivation and the N-type dopant during the creation of CQDs, enabling fine-tuning of the PL intensity. The CQDs' QY values rose to a maximum of 30.2% as the N content rose. The findings showed that CQDs are highly biocompatible, indicating that they have a lot of potential in the biomedical field.[24]

- *Thermal decomposition*

Organic compounds are dehydrated and carbonized during the thermal decomposition process to create CQDs. This process is inexpensive, doesn't call for a solvent, and is simple to scale up.[48] The supplemental tailored method has three key enhancements. A straightforward strategy must initially be created in order to extract a tiny fluorescent molecule from a heterogeneous group of particles. These particles are effectively produced by the technique (in the mg range). By isolating tiny molecules, which glow more than large particles but less than small particles, the second technique claims that the QY can be improved by 0.1 to 3%. The third approach allows for the direct entry of small particles into cells without further functionalization, allowing for the use of fluorescence-based cell imaging applications. Technology based on carbon black produces mixtures of colored particles that are challenging to discern using gel electrophoresis.[49]

AREAS OF APPLICATION

Biomedical Applications

CQDs are a fantastic candidate for biological applications because to their unique physicochemical and optical characteristics. They are great for bioimaging, biosensing, and drug delivery systems because they are small and don't hurt cells. Their fluorescence makes them easy to track inside the body. CQDs are useful in many biomedical settings because they are non-flickering, non-toxic, soluble in water, and chemically inert, and their PL emission is based on excitation and size, among other things. Biosensing with electricity and chemicals, delivering genes, making medicines, photodynamic and treating bacterial infections and photothermal therapy, and inflammation are a few examples.[24]

Biosensors

CQDs have been used as biosensor substrates because they are harmless, easily dissolved in water, emit multiple colors when excited, are compatible with living things, allow cells to pass through easily, and are stable under light. For the purpose of detecting nucleic acids, CQDs can serve as a fluorescence sensor plate with single base mismatch selectivity. The basic concept was that CQD would adsorb a fluorescently tagged dsDNA probe via p-p interactions, leading to considerable fluorescence quenching before the probe hybridized preferentially with its target to create dsDNA. The hybridized dsDNA is subsequently desorbed from the CQD surface, allowing for the examination of the target DNA.[50] The two-photon fluorescence probe was developed using electrochemically generated CQDs, which have an average size of 6 nm and can detect pH variations from 6 to 8.5 with good sensitivity and specificity. Such pH fluctuations in living cells and tissues have been monitored and detected with success and effectiveness using the aforementioned probe. In two-photon biosensing and bioimaging of living cells and tissues, it is employed. Fluorescence intensity fluctuations are attributed by Kong and colleagues to the covalent attachment of terpyridine-based receptor molecule (TPY) to the surface of CQD as a result of adsorption/desorption of H^+ ions. CQDs' 10% quantum efficiency makes the UCPL characteristics visible from UV to NIR wavelengths. Higher concentrations of H^+ ions and brighter emissions from the CQD-TPY nanoprobe in the 440 to 650 nm range show that it preferentially detects H+ ions over other metal atoms, biomolecules, and amino acids. pH of mouse lung cancer cell lines A-549 and LLC-MK2 is monitored in real-time. In this case, a two-photon microscope

was used. These cells are discovered in tumor tissues both *in-vitro* and *in-vivo* by cultivating tumor cells in nude mice.[7]

Electrochemical sensors

Because of their excellent stability, surface functionalization, and electrical conductivity, CQDs have a lot of potential for electrocatalysis, biosensing, optical sensing, photovoltaics, and chemical sensing. Because of their electrocatalytic characteristics, CQDs have generated a lot of interest. Recent studies on electrochemical biosensors have demonstrated their ability to detect a wide variety of biomolecules. Additionally, they work on H_2O_2 detection, reduction, and O_2 reduction. There have also been developed polymer CQDs. Additionally, it has been demonstrated that CQDs composed of polymers have excellent sensitivity and selectivity for the detection of hemoglobin.[24] Pt nanocrystals have been shown to contain CQDs in another study, which can be combined with N-doped GQDs to create electrochemical biosensors. This nanocomposite has strong catalytic activity in the electrochemical biosensing of DNA damage indicators. Another glucose oxidase–GQDs–carbon-ceramic electrode electrochemical biosensor for glucose detection was developed.[51]

