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A Review on Carbon Dots for Cancer Drug Delivery

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Abstract

Carbon dots are given attention nowadays in various fields such as nanobiotechnology, nanomedicine, pharmaceutics and so on because of its submicron size and biocompatibility. Carbon dots (CDs) in the size range of several dozen nanometers are zero-dimensional, carbon-based compounds and can be doped with heteroatoms such as N, S, P, and B. They can be modified chemically to boost and make additional functional properties possible. CDs have many inherent assets, such as high-photoluminescence and/or fluorescence tunable optoelectronic properties, strong biocompatibility and easy-to-prepare, tunable and post-moderate functional groups. Since it has these kinds of properties it can be used for biosensing, drug targeting, bioimaging especially it is used for cancer therapy. This review focuses on properties, various synthetic methods of preparation, and its merits, demerits of carbon dots and its therapeutic significance in treatment of cancer.

Keywords: Carbon Dots; Drug Delivery; Cancer

Abbreviations: CDs: Carbon Dots, QY: Quantum Yield, DOX: Doxorubicin, DLE: Drug Loading Efficiency.

Introduction

Carbon dots (CDs) are a new fluorescent carbon material with a diameter of less than 10 nm. Due to their structure and biocompatibility, CDs are becoming a promising alternative to metal-based quantum dots. During the purification of single-walled carbon nanotubes in 2004, carbon dots were first discovered. Because of their excellent fluorescence properties, good biocompatibility and low toxicity, CDs were researched as biosensors, gene transfer, drug carriers, and bio-imaging probes [1-8]. CDs are made up of mixed carbon networks of both sp2 and sp3. In addition, hydroxyl, carboxyl, carbonyl, amino, and epoxy groups can be easily functionalized over their surfaces, offering additional benefits for binding with inorganic as well as organic moieties [9-11]. Applications in analytical chemistry, particularly in environmental and biology, cancer therapy and imaging have high potential for the beneficial fluorescence of CDs. These features make them a better candidate for many applications than the well-known quantum point semiconductor (QDs). In addition, their simple and inexpensive methods of preparation gives unique nanotechnology advantage in terms of rapid and cost-effective development. In recent years, several efforts have been made to prepare high quantum yield (QY) biocompatible CDs, consisting of values greater than 20 percent, which offer better bioimaging and biosensing capabilities [2-4,6,9,12-14]. Figures 1 & 2 describes the basic different types of carbon dots [3,12,15,16].

Cancer is a worldwide public health issue and its early diagnosis is of considerable significance [17-21]. Because of its anticancer efficacy, subcellular organelle-targeted cancer therapy has gained considerable interest as certain organelles (e.g., mitochondrion or sensitive to chemotherapy or light / X-ray irradiation). In addition, as mitochondria are correlated with the control of cell growth and death, mitochondria-targeted therapy appears as a potential way

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to enhance anticancer therapy [22,23]. Selective staining of cancer cells is an important goal in cancer research as it enables direct investigation of cell biology and therapeutic treatment results [23,24]. Several scientific studies have been undertaken to refine biochemical compounds that can precisely mark cancer cells and target them. Fluorescent dyes have been used widely as cell labelling agents, but achieving cell specificity and biocompatibility is a major difficulty for fluorescent dyes and nanoparticles. Fluorescent markers have been updated with recognition components and ligands to bind to cell surface receptors in order to achieve cell targetability. For visually observing FR and thus detecting cancer cells, fluorescent nanoparticles are predictable [23,25,26].

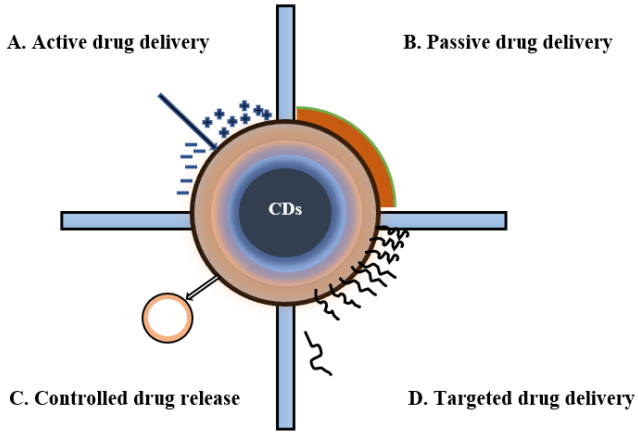

Figure 1: A. Positive or negative surface charge, B. Polymer coating, C. Hallow CDs, D. Ligand conjugation [6]

