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GREEN FLUORESCENT CARBON DOTS: A NOVEL DRUG TARGETING AND CELL IMAGING AGENT

D. Kala *, Christy Mary Jolly and P. S. Athiramol

College of Pharmaceutical Sciences, Govt Medical College, Thiruvananthapuram - 695011, Kerala, India

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Correspondence to Author:
D. Kala

Associate Professor
College of Pharmaceutical Sciences
Government Medical College,
Thiruvananthapuram - 695011,
Kerala, India.

Email: kaladmohan@gmail.com

ABSTRACT: Nanosized fluorescent carbon particles, carbon dots (CDs), are a kind of fluorescent material that has many applications in recent years. They have biological application like delivery of therapeutic payloads for cancer therapy mainly due to their biocompatibility and unique optical properties. Fluorescent carbon dots overcome the short comings of high toxicity of traditional nano materials. Moreover, the preparation procedure of fluorescent carbon dots is simple and easy. Therefore, fluorescent carbon dots have great potential applied in photocatalysis, biochemical sensing, bioimaging, drug delivery and other related areas. Many functional groups or passivation agents are used to cover the surface of the CDs outside the carbon core, to make CDs with high quantum yield (QY), chemical stability and good water solubility. CDs can be easily conjugated with target molecules to expand their functionality. These traits make them an ideal alternative to semiconductor quantum dots such as CdTe and CdSe. Amoung multi-coloured fluorescent carbon dots, green CDs(GCDs) shows high potential in biological labelling and bioimaging.

INTRODUCTION: In recent years, fluorescent nanomaterials have much interested applications in biological monitoring, chemical sensing and other related fields. The green fluorescence carbon nanoparticle (GCNP) shows high potential in biological labeling, bioimaging and other different optoelectronic device applications.[1, 2] These carbon nano-particles are biocompatible and chemically inert, which has advantages over conventional quantum dots. [3] The origin of fluorescence in carbon nanoparticle is not clear.

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CDs are promising for substantial applications in wide areas due to its excellent chemical stability, good biocompatibility, low toxicity, resistance to photobleaching and easy chemical modifications. Common methods for making fluores-cent carbon nanoparticle (FCNPs) includes high energy ion beam radiation based method followed by annealing, laser ablation of graphite followed by oxidation and functionalization, thermal decomposition of organic compound, electro oxidation of graphite and oxidation of candle soot with nitric acid.[4, 5, 6, 7, 8, 9]

A wide range of fluorescent carbon particle of different colours can be prepared by those approaches. The quantum yield of most of these particles are too low. In the high energy ion beam radiation based method, it is difficult to introduce a large number of point defects into ultra-fine nano carbon particles for bright luminescence. Candle soot based synthesis produce particle mixture of different colours. [10] It showed that surface passivation can lead to a significant increase in fluorescence quantum yield.[11]

In 2004, Xu et al. Discovered accidentally this kind of carbon nanoparticles with fluorescent properties for the first time when they separated single-walled carbon nanotubes using gel electrophoresis from carbon soot produced by discharge.[12] Based on this study, in 2006, Sun et al. Synthesised fluorescent carbon nanoparticles with diameter less than 10nm and named them carbon dots(CDs). Their low toxicity and stable chemical properties make them become powerful candidates for new types of fluorescent probe and overcome the common drawbacks of previous fluorescent probes. This paper reviews the recent progress in applications of green fluorescent carbon nanoparticles, such as in drug targeting and cell imaging.

