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Review article

Updated review on carbon dots: their synthesis, characterization and analytical applications

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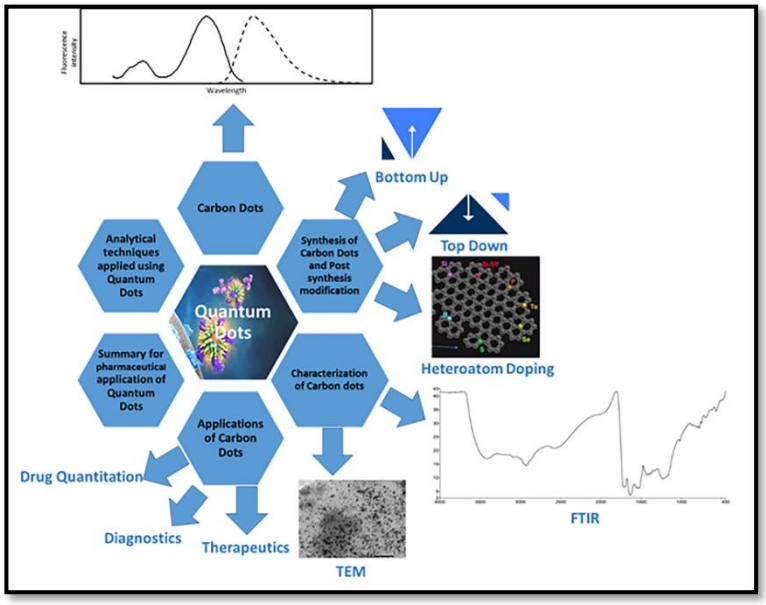
Abstract

One of the most significant advancements in the rapidly expanding field of nanotechnology is colloidal semiconductor nanocrystals, often known as quantum dots. Originally suggested as fluorescent biological markers, they are now discovering significant new applications in analytical chemistry owing to their promising optical, structural, and electrical properties. Carbon dots have attracted a lot of attention lately because of their sustainability, strong biocompatibility, water solubility, low cost of manufacture, and superior chemical stability. Two main methods are used to synthesize carbon dots; the first method is top-down technique while the second method is bottom-up technique. Enhancing the photoluminescence, electrical, and structural properties of carbon dots can be achieved via a dependable and versatile method called hetero-atom doping. Carbon dots are used in versatile fields such as; imaging, sensing, cancer treatment, drug quantitation, gene therapy, photodynamic therapy, photothermal therapy, and microorganism eradication. An overview of recent applications of quantum dots from 2011 to 2024 will be presented in this review, which has 50 references.



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Keywords: Quantum dots, Carbon dots, Sustainability, Photoluminescence, Therapeutics and Diagnostics.

1. Introduction

Quantum dots (QDs) also known as "artificial atoms, are created using nanotechnology and widely applied in numerous clinical and commercial items, as well as in biological sciences. QDs are nano-scale crystals made of semiconductor material, they are ultra-small, often falling between 2 and 10.0 nm in size. This size corresponds to about 10-50 atoms in diameter. The QDs can be compared to atoms: both have discrete energy levels and contain a number of electrons, However, in contrast to atoms, quantum dots do not always exhibit spherical symmetry. Moreover, the electrons do not move in the limited space, but inside the semiconductor crystal that hosts them [(1)].

They have unique electronic and fluorescent characteristics, such as narrow spectra, high photochemical stability, continuous absorption spectra, tunable fluorescence (from deep UV to NIR), stability against photobleaching (photoluminescence degrades over time) and photoblinking, and strong fluorescence. These extraordinary optical and electrical characteristics associated with small size and high surface area make them ideal for biomedical and biotechnological applications [(2)].

They have distinctive structural features such as extremely minute size, high surface-to-volume ratio, low toxicity, high biocompatibility, high permeability, weak interactions with proteins, easy clearance from the body, low cost, and low immune system evasion. Therefore, they are used in cell imaging and after suitable conjugation can be used for diagnostics and therapeutics.[2] Fluorescent probes are molecules that are used to analyze materials because they absorb light at one wavelength and emit light at another, usually longer wavelength. This phenomenon is known as fluorescence. The molecules, also known as fluorophores, can be attached to a target molecule and act as a marker for analysis. They have high sensitivity and fast response [(2, 3)]. However, quantum dots were proved to be superior over conventional fluorophores because they have a wide range of optical properties not present in organic fluorophores as they possess a broad absorption spectrum, which allows free selection of the excitation wavelength and large stokes shift which increases its sensitivity. They are also more stable because of their inorganic composition, which minimizes the impact of photobleaching. Moreover, multicolor quantum dots can be excited simultaneously without signal overlap using a single light source. QSs have prolonged activity in vivo; this is partially due to their inorganic composition, which also increases their resistance to metabolic degradation. Furthermore, the multicolor property of QDs allows the use of many probes to track several targets in vivo simultaneously. Additionally, the fluorescence duration of quantum dots is approximately 10 to 40 ns, while the fluorescence of fluorophores fades away after few nanoseconds [(2, 3)].

2. Analytical techniques applied using quantum dots

2.1. Fluorescence

From the viewpoint of chemical analysis, QDs' photoluminescence properties are their most significant characteristic. QDs have the ability to absorb light at a broad bandwidth and to emit at a narrow spectrum. The emission intensity is dependent on the quantum yield, which in turn is conditioned by the type of surface interactions between QDs and the proposed analyte. [(4)].

2.1.1. Direct fluorescence measurements

Several techniques for modifying the fluorescence of QDs have been used,

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including emission wavelength shifting, intensity enhancement, and quenching. The most widely used mechanism is the quenching effect, which occurs when a certain analyte suppresses the fluorescence of QDs [4].

2.1.2. FRET (Förster resonance energy transfer)

Process of non-radiative transfer of energy from a donor chromophore in an excited electron state to an acceptor chromophore. QDs act as FRET donors and labelled target analyte act as FRET acceptor. [4].