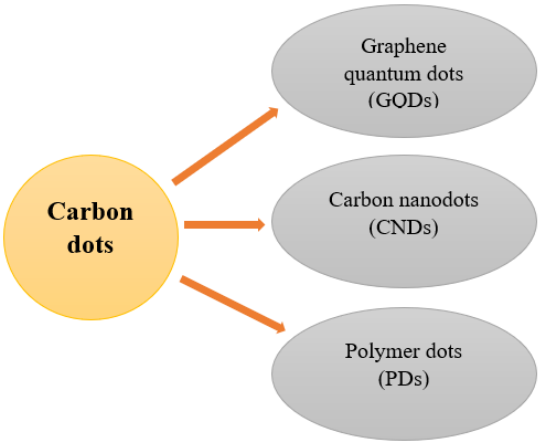

Figure 2: Various types of carbon dots.

In the last few years, significant efforts have been made to manipulate, design, synthesis and produce well-organized drug carriers for passive and active drug delivery, including micro particles, nanoparticles (NPs), nanofibers, carbon dots, etc. These carriers released the therapeutic agents after administration based on their characteristics in the exact portion of the tissues, organs, or even the inside of the cell. However, in physiological media and unspecific contact with biomatter, the CDs have low colloidal stability and need to change surface functionalities to promote active nuclear entry. In addition, the inherent toxicity of CDs-containing heavy metal ions restricts their application to a wider clinical environment [7]. This review focuses on various properties and synthesize methods of carbon dots and emphasized on its therapeutic use to treat cancer.

Ideal Properties of CDs

a) CDs have good water solubility and chemical stability.

b) It has good photo bleaching resistance.

c) Ease of large-scale preparation and surface functionalization.

d) It inherits the excellent optical properties of traditional semiconductor quantum dots [5,9,12,15,27-29].

e) It has excellent biocompatibility and non-blinking character [2,3,8,13,15,30,31].

f) It has high photo stability and low molecular weight [3,30].

g) CDs with a size of 10 nm, low to no cytotoxicity [3,11,32].

h) It has high quantum yield and chemical inertness [3,5,15,27].

i) It has good surface activity and enhanced cellular uptake [19,33].

Synthetic Methods

Synthetic methods for CDs are mostly divided into two categories: "top-down" and "bottom-up." In top-down process, the macromolecule is dispersed or destroyed into smaller CDs with graphite material as sources of carbon while the polymerization and carbonization of a number of smaller molecules into CDs with organic molecules as sources of carbon is the bottom-up process. Figure 3 shows the various synthetic methods [2,9,34,35].

Arc Discharge Method

Arc discharge is the electrical breakdown of a gas with anode and cathode electrodes to produce plasma using electrical current. The anode is filled with carbon precursors and started to generate plasma at a high temperature of almost 4000 K with an arc current under a gas medium. The carbon vapour then aggregated toward the cathode in the gas and cooled down.

Laser Ablation Method

An effective laser pulse is easy to heat and evaporate to a plasma-state in order to irradiates the object surface into a hot and high-pression thermodynamic state in which the vapour crystallises to form nanoparticles.

Chemical Oxidation

Chemical oxidation methods generally use strong oxidants such as concentrated acids in order to provide an oxidative atmosphere for the treatment of a number of carbon precursors. Using different carbon precursors, such as single-walled CNTs, graphite, and multi-walled CNTs. Tao et al. prepared carbon dots through this technique. As H2SO4 and HNO3 have been used as the oxidising agent, and it should be noted that the resulting CDs from various precursors exhibited similar distributions of size, structure, composition, PL properties.