Classification of Carbon Dots:
All carbon dots have similar photo luminescent (PL) properties, but have different intrinsic structure and surface functional groups. Based on this they are classified into three:

1. **Graphene Quantum Dots (GQD):**

- Possess single or few layers of grapheme which are connected by chemical groups on the edges.
- They are anisotropic.
- Their lateral dimension is always larger than height

2. **Carbon Nanodots (CND):**

- Always spherical in shape
- Particles without crystal lattice- carbon nano particles
- Particles with crystal lattice-carbon quantum dots

3. **Polymeric Dots(PD):**

- They are aggregated or cross linked polymer which is prepared from linear polymer or monomer.
- Carbon core and connected polymer chains assemble to form polymer dots.[15,16,19]

Advantages:
Compared to the conventional semiconductor quantum dots, carbon dots have the following physical, structural, biological and electrochemical advantages:

- High aqueous solubility or dispersibility
- Robust chemical inertness
- Facile modifications
- High resistance to photobleaching
- Low toxicity
- Good biocompatibility
- Low cost production methods
- Wide excitation spectrum ranging from UV to visible region, which can be further extended to near IR through surface engineering.
- Small particle size which facilitates strong cellular permeability
- Stable fluorescence both in vivo and in vitro
- Availability of green methods of synthesis
- Tunable emission

Disadvantages:

- Large scale synthesis and purification is difficult
- Inadequate purification techniques
- Low fluorescence without functionalization

FIG. 1: CARBON DOTS

CNDs obtained from carbon structures:

Since the discovery of CNDs in 2004, top-down methods predominated in the following years. The starting materials included amorphous carbon (candle soot, and carbon black) and regular sp2 carbon layers (graphite rod and carbon nanotubes). Many methods have been developed to break down the carbon structure: arc discharge, laser ablation, electrochemical oxidation, and nitric acid/sulfuric acid oxidation. The synthetic methods are complicated, and the QY of the CNDs is low; thus, the resultant CNDs may not be suitable for direct cell imaging.[13, 14]

Liu et al. reported a multi-step method to obtain multicolor photoluminescent CDs in 2009.[15] Satellite-like polymer/F127/ silica composites were prepared as carbon precursors. The subsequent high temperature treatment and removal of silica carriers generated nanosized CNDs. Acid treatment and simple surface passivation finally resulted in the product.[16] The aqueous CNDs with excitation dependence PL properties were applied to image *E. coli* ATCC 25922 cells with blue/green/red colour.[17,18] Qiao et al. developed a general and facile method to prepare multicolour photo-luminescent CNDs. [19, 20, 21] The activated carbon with an amorphous structure was easily etched into individual CNDs by treatment with nitric acid, and then the CNDs were passivated using amine-terminated compounds. The CNDs were excellent candidates for a live cell fluorescent imaging agent. In 2006, Sun et al. reported that laser-ablated, amorphous carbon nanoparticles could emit in the visible spectral range upon surface functionalization with polymer chains. [22] Nanosized pure carbon particles may be surface passivated to exhibit bright photo-luminescence in the visible wavelength section. Then, surface passivation became an important means to increase the QY of CNDs substantially, because surface energy trapped on the bare dot surface became emissive after passivation.

Li et al. reported that the passivated CDs exhibit no apparent cytotoxicity, and they were shown to successfully target cancer cells by conjugation with transferrin. [23, 24, 25] Moreover, the CNDs were applied in in-vitro cancer diagnostics. Through conventional bioconjugation chemistries, these CNDs can be transformed into functionalized nanoprobes.[26]

CNDs obtained from small molecules:

Through dehydration and carbonization, small molecules can form CNDs. The PL colour and QY can be tuned via adjusting the ratio of reagents or the amount of assistant inorganic substrate (e.g.

NaOH, H3PO4, KH_2PO4). Citric acid, glycerol, amino acid, ascorbic acid and other molecules with abundant hydroxyl, carboxyl and amine groups are suitable carbon precursors. Moreover, carbohydrates are often referred to as the ideal carbon resource. Yang et al. Synthesized green fluorescent CNDs by hydrothermal treatment of glucose in the presence of monopotassium phosphate. Bhunia et al. attempted to synthesize CNDs from different kinds of carbohydrates. Highly fluorescent carbon nanoparticles with tunable visible emission from blue to red have been synthesized at the gram scale. The CNDs were further applied in cell labeling.[27, 28, 29, 30] Water soluble CNDs made from biomaterials (even food). These kinds of CNDs are always highly water-soluble and possess no obvious cytotoxicity. CNDs can be derived from plant extracts, such as banana juice, strawberry, grape juice, orange juice, pomelo peel, watermelon peel, pepper, soy milk, honey, grass, willow bark and leaves from different plants.[31,32] Bio-products from animals, such as, bovine serum albumin, silk, hair fibre, barbecue meat and eggs, can also be regarded as CND raw materials. Considering the examples listed above, we found that carbon sources are macromolecules (proteins or polysaccharides) in nature.