2.2. Chemiluminescence

Basically, chemiluminescence occurs as the result of a chemical reaction. The involvement of quantum dots in a chemiluminescence process can be explained by one of three approaches: a) QDS can act either as a catalyst of a reaction involving other luminophores, b) as emitter species, after direct oxidation, or c) as emitter species, after chemiluminescence resonance energy transfer. This can be explained as the transfer of non-radiative energy between a fluorescent acceptor and a chemiluminescent donor [4].

2.3. Liquid chromatography

Fundamentally, mixtures can be physically separated using the widely applied liquid chromatographic technique. Resolution is determined by the analyte's dispersion between liquid and stationary phases. QDs can be an effective tool in liquid chromatography since they can serve as labels that facilitate analyte identification and signaling [4].

Ideal liquid chromatography detector should provide high sensitivity, fast response, and low noise level. This is where fluorescence has proven to be incredibly helpful as a detection method, providing some of the highest sensitivities and selectivity in liquid chromatography [4]. Quantum dots were also selected as functional materials to enhance the C18 column's separation performance; because carbon dots may offer a variety of interactions, including hydrophilic, π-π bonding, and hydrogen bonding interactions. [4].

2.4. Capillary electrophoresis

When an analyte is subjected to a uniform electric field, its varying charge/size ratios cause it to move differently, thus explaining how the capillary electrophoresis technique is used for separation. QDs have an electric surface charge, thus rendering them ideal for employment in capillary electrophoresis. Capillary electrophoresis is one of the most powerful separation techniques with noteworthy advantages in terms of simplicity, low sample consumption, high separation efficiency, and rapidity. QDs separation, composition, and size distribution have been almost characterized using the capillary electrophoresis technique [4].

3. General information about carbon dots

3.1. Structure of carbon dots (C-dots)

Carbon-based materials are composed of graphene, diamond, graphite, and carbon nanotubes. C-dots are commonly described as possessing a carbogenic core consisting of crystalline and amorphous constituents with surface functional groups. The structures of C-dots core are particularly abundant with oxygen/nitrogen-based moieties, including carboxyl, hydroxyl, aldehyde, and amino groups [5].

3.2. Synthesis of C-dots

The two main methods for synthesizing C-dots are top-down and bottom-up **(Table 1)**. Four processes are involved in the creation of C-dots from precursors: passivation, carbonization, polymerization, and dehydration. After the synthesis step, there are typically unreacted precursors, side products, and big carbon particles present in addition to C-dots. Thus, several cycles of centrifugation/ washing are required to remove the remaining large carbon particles, as well as the undesirable products. High-

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purity C-dots can be obtained by dialysis of the supernatant once more [6].

Table 1. Comparison between top-down and bottom-up strategies employed in C-dots synthesis.

	Top-down methods			
	Electrochemical oxidation	**Laser ablation**	**Chemical oxidation**	**Ultrasonic synthesis**
Advantages	• Good reproducibility • Controlled size • High purity • High yield	• Easy to set up and to modify the experimental conditions to produce particles with varying sizes and adjustable shape	• Low-cost technology that can generate C-dots on a massive scale	• Simple to use
Disadvantages	• Challenging process, particularly when doping with heteroatoms	• High cost and low yield	• Many laborious steps, typically involving strong acid/base and hazardous reagents. • Distribution of sizes is not uniform	• Excessive waste and energy consumption
	Bottom-up methods			
	Hydrothermal treatment	**Microwave synthesis**	**Thermal decomposition**	
Advantages	• Inexpensive • Easy control over important variables including reaction vessel pressure, temperature, and time. • Non-toxic • Generated C-dots have a high quantum efficiency.	• Quick reaction time • Easy particle size management	• Solvent-free • Low cost • Simple to use • Capable of producing enormous quantities of C-dots	
Disadvantage	• Extended synthesis • Poor yield	• Cost high energy	• Low yield	

3.2.1. Top-down methods

The term is employed to describe the dissolution or cleavage of bigger carbon structures through physical, chemical, or electrochemical means. These larger carbon precursors include carbon black graphite powder, carbon nanotubes, carbon rods, and carbon fibers. The top-down cleaving techniques include electrochemistry, chemical oxidation, and laser ablation. However, this approach has many disadvantages such as the use of expensive materials, harsh reaction conditions, and long reaction times **(Fig. 1)** [6].

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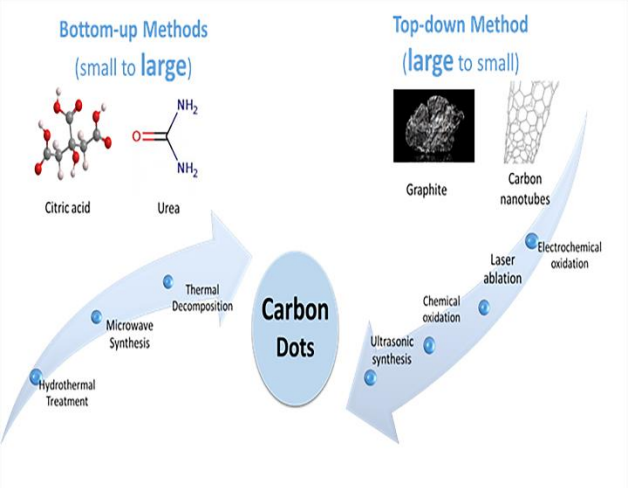

Fig. 1. Summary of methods utilized for C-dots synthesis.

3.2.2. Bottom-up methods

Bottom-up techniques, which include transforming tiny carbon structures into C-dots, are the second main strategy to manufacture C-dots. In general, bottom-up methods are economical and effective for mass-producing luminescent C-dots. The dehydration and carbonization processes can be carried out in a variety of ways, including; pyrolysis in concentrated acid, hydrothermal, microwave, and combustion procedures **(Fig. 1)** [6].