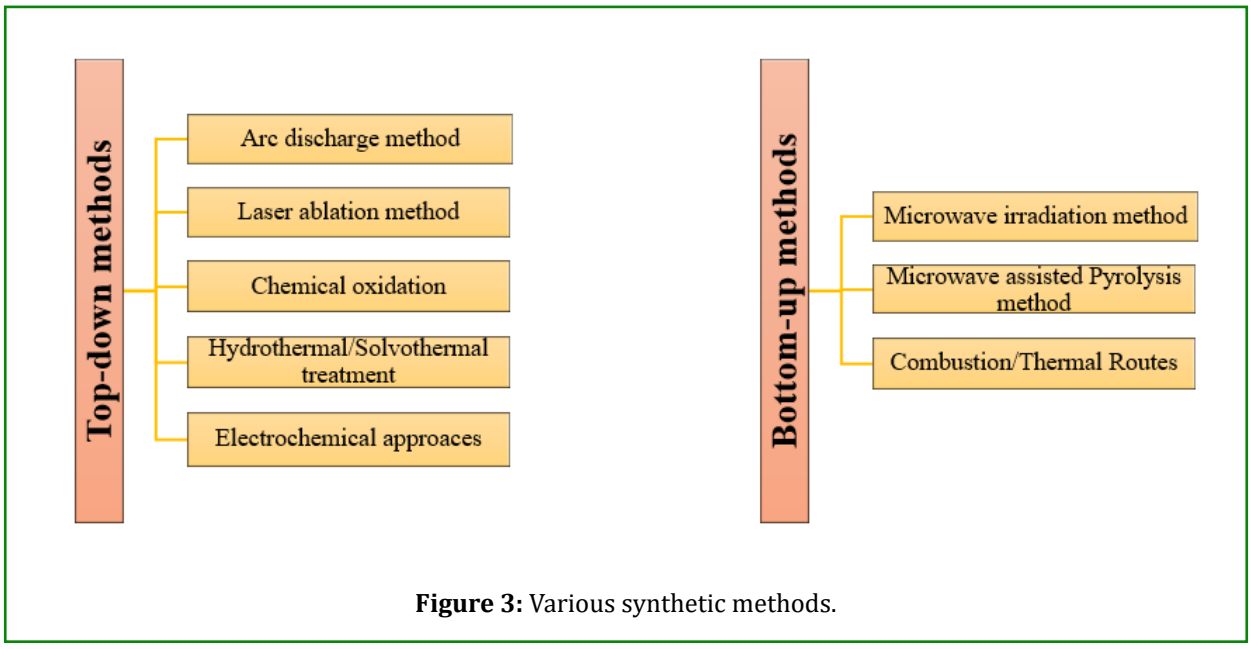

Figure 3: Various synthetic methods.

Hydrothermal/Solvothermal Treatment

In order to form the reaction catalyst, small organic molecules and/or polymers are dissolved in water or organic solvent and then transferred to a Teflon-lined autoclave of stainless steel. Organic molecules and/or polymers have fused to form carbon seeding cores at relatively high temperatures and then grown into CDs with a particle size of less than 10 nm.

Electrochemical Approaches

Three electrodes are used in a standard electrochemical synthesis setup: a carbon precursor acts as the working electrode, while the counter and reference electrode are the other two electrodes. It is possible to use different carbon precursors and adjust the experimental setup for better results.

Microwave Irradiation Method

There are three major stages of N-doped Carbon Dots (CD) preparation: polymerization, carbonization and dehydration by microwave radiation. The organic amine-rich precursors were paired with general sonication and the intermolecular and intermolecular dehydration of the cross-linked cluster was carried out for 10 min at 1600°C. This biological clusters have a high QY, similar to heavily blue fluorescent fluorescence dyes associated with the rich amine bonds. These amine bonds were hydrolysed at 200°C and to produce a carbon centre, a part of the organic groups was eventually carbonised. As certain fluorescence groups were depleted during the carbonization stage, the QY of these materials was reduced. In the carbon centre, more fluorescence groups can be carbonised as the heating time is increased, and the QY decreases further. Table 1 shows the advantages and disadvantages of various synthetic methods.

Methods	Advantages	Disadvantages	References
Arc discharge method	Large particle size distribution, Good water solubility	Presence of impurities, High cost of equipment	[6,15,35]
Laser ablation method	Narrow size distribution, Good fluorescence characteristics, particles with different size	Complex operation, High cost, low yield	[6,12,35]
Electrochemical Approaches	Greater product yield, Low cost	Difficult purification process, doping with heteroatoms is hard	[6,35]
Chemical oxidation	Greater QY, Large-scale production, low cost of equipment	Using toxic reagents, Complex process, prolonged synthesis duration	[6,9,12,35]
Hydrothermal/ Solvothermal treatment	Homogenous size, Greater QY, Consuming low energy, Cheap instrumentation, Greater product yield	Prolonged synthesis duration	[6,12]
Microwave irradiation method	Energy efficient, Environment friendly, Low reaction time	Reduced solvent usage, limited pressure of the system	[6,9,12]
Microwave assisted pyrolysis Method	Low reaction time, Greater product yield, Rapid synthesis, Eco-friendly	Difficult to scale up due to uneven heating, Broad size distribution	[6,9,12]
Combustion/Thermal Routes	Feasible scale up production, Low cost, Eco-friendly	Long synthesis duration	[12]

Table 1: Advantages and disadvantages of various synthetic methods.

Microwave Assisted Pyrolysis Method

The combination of polyethylene glycol (PEG200) and saccharide (glucose, fructose, etc) in water forms a transparent solution for carbon dot synthesis, followed by microwave heating. The CQDs obtained showed excitation dependent PL characteristics.