Structures and Properties of CDs:
Generally, CDs are nearly spherical nanocrystals with the diameter less than 10nm. Compared with those larger particles like quantum dots, the size of carbon particles is generally only a few nanometers, and molecular weight is also only a few thousand to tens of thousands. Generally, there is a large amount of-OH and-COOH and -NH2 and other groups on CDs surfaces, which makes CDs with good water solubility and polymerization ability with various inorganic, organic, or biologically active substances.

The Optical Properties of CDs:
Green fluorescent CDs have strong absorption in the ultraviolet region, which can also extend to visible region. After attachments of passivating agents, the absorption spectral region may show red shift. The luminescence properties of GCDs are mainly the photoluminescence and electrochemical luminescence, in which photoluminescence is the most prominent performance. As an important role in almost all areas of fluorescent nanomaterials, the excellent optical properties of GCDs mainly include high fluorescence stability, non blinking, tunable excitation, and emission wavelengths.[33, 34, 35, 36] However, the emitting mechanisms of GCDs are still not clear, only keeping the phenomenon levels. The in- depth quantum interpretation needs to be established. Some researchers speculated that the emitting mechanisms of GCDs involve quantum confinement effect, stabilizing surface trap, or exciton recombination radiation.

Biocompatibility and Low Toxicity of GCDs:
Since carbon element is the skeleton of all living body, full carbon nanomaterials have a lower toxicity compared with other nanomaterials; simultaneously, the particle size of GCDs is smaller and then more convenient to enter the cell in vivo, which makes GCDs have great potential application in the biological fields. In addition, the surface of GCDs contains a lot of functional groups, so that the surface of GCDs can be modified with organic, inorganic, polymer, and other substances endowing different functional properties. Photostability is a key property for the fluorescent materials, which hold potential for application in bioimaging field. Photo blinking impairs the bioimaging results of QDs. Although CNDs have been synthesized via both the top-down cutting and bottom-up carbonization routes, many types of CNDs possess excellent photostability, making them ideal materials for bioimaging. Sahu et al prepared CDs from orange juice. In addition, the authors claimed that there was no reduction in luminescence intensity even after excitation for a prolonged time. Qiao et al. developed a direct chemical oxidation route to prepare biocompatible CNDs with multicolor photoluminescence. No obvious PL intensity reduction was observed in an experiment of continuously repeating excitations for 10 h with a UV lamp at a wavelength of 365 nm; however, all the CNDs are not completely photostable.

The CNDs synthesized via top-down methods seem to have better photostability compared with the CNDs prepared via bottom-up carbonization methods. The weak photostability may be derived from the unstable PL centers (molecular states). During the lengthy UV irradiation, the PL intensity may decrease in some situations. But with the help of compositing, the photostability of GCDs can be improved.

Synthetic methods:
The methods used for the synthesis of fluorescent carbon nano particles can be broadly classified into two:

Top down method and bottom up method:

- **Top Down Methods:**

The top down methods for the synthesis of carbon nano dots involves the cleaving or breaking of large carbonaceous materials via physical, chemical and electrochemical approaches. These include various techniques like arc discharge, laser ablation, electrochemical oxidation. The top down method based on the approaches employed can be classified into many and discussed in the antecedent section.

Oxidative Cutting/Chemical Ablation:
This method is also known as acid oxidation. Larger carbonaceous materials like nano diamonds, graphite, carbon nanotubes, carbon soot, activated carbon, coal, carbon rods, carbon acid etc are oxidised to produce fluorescent carbon dots. The factor that is common in these precursor materials are they all possess perfect sp^2 structures. But they do not have the band gap which is an essential requirement for fluorescence. Various studies indicate that sufficient band gap for these compounds can be achieved through particle size control and surface chemistry modulation.