3.2.3. Post-synthesis modification (Passivation methods)

Modifications to C-dots can be made to their surface functionalization, also known as passivation, or to their core structure by partially substituting other elements for carbon [6].

In order to enhance the electrical and optical characteristics of C-dots, passivation techniques are required. Doped heteroatoms include nitrogen, sulfur, boron, phosphorous, and silicon. Heteroatom doping boosts the fluorescence quantum yield and improves the photoluminescence characteristics of C-dots. Reactive sites are introduced to the C-dot surface during the passivation process in order to modify their functional properties. These sites include hydroxyl, amine, and carboxyl groups. It is possible to attach various specific inorganic, organic, polymeric, or biological materials to the C-dot surfaces via covalent bonds, hydrogen bonds, or electrostatic interactions. [6].

A good example of passivation agents is polyethyleneimine (PEI), a cationic polymer that promotes the binding of functional moieties to C-dots and has a high density of amino groups. PEI modifies C-dots by electrostatically interacting with the carboxyl groups (-COOH) on the surface of the C-dots and the positively charged amino groups of PEI [6].

Numerous research groups have made extensive use of N and S co-doped C-dots because nitrogen possesses five valence electrons that allow it to form bonds with carbon atoms in the C-dots and an atomic radius that is similar to that of carbon. Additionally, because of their significant Stokes shift, sulphur atoms can produce energy that changes the electronic structure of C-dots and further prevents self-quenching. The N, S co-doping was found to possess excellent fluorescence properties with minimum toxicity and various applications. N, S, and C-dots were synthesized by different reagents such as citric acid and L-cysteine or by citric acid and ammonium thiocyanate as precursors. [7].

3.3. Characterization of C-dots

It is thought that one of the most crucial tasks in learning about the synthetic features of the C-dots is to characterize them [1, 7]. Thus, various techniques have been exploited for their characterization as discussed below.

3.3.1. UV Spectrophotometry

Typically, C-dots exhibit optical absorption in the ultraviolet spectrum along with a tail that reaches into the visible spectrum. Absorption peaks corresponding to the π-π* transitions of C=C bonds and the n-π* transitions of C=O bonds might be present [1, 7].

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3.3.2. Spectrofluorimetry

One of the most interesting features of C-dots is photoluminescence. QDs' size and shape are directly correlated with their fluorescence qualities (quantum dot size can be modified during manufacture). The band gap of a quantum dot, for instance, is inversely correlated with its size and controls the frequency range of light emitted. When the QD's size reduces, the frequency of light released increases, and the light's colour changes from red to violet. Due to their longer lifespan and more closely spaced energy levels. Larger dots appear to have a longer lifespan as explained in **(Fig. 2.)** [1, 7].

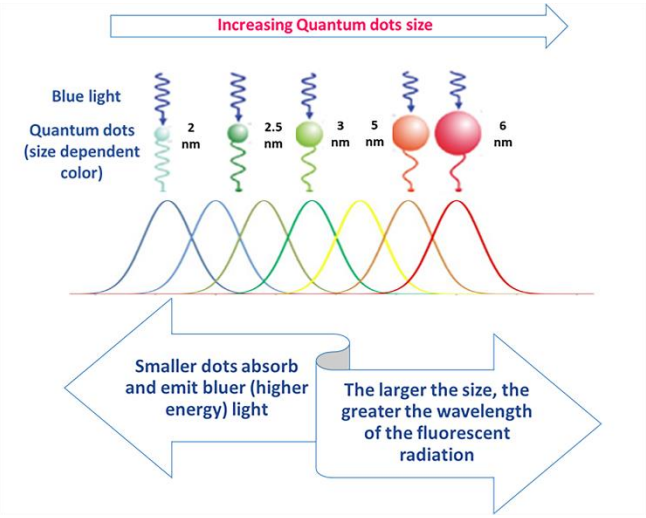

Fig.2. Effect of size on fluorescence of QDs.

3.3.3. Transmission Electron Microscopy (TEM)

Owing to TEM's excellent resolution (0.1–0.2 nm), which allows materials to be amplified from tens of thousands to millions of times, it is frequently used to examine C-dots morphology and determine characteristics like size, shape, and dispersion **(Fig. 3)** [1, 7-9].

3.3.4. X-ray Diffraction (XRD)

The primary application of XRD in the characterization of C-dots is to disclose details regarding their crystallinity and particle size. Consequently, creating a straightforward method to investigate clustering at atomic resolution [1, 7].

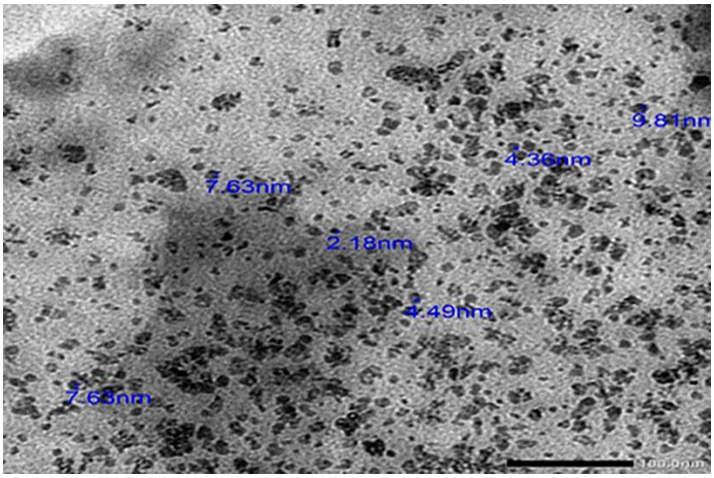

Fig.3. Typical TEM image of N, S-C-dots [8,9].

3.3.5. X-ray Photoelectron Spectroscopy (XPS)

To evaluate the elemental composition, chemical state, and electronic state of the elements within C-dots, XPS is a useful quantitative spectroscopic technique [1, 7].