Combustion/Thermal Routes

For example, citric acid combustion followed by carboxyl groups functionalization through conjugation under high temperature of acetic acid moieties. The CDs obtained had a uniform particle size of 8.5 nm and the surface of the carbon dots had rich carboxyl groups. Such moieties containing oxygen would facilitate the adsorption of water molecules, which is beneficial in an aqueous solution for the electrocatalytic process.

Carbon Dots for Cancer Therapy

Some chemotherapeutic drugs have systemic toxicity and serious side effects, including weak pharmacokinetic profiles, contributing to many drawbacks associated with them. Therefore, it becomes a challenge to develop drug carriers for selective drug delivery without systemic cytotoxicity. Nanomaterial applications based on CDs in cancer therapy have been identified in different studies. CDs containing solid lipid nanoparticles, polymer nanoparticles, Liposomes

and other therapeutic carriers shall be changed in ligands for cancer care [6,36-47].

To improve anticancer drug delivery, Feng et al. created pH/redox dual-responsive carbon dots. The authors combined an ensemble of compounds that were placed on CDs prepared using citric acid and diethylenetriamine under a nitrogen atmosphere at 170°C for 3 hours. Carbon dots with Arg-Gly-Asp (RGD) peptide as a targeting ligand, cisplatin (IV) as a prodrug and methoxy poly (ethylene glycol) (mPEG) as passivation for immune system inhibition were established, In the tumour area, these CDs (CDs-RGD-Pt(IV)-PEG) undergo decomposition of PEG due to hydrolysis of the benzoic-imine bond at pH 6.8. Consequently, the RGD peptide is deshielded, inducing an enhanced affinity towards the integrin αvβ3 receptor. After CDs-RGD-Pt (IV) enters the cell membrane, the cisplatin (IV) prodrug is converted to cisplatin, which binds to the nucleus' DNA and kills the cancer cell [3].

Zheng, et al. prepared hollow CDs using solvothermal reaction from bovine serum albumin. The obtained hallow carbon dots were 6.8 nm in diameter and had a quantum yield of 7%. Their bright photoluminescence ensures that it is easy to use cellular images. Structure and composition studies indicate that there is a hollow structure in the hallow carbon dots. HCDs are used as doxorubicin (DOX) delivery systems with a pore size of 2 nm. The pH-controlled release of the DOX- hallow carbon dot drug delivery system is easily absorbed by cells. The experimental findings found that an advanced carrier has better therapeutic effectiveness in the microenvironment of the tumour than in other parts of the body. The multifunctional HCDs prepared here demonstrate ability for use in both cancer therapy and cell imaging, owing to their special nanostructure and photoluminescence properties [15].

Yun, et al. prepared an inventive zwitter ionic carbon dot targeting the nucleus. The zwitter ionic functional groups of CDs, introduced by a simple one-step synthesis using β-alanine as a passivating and zwitter ionic ligand, allow for cytoplasmic uptake and subsequent nuclear translocation of CDs. In addition, multicolour fluorescence increases the accuracy of the CDs as an optical code. The non-covalent doxorubicin grafting carbon dot-based drug delivery system exhibits superior antitumor efficacy due to increased in vitro nuclear delivery and in vivo tumour accumulation, resulting in highly effective inhibition of tumour growth [48].

Lai, et al. prepared a modified carbon dot PEG and introduced the loading and distribution of doxorubicin (DOX). The release mechanism of doxorubicin in cells was seen in fluorescence images. Green fluorescence was shown predominantly by cytoplasm from CDs. It was possible to detect red fluorescence from DOX in the nucleus. It showed that DOX is introduced into the cells and then released into the nucleus for treatment.

Using simple microwave synthesis, Shan, et al. prepared green-emitting CDs using citric acid and urea, as the precursors can serve as a targeted and trackable drug delivery agent in a mouse model of liver cancer for localised cancer treatment. The CDs are combined with Doxorubicin (DOX), the native carboxy group on CDs and the amine movement on DOX molecules by non-covalent binds. As the activating mechanism for DOX release the pH difference between cancer and normal cells was exploited successfully. Due to the sensitivity of the non-covalent pH bond and the pH difference between cancer and normal cells, the CD-DOX conjugates displayed no substantial adverse impact on normal cells, but a strong killing effect on cancer cells, suggesting the expected effect of drug release. The adequacy of fluorescent CDs as an in vivo bio imaging probe and more importantly the stability in an in vivo setting of a CD-DOX conjugate and enhanced drug efficacy against cancer cells were demonstrated by in-vivo research into liver cancer mouse models [4].