The most popular method used is the acid based oxidation. Acids commonly used include concentrated nitric acid or a mixture of concentrated nitric acid and sulphuric acid. The process not only abates the large materials but also modifies the surface groups present via oxidative reactions.

The main advantage of this method is that it enables large scale production of carbon dots from low cost starting materials, which makes the process cheap. This method also generates negatively oxygenated groups in carbon nano dots leading to its superior hydrophilicity. These C dots will also have defective graphite structure. Tedious removal of excess acid from the reaction mixture and final purification is thought to be the major drawback of chemical ablation method.

Hydrothermal/Solvothermal Synthesis:
Oxidized carbon sources like graphene oxide and oxidized nanotubes can be cut into small pieces by hydrothermal or solvothermal treatment at high pressure and temperature. These precursors possess defect based chemical groups, which usually contain oxygen.

In the case of reduced graphene oxide sheets, they are treated with oxidizing agents resulting in the introduction of epoxy groups, which in turn act as sites for cleavage during hydrothermal or solvothermal treatment.

Electrochemical Exfoliation:

It is also known as electrochemical soaking or electrochemical carbonization. This is a method of preparation of carbon quantum dots by exfoliation of carbon precursors like reduced grapheme oxide film, carbon nanotubes. During exfoliation in water due to the electrochemical oxidation of water at the anode OH^- and $O^·$ free radicles are formed. These free radicals acts as electrochemical scissors and release FCNPs from the surface of carbon precursors.

Arc Discharge Method
This method is also known as direct current arc discharge method. Xu et al discovered carbon dots by serendipity thorough arc discharge of soot during the purification of single walled carbon nanotubes. In this a direct current arc voltage is applied across two graphite electrode. These electrodes are immersed in an inert gas such as helium.

Laser Ablation:
Laser ablation is the process of removing materials from the surface of solid by irradiating pulsed or continuous laser. A Suspension of carbonaceous material in organic solvent is prepared and can be irradiated to produce FCNPs. It is also obtained from carbon nano material precursor. The precursor dispersed in a solvent can be ultrasonicated and resulting mixture was subjected to laser irradiation

on a slide which is further centrifuged to obtain CQDs.[37, 38, 39]

Bottom Up Approaches:

This is an efficient route for the synthesis of fluorescent carbon nanoparticles in large scale. Here dehydration and further carbonization of smaller molecule occur resulting in the production of FCNPs. The applied molecules always contain hydroxyl, carbonyl, carboxylic acid and amino groups which are easily dehydrated at elevated temperature.

Microwave Irradiation:

Microwave irradiation is one of the fastest and economic methods used for the synthesis of fluorescent carbon nanoparticles. The conventional methods used for the synthesis of CQDs employs high temperature (near 300^0 C) to ensure complete carbonization of the precursors. One of the main disadvantages of this method is that high temperature treatment may result in destruction of capping moieties which in turn leads to poor passivation. But the use of microwave irradiation for the synthesis and passivation leads to the production of well passivized and functionlized FCNPs with superior optical quality. The size and photoluminescence of CNPs synthesized by this method depends on the duration of microwave heating.

Supported Synthetic Methods/Confined Pyrolysis:

Supported synthetic methods are used for the synthesis of mono dispersed carbon dots. Here a support is used to localize the growth of CQDs and block agglomeration during the high temperature treatment. The support used is known as non-reactors. The supports commonly used include modified silica spheres, ion exchanged Na Y zeolite and mesoporous silica.

Pyrolysis/ Carbonization of Organic Precursors:

This involves the treatment of an organic precursor solution in a sealed chamber under large pressure to a high temperature. If the solvent used is water, the method is said to be hydrothermal synthesis. The organic precursors used for the treatment include glucose, orange pericarp, coconut husk, banana juice, gelatin, chitosan, citric acid, ascorbic acid, glycerol etc.