3.3.6. Fourier-Transform Infrared Spectroscopy (FTIR)

Since C-dots are created by partial oxidation of carbon precursors, their surfaces are rich in epoxy/ether, hydroxyl, carbonyl, or carboxylic acid groups. FTIR is a powerful tool for examining these important functional groups as illustrated in **(Fig. 4).** C-dots are typically composed of carbon, oxygen, and hydrogen. Accordingly, FTIR analysis of these oxygen-containing groups is simple [1, 7-9].

3.3.7. Nuclear Magnetic Resonance (NMR)

To gain more structural insight into C-dots, NMR technique is widely utilized to ascertain the binding mechanism between carbon atoms and their hybrid forms in crystalline lattices [1, 7].

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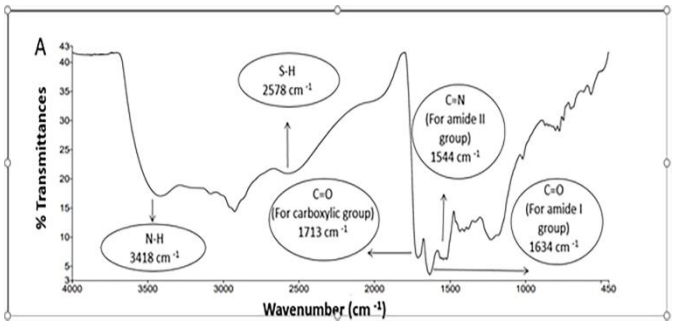

Fig. 4. FTIR spectrum of N, S-C-dots [8,9].

3.4. Applications of C-dots

C-dots have different applications in different fields **(Fig. 5).**

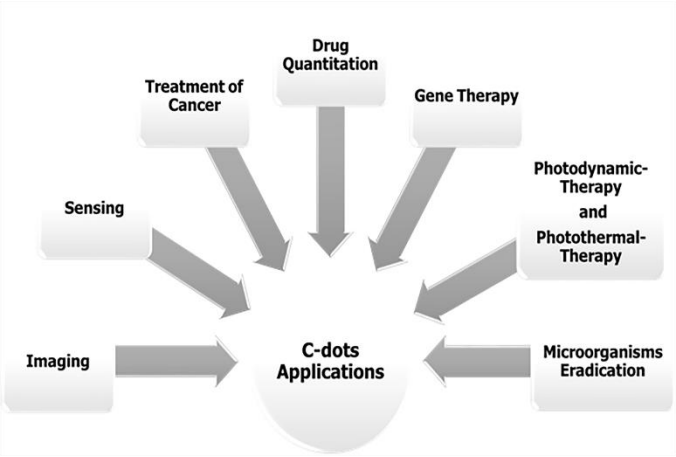

Fig.5. Schematic representation for C-dots applications.

3.4.1. Diagnostic

The unique optical features, high surface area, variable surface functionalization capabilities, low toxicity, and good biocompatibility of C-dots have made them useful for a wide range of biomedical applications as displayed below [6].

3.4.1.1. Imaging

Since C-dots do not typically photobleach like the majority of currently employed fluorescence tracking dyes, they are generally preferred over current organic dyes because of their advantages, which include: a multicolor emission profile, tiny sizes, minimal cytotoxicity, strong biocompatibility, and outstanding photostability. Long excitation wavelengths have the capacity to penetrate deep tissue, which makes them particularly attractive for in vivo imaging. owing to the small size of C-dots, they are easily internalized into the cytoplasm. However, due to the prevalence of carboxylate groups on their surface, C-dots are primarily negatively charged, making it difficult for them to penetrate the cell nucleus [6].

3.4.1.1.1. Example of C-dots used in imaging

Fluorescent-core C-dots were synthesized through carbonization of ammonium citrate via dry heating. Afterward, the C-dots were heated with mannose and folic acid to prepare mannose-functionalized C-dots and folic acid-functionalized C-dots through a dehydration reaction in the solid state. C-dots prepared via a dry heating approach have been used for elective labeling of E. coli and folate receptor-positive cancer cells [10].

3.4.1.2. Sensing

The unique properties of C-dots, such as their water solubility, reduced cytotoxicity, greater photostability, and excitation-dependent emission, make them useful as chemical-sensing materials. The typical method of this sensing is a change in their fluorescence characteristics, which can happen through a variety of processes, including; photo-induced electron and charge transfer, inner filter effect, and resonance energy transfer. C-dots can be used for sensing several biological molecules and intracellular metal ions, such as hydrogen peroxide (H_2O_2), Fe^{3+}, glucose, vitamin B12, and galactose [6].

3.4.1.2.1. Metal ion sensors

C-dots can be used for direct chemical sensing of metal ions. These interactions with the C-dots' surface functional groups lead to the change in the fluorescence nature of the C-dots, therefore they are used for the detection of Hg^{2+}, Ag^{+}, $Cu^{2+,}$ and Fe^{3+} ions.

Water-soluble C-dots were prepared by pyrolysis of ethylenediamine-tetraacetic acid

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(EDTA) salts. The addition of Hg^{2+} to the synthesized C-dots leads to fluorescence quenching. However, the subsequent addition of biothiols to the Hg^{2+}/C-dots recovered the fluorescence via the removal of Hg^{2+} ions, which has a high affinity towards the thiol (-SH) groups [11].

3.4.1.3. Drug quantitation

It has been demonstrated that C-dots help quantify abused medicines. C-dots prepared from L-arginine through a hydrothermal route have been used for quantitation of 4-chloroethcathinone which induces fluorescence quenching of C-dots through an electron transfer process [12].

3.4.2. Biomedical applications of C-dots (therapeutic)

Designing systems for drug delivery requires ensuring the drug's appropriate interactions with the target while also enabling the drug to be transported to a specified location within the body. It is possible to enhance drug delivery systems in terms of drug absorption, distribution, and elimination by conjugating nanostructured materials with the drug [6]. C-dots have many advantages as a method of delivery to a specific cell or tissue; as they enhance the delivery of drugs with low water solubility, deliver two or more drugs at the same time, transfer large macromolecule drugs, and also we can monitor drug sites using imaging agents on the drug carrier [6].