Food Analysis

Metal ion detection

Metal ions such as copper (Cu^{2+}), mercury (Hg^{2+}), and aluminum (Al^{3+}) are toxic and non-degradable. Including them in the food chain can result in a number of health issues. Therefore, it is essential to identify them for tracking food safety. Hg^{2+}, Au^{3+}, Cr^{6+}, Ag^{+}, Fe^{2+}, Cu^{2+}, and Fe^{3+} are examples of heavy metal ions. Due to their rapid accumulation in plants and animals, these substances considerably contribute to environmental or water contamination. Through the food chain, toxins are brought into the human body. A carbon-based ceramic electrode was created for the detection of glucose, and it is essential to design a method for the precise, usable, and sensitive detection of heavy metal ions in food.[52]

Detection of foodborne pathogens in food

Food poisoning is a widespread issue. The identification of food pathogens may be affected by new food and health legislation. Phage-based biosensors have gained a lot of attention recently as a type of contemporary biosensor. Bacteriophages (phages) are intracellular parasitic bacteria that multiply by making use of one or more aspects of the host's biosynthetic machinery. Phages' longevity and selectivity are essential qualities for their potential usage as biosensing components in the future. Phages are able to follow pathogens, microbes, and spores in the field for longer lengths of time than antibodies because they are less vulnerable to environmental challenges including pH and temperature fluctuations. The tail spike proteins on phages enable them to identify phage receptors. Because of how precisely the identification is made, it can be used to categorize bacteria and pave the way for the creation of systems for more accurate pathogen detection.[52]

Detection of food additives

Processed foods often contain food additives to boost their flavor, freshness, and healthfulness. Additives, which have been widely misinterpreted, have a major role in the spread of foodborne illness. Therefore, it is vital to design a quick and efficient food additive detection system in order to optimize the tracking of food additives. A quick and accurate food additive diagnostic instrument must be created in order to improve food additive monitoring. Scientists produced carbon quantum dots with a static process using *Aloe vera* in the presence of tartrazine fluorescence. This sensor was used to detect low concentrations of tartrazine in honey and candy with a sensitivity of 73 nM.[53]

Food toxin detection

CQDs are utilized to detect contaminants, heavy metals, and pathogens in food due to their distinctive optical properties.[54] Although heavy metals are prevalent in the soil, microorganisms do not absorb them. These are absorbed by plants, where they eventually find their way into food products where they contaminate living things. Therefore, it is crucial to be concerned about their discovery. CQDs from honey, cornmeal, and Chinese grass were employed as fluorescent probes to image Fe^{2+} (iron ions), Cu^{2+} (copper(II) ions), Cr^{6+} (hexavalent chromium ions), Hg^{2+} (mercury(II) ions), and other similar metal ions. For instance, apple juice-derived CQDs are utilized to identify and detect *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa,* and *Magnaporthe oryzae* fungus cells, all of which are typically present in natural food items. As a result, these CQDs are used to identify and detect food poisons.[55] In one work, the one-pot synthesis approach was employed to synthesize two different types of CQDs from citrus sinensis and citrus lemon peel. Although newly manufactured CQDs had many characteristics, there were several significant variations that should be noted. Because of their powerful PL characteristics and the presence of oxygen and nitrogen functional groups on their surface, CQDs have several possible applications. CQDs are a type of chemosensor developed for the detection of Fe3+ and tartrazine.[56] Because of this, CQDs derived from natural sources may be used to detect dietary poisons such as viruses, heavy metals, and poisonous chemicals.[24]

Pharmaceutical Analysis

Drug and pesticide residues

Pesticide and veterinary drug residues in crops, drug prototypes, and their metabolites that accumulate in food all pose a concern to human health. One of the main issues in food safety science is the effective analysis of these residues. Widespread usage of insecticides in agriculture is used to reduce weeds and pests and boost crop yields. Pesticides can contaminate the environment outside of their designated area if they are used excessively, which can contaminate food. The recently produced CQDs have the ability to deliver fluorescence measurements that are more exact, accurate, faultless, dependable, reproducible, and reasonably priced. This is

what has caused CQDs to detect and identify pesticide and veterinary medicine residues in food with exponential success over the past few decades. Insecticides have several harmful consequences on humans, such as neurotoxicity, endocrine problems, mutagenicity, and carcinogenesis. Consequently, a technique that can analyze these chemicals sensitively and specifically is needed. Carbon dots have been utilized in recent studies to identify pesticides with limited detection ranges.[52]