This route of synthesis is not only low cost but also is a green and nontoxic method. After solvothermal treatment the carbon quantum dots are extracted with organic solvents and finally purified and concentrated. This is an economic, simple and scalable method. This method allows the carriage of heteroatoms from precursors to product. [40, 41, 42]

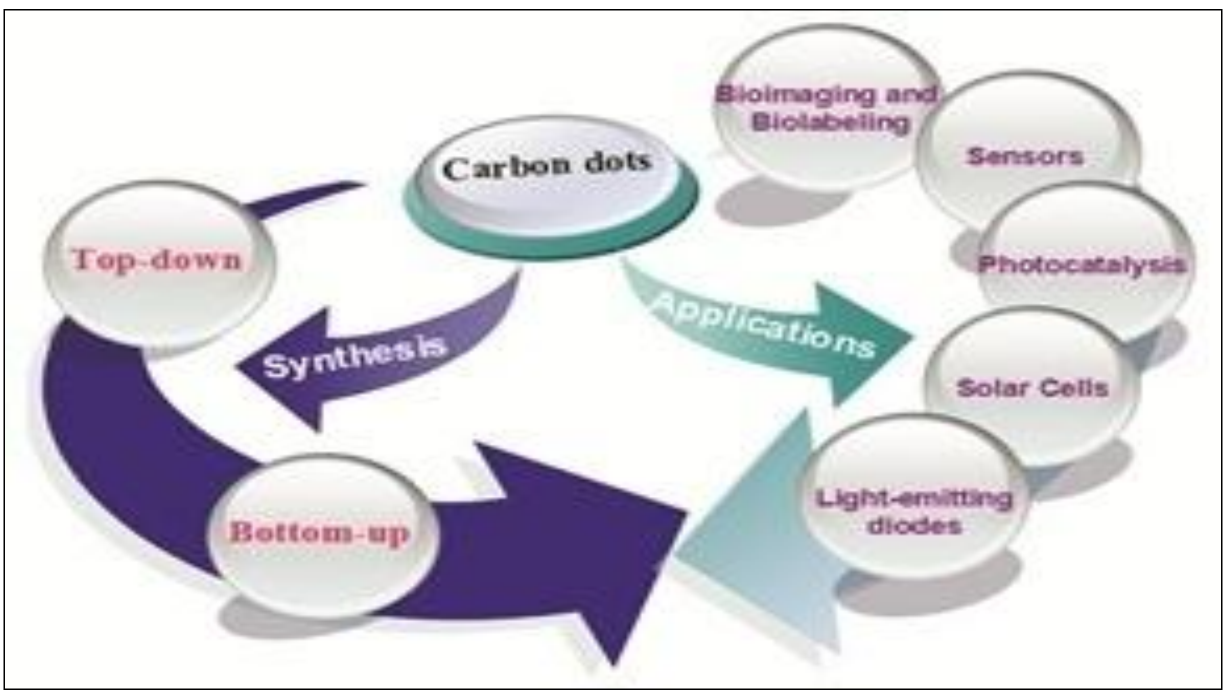

FIG. 2: OVERVIEW OF SYNTHESIS AND APPLICATIONS OF CNDS

TABLE 1: PROBLEMS FACED DURING THE SYNTHESIS OF CARBON NANODOTS

Barriers	Prevention
Carbonaceous aggregation	Electrochemical synthesis Confined pyrolysis Solution chemistry methods
Size control and uniformity	Gel electrophoresis Centrifugation Dialysis
Surface properties	Manipulating preparation Post treatment

Applications in bioimaging:

As described above, GCDs are certainly viable candidates for cellular imaging. Actually, some CDs really possess PL up-conversion properties. Furthermore, two- or multi-photon absorption is a common property in carbon-based materials.[43, 44, 45] Cao et al. reported that CNDs exhibited strong luminescence with two- photon excitation in the near-infrared region. Two-photon luminescence microscopic imaging of CNDs internalized in MCF-7 cells was demonstrated. In 2009, Yang et al. reported the first study of CDs for optical in vivo imaging. Surface passivated and ZnS-doped CNDs were synthesized. Upon injection of a CND solution, mice were imaged using a Lumazone FA in vivo imaging system.