3.4.2.1. Cancer treatment

C-dots are often superior to conventional drug delivery systems in cancer treatment. Doxorubicin (DOX) can be efficiently delivered to the desired location of interest using the C-dots methodology [13]. C-dot's fluorescence intensity decreases and DOX fluorescence increases as a result of the high FRET efficiency phenomenon between C-dots and DOX. C-dots act as electron donors whereas, DOX is regarded as an electron acceptor. This FRET-based two-photon imaging C-dots-DOX system provides real-time monitoring of the drug release profile. The C-dots themselves remained in the cytoplasm, but the DOX could progressively separate from their surface and enter the cell nucleus [13].

3.4.2.2. Gene therapy

Numerous achievements have been made in gene therapy as a therapeutic strategy to treat numerous severe diseases. Viral vectors are the most efficient vectors in the delivery of genes. But viral sectors have serious issues such as; strong immunogenic reactions, very limited capacity to accommodate long nucleic acids, and high production costs. C-dots have the potential to be a multipurpose delivery system that can carry genes and medications [6].

3.4.2.3. Photodynamic therapy (PDT) and photothermal therapy (PTT)

PTT and PDT represent a novel class of therapeutic approaches that use laser light to treat medical conditions. For PTT, in order to transform the absorbed energy into heat, the photo absorber needs to have a high absorbance in the near-infrared spectrum. Photons cause localized heat generation, which causes the target cells to be thermally ablated and eventually die. PTT has considerable advantages over other conventional therapeutic procedures for cancer treatment, such as harsh surgery, chemotherapy, or radiotherapy. These advantages include non-invasiveness, high specificity, and exact temporal selectivity [6]. There are a lot of electrons in the inherent C-dot structure, which leads to strong electron-electron interactions. This implies that a variety of non-radiative mechanisms can convert the majority of the absorbed light into heat. Because of their ease of synthesis, surface functionalization, superior carrying capacity, and outstanding biocompatibility, C-dots have been widely employed to deliver photosensitizer chemicals to target tissue [6].

3.4.2.4. Microorganisms eradication

Using a one-step dry heating synthesis of fluorescent carbon quantum dots from

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spermidine, the therapeutic application of C-dots in infectious disease has been proven in the treatment of bacterial keratitis caused by S. aureus [14]. Super-cationic carbon dots effectively kill both gram-positive and gram-negative bacteria, as well as multidrug-resistant bacteria, such as Methicillin-resistant Staphylococcus aureus (MRSA). Positively charged amino groups in the carbon dots that were synthesized were thought to be the triggering factor behind the antibacterial activity of C-dots, leading to bacterial mortality and significant damage to the membrane [6, 14].

Moreover, a detailed summary of the recently published [15-51] pharmaceutical applications of Quantum dots (QDs) is demonstrated in **Table 2**.

Table 2. Summary for pharmaceutical application of quantum dots (QDs).

Method name	Analyte	C-dots	Linearity range	LOD	Method of detection
1-Sensitive determination of kaempferol using carbon dots as a fluorescence probe[15]	Kaempferol used for treating cough, ulcer, bronchial asthma, diabetes, cataract, and can be used as an anti-inflammatory drug	C-dots were prepared by simply mixing acetic acid, water, and diphosphorus pentoxide	3.5–49 mM	38.4 nM	Fluorimetric determination as the drug greatly quenches the fluorescence intensity of the C-dots
2-Optical Nanobiosensing of stibogluconate in plasma and urine using green synthesized fluorescent carbon Nano dots[16]	Stibogluconate used as anti-leishmaniasis drug	Fluorescent carbon nanodots prepared from a green source of carbon atoms (garlic peels)	0.01–0.10 µg/ mL	0.003 µg/ mL	Fluorimetric determination by the quenching effect of antimony found in stibogluconate drugs.
3- Utilization of N, S-doped carbon dots as a fluorescent nanosensor for determination of cromolyn based on inner filter effect: application to aqueous humour [17]	Cromolyn sodium used as anti-allergic drug	N- and S-co-doped carbon quantum dots probes synthesized from thiosemicarbazide and citric acid	10.0–150.0 µM	2.0 µM	Fluorimetric determination as adding increasing concentrations of the drug to N, S-CQDs led to quenching of its fluorescence intensity
4- Turn-off fluorescence of S, N-doped carbon dots for determination of two nitro-containing drugs in dosage forms and human plasma [18]	1-Nitrofurantoin used as an antibacrerial drug 2- Dantrolene used as a muscle relaxant	N- and S-co-doped carbon quantum dots probes synthesized from thiosemicarbazide	1- 0.5-80 µg/ mL 2- 1-10 µg/ mL	1-0.14 µg/ mL 2-0.23 µg/ mL	Fluorimetric determination as adding increasing concentrations of the drug to N, S-CQDs led to quenching of its fluorescence intensity
5- Azithromucin detection in cells and tablets by N, S co-doped carbon dots [19]	Azithromycin used as a broad-spectrum antibiotic	N, S co-doped carbon dots prepared from 3aminothiophenol	2.5-32.3 µM	0.6 µM	Fluorimetric determination as adding increasing concentrations of the drug to N, S-CQDs led to quenching of its fluorescence intensity
6-Fluorescent carbon dots as nanoprobe for	Lidocaine hydrochloride	Fluorescent N-doped carbon dots	0.185-1.29 mmol/ L	0.054 mmol/L	Fluorimetric determination as