Pharmaceutical formulations

In a number of biological applications, CQDs have previously been employed to replace dangerous nanoparticles, but research on how they affect peptides and protein fibrillation is still limited.[3] gel formulations containing N-hydroxyphthalimide-CQDs were developed for this research, and their efficacy against cancer was assessed. Rheological analysis was used to look at loaded gels. The study's findings showed that NHF-CD-loaded gels are more likely to have a noticeable effect on tumor cell proliferation and their tendency to aggregate into spheroids, as well as on the size, abundance, and organization of spheroids.[57] They may stop insulin fibrillation depending on the concentration. This study found that human insulin without CQDs starts to denature within 3 hours at the same temperature conditions, whereas human insulin with CQDs can prevent fibrillation for 5 days at 65°C. Together, CQDs and the monomers and oligomers of insulin have the effect of inhibiting fibrillation. CQDs are a viable choice for usage in the pharmaceutical industry and biological applications for the formulation of insulin because of their inhibitory properties.[58]

Rationale of Development

In a variety of scientific fields, HPLC has become a vital technology for analyzing materials, determining physical constants, and isolating pure components from complex mixtures. Packed particle columns are still popular devices for use in liquid chromatographic separations since of their great usability, good performance, and broad diversity. To improve chromatographic separation's selectivity, specificity, and throughput, scientists are constantly striving to create new stationary phases.[59] Even though new kinds of stationary phases are being made all the time, most columns for (RP-HPLC separations are still made of silica materials. However, silica-based packings are not as stable at very high or very low pH levels, and old or non-silicon-capped reversed-phase columns show some retention issues (RP-column). Other non-living things, like zirconia,[60] titania,[61] and alumina,[62] to get around these problems, HPLC stationary phases with better chemical and temperature stability have been created. They are amphoteric, meaning they share anions and cations, yet they still contain metal hydroxyl and metal oxo-metal groups. Polymer stages have been proposed as a solution to the issues with inorganic RP columns. The most common types of organic beaded polymer support in RP-HPLC are polystyrene-divinylbenzene (PS-DVB) and polymethacrylate.[63] However, polymer phases are not as effective as their inorganic-based cousins because they are not as stiff. For years, scientists have been working on new composite materials that can be used as stationary phases in chromatography. These materials combine the best features of organic polymers and artificial supports to make them better than traditional packings. Coating and coupling methods are often used to make composite materials because it is hard to join macromolecules together. One example is polymer-coated silica. The best thing about polymer-coated inorganic stationary phases is that they have a pH-stable layer that can be easily derivatized for different uses.[64]

Also, these coating methods have some major drawbacks, such as the fact that they lose a lot of specific surface area and don't make the polymer coating spread out evenly. Fortunately, as material science advances, particularly in the field of nanomaterials, new stationary phases emerge on a regular basis. In analytical chemistry, carbon-based nanomaterials, particularly carbon nanotubes (CNTs), play an essential function. CNTs are made of single-walled carbon nanotubes (SWCNTs) or SWCNTs with extra graphene tubes around the core multi-walled carbon nanotubes (MWCNTs). They are constructed from rolled graphite sheets into nanotubes.[65] When applied to conventional materials, this nanostructure modifies their modulus, tensile strength, impact resistance, thermal stability, electrical conductivity, and mechanical stability.[66] CNTs have been investigated for their potential in separation processes due to their excellent thermal and mechanical stability, large surface area for chemical interactions, and amenability to direct synthesis. CNTs have been used as (i) a novel monolithic stationary phase for HPLC and capillary electrochromatography (EC).[67] (ii) an organic solid phase extraction adsorbent.[68] (iii) For liquid chromatography, a stationary phase grows *in-situ* in microfluidic channels on a microfabricated device.[67] (iv) a novel gas chromatography stationary phase.[69] All research addressing the CNT composite stationary phases of HPLC, to the best of our knowledge, referred to the silica-based stationary phases, regardless of how the Si-CNTs material was manufactured. In order to enhance chromatographic behavior in HPLC, we first detail the production of a polymer-CNT composite material for use as column packing. Three distinct synthetic pathways have been explored, with characterizations compared to standard polymer packings. In addition, the applications of this novel stationary phase are discussed.[70]