The injected CNDs in mice diffused relatively slowly with the fluorescence fading about 24 h post-injection. GCDs can be injected into mice via subcutaneous, inter dermal and intravenous injection and can be detected by 470 nm or 545 nm excitation. The biocompatibility and nontoxic characteristics of GCDs were also demonstrated [46].

In 2012, Tao et al. obtained their product from carbon nanotubes and graphite after a mixed-acid treatment. In vivo fluorescence imaging with GCDs was then demonstrated in mouse experiments, by using various excitation wavelengths, including some in the near-infrared region. Furthermore, in vivo bio-distribution and toxicology of those GCDs in mice over different periods were studied: no noticeable signs of toxicity of GCDs in the treated animals were discovered. Shi et al. reported a method for hydrothermal treatment of ethylene diamine tetra acetic acid to obtain highly soluble nitrogen doped CNDs. Zebra fish were incubated with the GCDs, and the GCDs could be absorbed through swallowing and the skin. The GCDs accumulated selectively in the eye, yolk sac and tail of the zebra fish, and the green emission of CDs could be easily observed. The application of GCDs in the zebra fish supports the eventual use of CDs in clinical applications as a probe with low toxicity.[47, 48, 49]

Functionalization and nanocomposites:

GCDs can be modified to exploit enhanced properties and diverse functions. Chandra et al. prepared green-PL-colored CNDs by microwave irradiation of sucrose with phosphoric acid. Fluorescein, rhodamine B and a-naphthylamine were functionalized onto the dots through EDC condensation. The fluorescence was improved, while the cytotoxicity decreased. The functionalized GCDs achieved maxi-mum fluorescence intensity when excited at 225 nm, and the peak position was the same as that of the position of CDs. The GCDs entered into human red blood cells (RBC), suggesting their potential application in bio-sensing and drug delivery. Song et al. prepared GCDs via a microwave pyrolysis method. Then, folic acid was conjugated onto the dots, and the functionalized GCDs can be utilized for targeting and detecting cancer cells. The surface functionalization on the dots was further stabilized to achieve probes with high physicochemical and photochemical stabilities.[50, 51, 52] Goh et al. reported cellular and *in vivo* bioimaging of PEG diamine-capped CNDs synthesized via the pyrolysis of citric acid in a hot solvent. Hyaluronic acid was linked to the carbon dots to improve receptor-mediated endocytosis and specific delivery. These particles showed excellent properties for bioimaging applications.

CONCLUSION: GCDs are a versatile material formed from a wide range of starting materials and via various synthetic methods. In addition to their excellent photoluminescent properties, their biocompatibility and low toxicity make them ideal candidates for cell imaging. GCDs will show more advantages in bioapplications after proper functionalization, namely, passivation with polymer, decorating with organic molecules, doping with inorganic salt and hybridization with silica. GCDs can be applied in drug/gene delivery and cancer diagnostics. Doxorubicin (DOX) was adsorbed onto the GCD surface via electrostatic interaction and p–p stacking. The release of DOX can be monitored by the FRET PL system and tuned by the pH of the environment. Folic acid was also covalently attached to GCDs for specific targeting of human cancer cells. Recently, Karthik et al. developed fluorescent GCDs tethered to a quinoline based phototrigger for regulated delivery of anticancer drugs. [53] The decorated CNDs can enter the cytoplasm, as well as nucleus of cells, and loaded drug can be released using both one-photon and two-photon excitation.

In a word, GCDs are novel fluorescent nanomaterials with out-standing fluorescence properties. They have numerous excellent applications in a variety of fields involving chemical and biological sensing, biological imaging, drug delivery, and photocatalysis, which are greatly promising for the future development.

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