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determination of lidocaine hydrochloride [20]	is used as local anesthesia and antiarrhythmic	were synthesized through hydrothermal treatment of an easily available fish scales precursor			Adding an increasing concentration of the drug to N, CQDs led to quenching of its fluorescence intensity
7- Fast one-pot microwave-assisted green synthesis of highly fluorescent plant-inspired S, N-self-doped carbon quantum dots as a sensitive probe for the antiviral drug nitazoxanide and hemoglobin [21]	1- Nitazoxanid is used as antiviral and antibiotic drug 2- Hemoglobin in blood samples	Co-doped carbon quantum dots (S, N-CQDs) prepared by 4-min microwave treatment of onion and cabbage juices	1- 0.25–50.0 μM 2- 36.3–907.5 nM	1-0.07 μM 2- 10.30 nM	Fluorimetric determination as adding an increasing concentration of the drug to N, S-CQDs led to quenching of its fluorescence intensity
8- Tuning of carbon dots emission color for sensing of Fe^{3+} ion and bioimaging applications[22]	Fe^{3+} ion in iron tablets and biofluids	Three (blue, green, and yellow) fluorescent color carbon dots obtained from tomato	0.1 to 2.0 μM	0.016, 0.072, and 0.065 μM using blue-, green- and yellow C-dots	Fluorimetric determination, as the fluorescence intensity of three fluorescent color CDs was quenched linearly with increasing Fe^{3+} ion concentration
9- Carbon dots as a dual sensor for the selective determination of D-penicillamine and biological applications [23]	Penicillamine used as chelating agent to treat Wilson's disease, cystinuria, and rheumatoid arthritis	Fluorescent carbon dots obtained from Mahogany fruit shell	0-48 μg mL^{-1}	-	Fluorimetric determination depending on fluorescence quenching
10-Simultaneous determination of paracetamol and p-aminophenol using glassy carbon electrode modified with nitrogen- and sulfur- co-doped carbon dots [24]	1-Paracetamol is used as analgesic and antipyretic. 2- P-aminophinol is a main paracetamol impurity	N, S co-doped carbon dots prepared from walnut used to prepare novel electrochemical sensor	1- 0.1 - 220 μM 2- 1-300 μM	1- 26 nM 2- 38 μM	Cyclic voltammetry as the modified electrode exhibits good catalytic ability towards paracetamol and p-aminophenol, and baseline separation of their oxidation peaks
11- Electrochemiluminescence sensor for pentoxifylline detection using Au nanoclusters@graphene quantum dots as an amplified electrochemiluminescence luminophore [25]	Pentoxifylline is used for treatment of peripheral vessel diseases	Luminophore was synthesized through an amide coupling reaction between Au nanoclusters and graphene quantum dots	7.0 × 10−7 to 1.2 × 10-4 mol/L	9.0 × 10-8 mol/L	The fabricated electrochemiluminescence sensor based on the quenching effect of pentoxifylline on the signal of Au NCs@GQDs
12- Defective mesoporous carbon ceramic electrode modified graphene	Zolpidem is used as sedative and hypnotic	Carbon ceramic electrode with graphene quantum dots	0.1 and 1 and 1–10 μM	0.061 μM	Differential pulse voltammetry was used as electrochemical

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quantum dots as a novel surface-renewable electrode: the application to determination of zolpidem [26]					technique for drug determination.
13- Synthesis of glycine-functionalized graphene quantum dots as highly sensitive and selective fluorescent sensor of ascorbic acid in human serum [27]	Ascorbic acid is used as antioxidant	Photoluminescent glycine functionalized graphene quantum dots using ethylene glycol as carbon source	0.03–17.0 μM	25 nM	The fluorescence of GLY-GQDs was intensively quenched by Ce^{4+} via forming nonluminescent complexes of GLY-GQDs-Ce^{4+}. When ascorbic acid was added, Ce^{4+} was reduced to Ce^{3+} , and the fluorescence of GLY-GQDs was regained
14- Development of molecular imprinted sensor including graphitic carbon nitride/N-doped carbon dots composite for novel recognition of epinephrine [28]	Epinephrine or adrenaline is a neurotransmitter agent in central nervous system	Carbon nitride/N-doped carbon dots composite	1.0×10^{-12} - 1.0×10^{-9} M	3.0×10^{-13} M	Electrochemical recognition based on graphitic carbon nitride/N-doped carbon dots. (cyclic voltammetry)
15- Simultaneous determination of ascorbic acid, dopamine, and uric acid using graphene quantum dots/ionic liquid modified screen-printed carbon electrode [29]	1-Ascorbic acid is used as an antioxidant 2-Dopamine is a neurotransmitter. 3- Uric acid is a product of purine metabolism	Graphene quantum dots	1- 25–400 μM2- 0.2–10 μM 3- 0.5–20 μM	1- 6.64 μM 2- 0.06 μM 3- 0.03 μM	Graphene quantum dots (GQDs) and ionic liquid (IL) modified screen-printed carbon electrode exhibited excellent electrocatalytic activity for the oxidation of the 3 analytes
16- Graphene quantum dots-functionalized C18 hydrophobic/hydrophilic stationary phase for high-performance liquid chromatography [30]	Aromatic hydrocarbons, alkylbenzenes, anilines, phenols, aromatic acids, alkaloids, nucleosides and nucleobases	Graphene quantum dots	-	-	Graphene quantum dots (GQDs) were chosen as functional material to improve the separation performance of C18 column in HPLC
17-Determination of pesticides by capillary chromatography and SERS detection using a novel Silver-Quantum dots "sponge" nanocomposite [31]	Pesticides As chlortoluron, atrazine, diuron and terbuthylazine	Silver quantum dots	-	0.2 ng	Capillary-liquid chromatography-(microdispenser)-surface-enhanced Raman spectroscopy
18- Selection of the Optimal Chromatography	Cadmium selenide (CdSe)/	CdSe/ZnS QDs	-	-	Size exclusion chromatography (SEC) for the