Applications of HPLC amplified with Carbon-based Nanomaterials

Layer-by-layer self-assembly of MWCNTs on silica microspheres

After spending 24 hours in 37% hydrochloric acid, the silica particles were cleaned in deionized water and dried at 60°C under vacuum for 8 hours before being put together. The process included adsorbing MWCNTs onto a silica microsphere template layer by layer, cleaning the tubes, and testing their stability. Adsorption was initiated by adding 1 g of hydroxyl MWCNTs to 100 mL of 1-mg/mL PSS solution, which was then ultrasonically treated for 2 hours to disperse the MWCNTs so that they could be evenly distributed throughout the surfactant. The dispersion was centrifuged for 20 minutes,

and the supernatant liquid was drained, following which it was ultrasonically treated for 20 minutes and agitated for 3 hours to absorb MWNCTs. Following the above steps, MWNCTs/SiO_2 were washed with water in the centrifuge tube, first by adding 20 mL of water and swirling to generate a turbid liquid, then by centrifuging for 20 minutes and decanting the supernatant liquid. After 10 iterations, no black MWCNTs were detected in the supernatant liquid.[71] So, MWNCTs/SiO_2 can be sintering at 4000C while being protected by high-purity nitrogen. MWNCTs is very stable in this setting, and the hydroxyl groups on MWNCTs and SiO_2 quickly lose their water.[72]

Chromatographic separation of PAHs

The column efficiency was not mentioned,[73] the reason for this is that the PAH chromatographic separation graphs on the two columns are distinct from one another. When it comes to separating PAHs, the MWCNTs/$SiO_{2\text{-}5}$ column performs better. Because the number of MWCNTs atop SiO_2 determines their chromatographic characteristics, this is the case. When the synthesized column was applied to SiO_2, several CNTs bonded to the surface of the semiconductor. As a result, the p-p interactions with PAHs became much stronger, resulting in extended retention durations. The asymmetry factors of PAHs are nearly identical on conventional HPLC columns, but they increase dramatically on the MWCNTs/$SiO_{2\text{-}5}$ column as the PAHs' p-electron system becomes more dominant. This is due to the difference between the hydrophobic interaction of the commercial column and the p-p contact interaction of MWNCTs/$SiO_{2\text{-}5}$ with PAHs.[74]

SWCNTs and MWCNTs for achiral separation of pharmaceuticals and chemicals

As a next step in both quantitative and qualitative research, SWCNTs and MWCNTs have been utilized to extract achiral chemicals from a mixture of pharmaceuticals.[75] It was easier to separate catecholamines, caffeine, and theobromine when they were mixed in a run buffer in CE that had SWCNTs that had been changed with carboxylic acids. We looked at how an electrophoretic solution containing theobromine and caffeine (1:1) behaved in CE by adding c-SWCNT as a buffer. It took longer for theobromine and caffeine to move, the peak width grew, and the peak height went down when c-SWCNT was added to the buffer solution. When c-SWCNTs concentration was 0.1 mg/mL, the retention time and peak shape were better (Rs = 1.34) than when the buffer solution was used alone (Rs = 0.69).[76] These groups may form because of Van der Waals forces pulling free CNTs toward the hydrogen bonding sites of the carboxylic groups connected to c-SWCNTs. Analytes with different pore sizes move through these clusters during the separation process. This shows how important CNTs are in creating network-like structures and, by extension, in separating analytes.[77]

CONCLUSION

The importance of CQDs in enhancing analytical technique responses is becoming increasingly evident. The construction of a very sensitive sensing platform is made possible by the physiochemical capabilities of CQDs, such as their fluorescence qualities with photobleaching and photo blinking, emission tuning, and chemical stability. When it comes to nanotechnology applications including sensors, bioimaging agents, assays, phototherapy, photocatalysis, drug carriers, and electrocatalysis, CQDs have already proven to be quite promising. However, further research is needed to enhance the sensitivity, selectivity, and robustness of CQDs so that they can be used in a wider range of sensing and bioimaging applications. In an effort to lessen the distraction caused by the auto-florescence of the biological sample and to reduce the amount of background noise, the delayed fluorescence approach was employed.

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