By hydrothermal approach with the combination of citric acid and ethylene diamine, Kong, et al. synthesized Doxorubicin conjugated carbon dots. For assessing drug loading efficiency (DLE) and release profile of the CDs-DOX, a fluorescence spectrophotometer was used. The CCK-8 test analysed cell toxicity and pharmaceuticals of L929 and MCF-7 cells in CDs and CDs-DOX. The CDs obtained were extremely biocompatible and demonstrated a possible capacity to facilitate proliferation. Compared to free DOX, the carbon dots-DOX complex had greater cellular uptake and greater anti-tumour efficacy on MCF-7 cells [19].

Zhou, et al. anchored CDs via chemical bond on heparin, and DOX was loaded on CDs-Hep. The efficient attachment of heparin and DOX to the CDs was assisted by UV-vis, fluorescence, 1H-NMR, and FTIR spectroscopy. In vitro and in vivo experiments were shown the high biocompatibility and low toxicity of CDs. The delivery mechanism for CDs-Hep/DOX drugs displayed good stability. This systematic examination indicates that the use of Hep enhances consistency with blood. Furthermore, laser scanning with confocal microscopy confirmed the internalisation of cells CDs-Hep/DOX with A549 cells. As a result, the integration of Hep and DOX solution was completed [5].

Narayan Chandra Das et al. discussed a simple and effective process to produce photo luminescent CDs doped with nitrogen and Sulphur, which has been judiciously designed to target cancer cells. Fluorescent C dots made from x-carrageenan and folic acid are a successful cargo for the labelling of cancer cells which expresses the folate receiver

on its surface. Strong water soluble, excellent photo stability and biocompatibility have been revealed in the prepared C-dots. The prepared carbon dots played the role of a nano-vehicle under different pH environments for the anticancer drug capecitabine. The folate receptor in C-dots has resulted in incredible cancer cell targetability, which is highly promising in biomedical studies [23].

Triple conjugated carbon dots that are 1.5-1.7 nm in average particle size were prepared by Leblanc et al. For the development of the triple conjugation process, transferrin (the target ligand) and two anti-cancer medicines, epirubicin and temozolomide were mixed in C-dots. In vitro experiments have shown the dramatically decreased cell viability of transferrin conjugate samples relative to non-transferrin conjugates. The three-fold (C-DT) mechanism is more cytotoxic than any dual C-TT and C-ET systems in the three transferrin conjugated samples to the glioblastoma brain tumour cell lines. The triple conjugate system (epirubicin, temozolomide and transferrin) on CDs has been reported to be a stronger therapeutic agent than its corresponding single drug delivery system [17]. Table 2 shows some example of drugs used in carbon dots.

Sl.no	Drug	Materials	References
1	CISPLATIN(IV)	Citric acid, diethylenetriamine.	[49]
2	EPIRUBICIN, TEMOZOLOMIDE	Carbon nano powder, sulfuric acid, NaOH solution, chloroform by acidic oxidation method.	[17]
3	PROTOPORPHYRIN IX	Citric acid, ethylenediamine.	[50]
4	DOXORUBICIN	Citric acid, ethylenediamine by hydrothermal method	[19]

Table 2: Some example of drugs used in carbon dots.

Sumanta Kumar Sahu, et al. Approach that combines the synthesis of NMOF (IRMOF 3) and the encapsulation of the target molecule (folic acid) in a single phase on the surface of magnetic nanoparticles modified by chitosan. Several days of control and pH-responsive drug release are a notable characteristic of chitosan. Doxorubicin (DOX) was integrated into the magnetic formulation of NMOF and showed elevated drug load (1,63 g DOX g-1 magnetic NMOFs).In contrast to normal (L929) cells, these folate-targeted magnetic NMOFs have more complex cellular internalization against folate-over expressed cancer (HeLa) cells [34].

Conclusion

CDs are nano materials having wide potentials in many requests especially in nanomedicine. These carbon dots are excellent drug carriers because of their favorable optical properties, biocompatibilityand retention time can be increased, which increases treatment efficacy. Generally, chemotherapy is used for treatment for cancer but it has its own bane which is totally contrast to patient compliance and to overcome these difficulties carbon dots pave way to effectively and beneficially treat patients. The emphasis of this review is on carbon dots recent advancements in terms of rational synthesis, properties, and applications in cancer drug delivery. Every year, thousands of new carbon dot synthetic methodologies are reported, despite the fact that their large-scale preparation remains a challenge due to their simple and high yields. Carbon dots can be utilized at its best with greater research by researchers in near future.

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