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Medium for Purification of Quantum Dots and their Bioconjugates [32]	zinc sulphide (ZnS) QDs				separation of QDs and byproducts of bioconjugation
19- Development of plasmonic thin-layer chromatography for size-selective and optical-property-dependent separation of quantum dots [33]	Au quantum dots	Au quantum dots	-	-	Plasmonic optical trapping with thin-layer chromatography
20-Separation of Bioconjugated Quantum Dots Using Capillary Electrophoresis [34]	-	CdSe/ZnS quantum dots bioconjugated with streptavidin, biotin, and immunoglobulin G	-	-	Capillary electrophoreses with laser-induced fluorescence (LIF) detection
21- Quantum dot-enhanced chemiluminescence detection for simultaneous determination of dopamine and epinephrine by capillary electrophoresis [35]	1- Dopamine 2- Ephedrine both are neurotransmitters	Cadmium telluride (CdTe) quantum dots	1- 8.0×10^{-8}–5.0×10^{-6} M 2- 4.0×10^{-8}–5.0×10^{-6} M	1- 2.3×10^{-8} M 2- 9.3×10^{-9} M	Capillary electrophoresis–chemiluminescence
22- Graphene quantum dots for enhancement of fluorimetric detection coupled to capillary electrophoresis for detection of ofloxacin [36]	Ofloxacin used as broad-spectrum antibiotic	Graphene quantum dots	50 -1000 ng/mL	10.7 ng/mL	Fluorimetric detection coupled to capillary electrophoresis
23-Study of Interaction between Metallothionein and CdTe Quantum Dots [37]	Metallothioneins are a group of proteins	CdTe Quantum Dots	-	3.6 μM	The mixtures were studied by spectrophotometry within the range from 200 to 750 nm
24- Electrogenerated chemiluminescence detection of trace-level pentachlorophenol using carbon quantum dots [38]	Pentachlorophenol is an environmental pollutant	Carbon quantum dots	10 pg L^{-1}~1.0 μg L^{-1}	1.3×10^{-12} g L^{-1}	Quenching of Electrogenerated chemiluminescence
25-Green one-pot synthesis of nitrogen and sulfur co-doped carbon quantum dots as new fluorescent nanosensors for determination of salinomycin and maduramicin in food samples [39]	1-Salinomycin 2-Maduramicin both are antibiotics	Nitrogen and sulfur co-doped carbon quantum dots (N, S-CQDs) using citric acid and thiosemicarbazide.	10.0–300.0 μM	1- 2.07 μM 2- 1.34 μM	Fluorimetric determination as adding increasing concentrations of the drug to N, S-CQDs led to quenching of its fluorescence intensity
26-Nitrogen and sulfur-doped carbon quantum dots as fluorescent	1- Olanzapine 2- Diazepam both are atypical	Nitrogen and sulfur co-doped carbon quantum dots (N,	1- 5.0–200.0 μM 2- 1.0–100.0 μM	1- 0.68 μM 2-0.29 μM	Fluorimetric determination as

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nanoprobes for spectrofluorimetric determination of olanzapine and diazepam in biological fluids and dosage forms: application to content uniformity testing [40]	antipsychotic medications	S-CQDs) using citric acid and thiosemicarbazide			adding increasing concentrations of the drugs to N, S-CQDs led to quenching of its fluorescence intensity
27- A Novel Quantum Dots-Based Fluorescent Sensor for Determination of the Anticancer Dacomitinib: Application to Dosage Forms [41]	Dacomitinib used as anticancer.	Nitrogen-doped carbon quantum dots were prepared using a microwave-assisted approach utilizing orange juice (a carbon source) and urea (a nitrogen source)	1.0−20.0 µg/mL	0.11 µg/mL	Fluorimetric determination as adding an increasing concentration of the drug to N, -CQDs led to quenching of its fluorescence intensity
28-Application of sulfur and nitrogen-doped carbon quantum dots as sensitive fluorescent nanosensors for the determination of saxagliptin and gliclazide [42]	Saxagliptin and gliclazide are. antidiabetic drugs	Nitrogen and sulfur co-doped carbon quantum dots (N, S-CQDs) using citric acid and thiosemicarbazide	1- 30.0–500.0 µM 2- 2-75.0–600.0 µM	1- 5.0 2- 10.15 µM	Fluorimetric determination as adding increasing concentrations of the drug to N, S-CQDs led to quenching of its fluorescence intensity
29- Sulfur and nitrogen co-doped carbon quantum dots as fluorescent probes for the determination of some pharmaceutically important nitro compounds [43]	1-Rifampicin 2-Tinidazole 3-Ornidazole 4-Metronidazole (antimicrobial drugs)	Nitrogen and sulfur co-doped carbon quantum dots (N, S-CQDs) synthesized using citric acid and thiosemicarbazide	1- 1.0–30.0 µM 2- 10.0–200.0 µM 3- 6.0–200.0 µM 4- 5.0–100.0 µM	1- 0.31 µM 2- 1.76 µM 3- 0.57 µM 4- 0.75 µM	Fluorimetric determination as adding an increasing concentration of the drugs to N, S-CQDs led to quenching of its fluorescence intensity
30- Green “turn-of” luminescent nanosensors for the sensitive determination of desperately fluorescent antibacterial antiviral agent and its metabolite in various matrices [8]	1- Nitazoxanide (antibacterial and antiviral drug) 2-Tizoxanide (Nitazoxanide metabolite)	Nitrogen and sulfur co-doped carbon quantum dots (N, S-CQDs) synthesized using citric acid and l-cysteine	15×10^{-3}–15.00 µg/mL	56.00×10^{-4} µg /mL	Fluorimetric determination as adding an increasing concentration of the drug/ its metabolite to N, S-CQDs led to quenching of its fluorescence intensity
31- White sustainable luminescent determination of nifuroxazide using nitrogen–sulphur co-doped carbon quantum dots nanosensor in bulk and various pharmaceutical matrices [9]	Nifuroxazide (antimicrobial drug)	Nitrogen and sulfur co-doped carbon quantum dots (N, S-CQDs) synthesized using citric acid and l-cysteine	0.04–15 µg /mL	0.005 µg /mL	Fluorimetric determination as adding increasing concentrations of the drug to N, S-CQDs led to quenching of its fluorescence intensity
32- A novel ultrafast synthesis of N, S-doped carbon quantum dots as a	1- Entacapone	Nitrogen and sulfur co-doped carbon quantum dots	1- 1.0 - 15.0 µM 2- 2.0 – 25.0 µM	-	Fluorimetric determination as

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fluorescent nanoprobe for entacapone and clonazepam estimation in tablets and human plasma: Compliance with greenness metrics and content uniformity testing [44]	2- Clonazepam (used in treatment of Parkinsonism)	prepared using thiourea and Dill (Anethum vulgaris)			adding an increasing concentration of the drugs to N, S-CQDs led to quenching of its fluorescence intensity
33- Copper-nitrogen doped carbon nanosheet-based electrochemical sensors for the detection of luteolin and baicalein [45]	1- Luteolin 2- Baicalein anticancer drugs)	Copper-nitrogen doped porous carbon materials prepared by one-step pyrolysis method	1- (0.05–20.0) × 10^{-6} mol/L 2- (0.05–20.0) × 10^{-6} mol/L	1- 5.30 × 10^{-8} mol/L 2- 9.10 × 10^{-8} mol/L	Differential pulse voltammetry.
34-Applications of Green Terbium- and Nitrogen-Doped Carbon Quantum Dots as a Fluorescent Nanoprobe for Omadacycline Analysis [46]	Omadacycline (antibiotic drug)	Terbium- and nitrogen-doped carbon quantum dots prepared by microwave from plum juice with terbium nitrate	40 - 60 parts per billion (ppb)	34.78 ppb	Fluorescence intensity showed a reduction upon addition of drug
35-A sensitive electrochemical sensor based on graphene quantum dots/hierarchical flower-like gold nanostructures for determination of cytostatic drug flutamide [47]	Flutamide (anticancer drug)	Glassy carbon electrode is modified with graphene quantum dots and hierarchical flower-like gold nanostructures	0.01 - 400 µM	6.2 nM	Electrochemical sensing
36- Fabrication of silicon quantum dots-methyl viologen nanohybrids: Turn-On-Off-On fluorescence nanoprobe for the detection of d-penicillamine [48]	d-penicillamine (used in treatment of rheumatoid arthritis, scleroderma, and progressive systemic sclerosis)	Silicon quantum dots modified with carboxylic acid functional group prepared by one-step hydrothermal synthesis	-	8 nM	Emission intensity quenching
37- Application of N-doped carbon quantum dots as a resonance light scattering probe for determination of fluvoxamine [49]	Fluvoxamine (used in treatment of depression and sleeping disorders)	Nitrogen-doped carbon quantum dots	0.01 -12.0 mg L^{-1}	5 µg/L	Resonance light scattering
38- Turn-off/turn-on biosensing of tetracycline and ciprofloxacin antibiotics using fluorescent iron oxide quantum dots [50]	1- Tetracyclic 2- Ciprofloxacin	Iron oxide quantum dots	1- 1–100 µM 2- 5–100 µM	1- 0.71 µM 2- 1.56 µM	Fluorescence intensity quenching
39-Carbon dots as fluorescent nanoprobes for assay	1- Azithromycin (antibiotic drug) 2- Rasagiline	Carbon dots Prepared from garlic peels	1- 0.001–0.005 (µg/mL) 2- 0.001–0.005	1- 0.00019 (µg/mL)	Fluorescence intensity quenching

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of some non-fluorophoric nitrogenous compounds of high pharmaceutical interest. [51]	Mesilate (used to treat idiopathic Parkinson's disease)	(μg/mL)	2- 0.02 (μg/mL)

3.4.2.5. Problematic areas in therapeutics

1. Compared to traditional drug delivery methods, these C-dotstechnologies are typically more complicated. This is partially because of their multifunctional characteristics and the complexity that originates from their incredibly small size [6].
2. Sterilization is necessary because the majority of these C-dots therapies are meant to be administered parenterally. Therefore, there should not be any negative consequences of the sterilization process on the components [6].
3. Having regulatory approval for such products is often difficult and expensive owing to their complicated composition [6].
4. Extensive research is needed to address the in vivo safety, pharmacokinetics, distribution, and compatibility of the constituents [6].

4. Conclusions

Quantum dots (QDs) continue to garner a lot of attention in different disciplines owing to their intrinsic characteristics. In this review different aspects related to QDs were discussed, focusing on their unique electronic and fluorescent characteristics, general information about carbon dots (C-dots) was illustrated in detail, and finally, different applications were presented. For the synthesis of C-dots many techniques, such as top-down and bottom-up approaches, have been discussed. The photoluminescent properties of C-dots were found to be strongly correlated with the synthetic approach. It was discovered that C-dots doping with various heteroatoms could enhance their optical and electrical features. To learn more about the synthetic properties of the synthesized C-dots, thorough characterization using a variety of techniques should be undertaken. The remarkable characteristics of C-dots, such as their hydrophilicity, stability, minimal cytotoxicity, and biocompatibility, have facilitated their widespread employment in scientific research. Finally, the photoluminescent properties of QDs have made the detection and quantitative analysis of numerous biological and pharmaceutical compounds feasible.

Highlights:

- Quantum dots nanotechnologically synthesized have unique features and wide applicability.
- Discussion of versatile applications of quantum dots within analytical techniques and methods.
- Different synthesis pathways and characterization techniques for C-dots were presented.
- Various aspects of C-dots applications were thoroughly illustrated with examples.

Authors' contributions statement:

Mai M. Elnaggar Methodology, Data analysis, Data validation, Writing- original draft preparation.

Hadil M. Elbardisy Supervision, Conceptualization, Methodology, Data analysis, Data curation, and Writing- Original draft preparation, Reviewing, and Editing.

Amira F. El-Yazbi Supervision, Conceptualization, Methodology, Data analysis, Data curation, and Writing- original draft preparation, Reviewing, and Editing.

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Conflict of interest:

The authors declare that there are no conflicts of interest.

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Data availability:

All data will be available upon request.

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