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Teaser Carbon dots show significant potential as theranostics for the improved management and treatment of cancer.

Carbon dots: emerging theranostic nanoarchitectures

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Nanotechnology has gained significant interest from biomedical and analytical researchers in recent years. Carbon dots (C-dots), a new member of the carbon nanomaterial family, are spherical, nontoxic, biocompatible, and discrete particles less than 10 nm in diameter. Research interest has focused on C-dots because of their ultra-compact nanosize, favorable biocompatibility, outstanding photoluminescence, superior electron transfer ability, and versatile surface engineering properties. C-dots show significant potential for use in cellular imaging, biosensing, targeted drug delivery, and other biomedical applications. Here we discuss C-dots, in terms of their physicochemical properties, fabrication techniques, toxicity issues, surface engineering and biomedical potential in drug delivery, targeting as well as bioimaging.

Introduction

Nanotechnology has gained significant interest from biomedical and analytical researchers in recent years. Nanoparticles (NPs), as a result of their florescent properties, show potential for use in biosensing, chemical sensing, imaging, and biological monitoring [1]. There is an emerging focus on developing new nontoxic nanocarriers. C-dots are discrete, spherical particles less than 10 nm in diameter. They have a sp^2 hybridized structure that includes oxygen in the form of various oxygen-containing species, such as hydroxyl (–OH), carboxyl (–COOH), and aldehyde (–CHO) groups. C-dots also comprise well-organized carbon atoms with a high aspect ratio, large surface area, high thermal and chemical stabilities, and a significantly higher drug-loading capacity compared with larger particles, such as quantum dots (Q-dots) [2]. The properties of C-dots include excellent water solubility, biocompatibility, good conductivity, photochemical

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stability, low toxicity, and environmental friendliness [3]. Thus, there have been a significant number of protocols developed for the fabrication of C-dots, involving both natural and synthetic precursor strategies. The former includes natural precursors, such as glucose [4], sugar, jaggery, and bread [5], grass [6], egg [7], soya milk [8], beverages such as Kvass, beer, and malta, [9], orange juice [10], glycerol [11], *Bombyx mori* silk [12], amino acids [13], *N*-acetyl cysteine [14], banana juice [15], citric acid [16], sucrose [17], Chinese ink [18], instant coffee [19], potato [20], beer [21], solid biomass, such as chicken eggs, orange juice with ethanol, coffee grounds, bee pollen, and oleic acid [22], and algal blooms [23], whereas synthetic methods include arc discharge [24], ultrasonic/microwaves [25], laser ablation [26], electrochemical synthesis [27], and hydrothermal treatments [16]. C-dots with different structure-specific properties can also be fabricated by surface engineering, illustrating their excitation-independent and -dependent properties [28].

The toxicological nature of a nanomaterial has an important role in understanding its mode of action. Toxicological properties have a role in inflammation, carcinogenesis and various other pathological processes [29]. For example, Q-dots attracted the attention of researchers because of their size-dependent optoelectrical properties, which are used in photovoltaics, sensors, and imaging. However, the core toxicity showed by Q-dots limits their biological application. Thus, there was a drive to develop a non-toxic Q-dot-like nanomaterial: C-dots. Given their superior water dispersibility resulting from the presence of –OH or –COOH groups, C-dots also exhibit strong fluorescence in the infrared (IR) and visible regions, as well as physicochemical and photochemical stability. A comparison of C-dots with other carbon-based nanomaterials, such as carbon nanotubes (CNTs) and graphene, is provided in Table 1.

Targeted drug delivery is one of the prominent properties of C-dots. Previously, traditional drug carrier moieties were hard to trace and/or observe. However, research showed that a fluorescent C-dot core combined with a drug moiety resulted in an excellent drug delivery tool. In addition, the combined effect of one or more functional groups incorporated on the surface of C-dots has resulted in a useful tool for the treatment of disease [2]. C-dots can also be applied for the delivery of anticancer drugs. Conventional chemotherapy can eliminate and reduce tumors but with the adverse effect of damaging healthy tissue. This can be overcome by targeted drug delivery using nontoxic C-dots [30,31].

As an alternative to Q-dots, C-dots show low cytotoxicity and good photostability; thus, they have been used extensively in diagnostic imaging. At a specific dot level, C-dots show high brightness, detectable emission wavelengths, and visible excitation [32]. Here, we describe recent progress in the use of C-dots, highlighting their potential for targeted drug delivery and diagnostic imaging.

Historical background of carbon dots

During the 1980s, carbon filaments were fabricated with a diameter of less than 10 nm, although few studies were performed with them at the time. The first systematic study of carbon filaments was performed following the discovery of fullerenes by Smalley *et al*. [33]. Carbon occurs in several nanoforms in addition to fullerenes and, thus, fluorescent carbon nanomaterials are the newest member of the carbon NP family [34].

C-dots were accidently discovered by Xu *et al*. in 2004 following the observation of fluorescence during the separation of single-walled CNTs (SWCNTs) using gel electrophoresis from carbon soot produced by arc discharge [24]. Based on this study, in 2006, Sun *et al*. synthesized fluorocarbon NPs less than 10 nm in diameter, naming them C-dots [35]. During their initial development, C-dots were manufactured from natural, biological sources of carbon; however, following modification, C-dots began to be

TABLE 1

Comparison of C-dots and other carbon-based nanomaterials

Nanomaterial	Characteristics	Applications	Limitations	Refs
Graphene	Comprises one atom-thick carbon (sp^2 hybridized) sheets of six-member rings, providing an exposed surface area that is nearly twice as large as that of SWCNTs	High mechanical strength, high elasticity, thermal conductivity	Absence of metallic impurities that can affect accuracy of sensor; commercial availability of graphene and graphene platelets is limited	[20,54]
CNTs	Unique combination of stiffness, strength, and tenacity compared with other fiber materials; high thermal and electrical conductivity	Can reach cytoplasm and nucleus through the lipid bilayer, thus have potential use in biosensors, biomedical devices, and drug delivery; greater ability of conjugation with various bioactive agents, such as peptides, proteins, nucleic acids, and therapeutic agents; greatest stability of nanocarriers	Severe toxicity in cultured cells, such as human keratinocytes, T lymphocytes, kidney cells, alveolar macrophages, and endothelial cells *in vitro*; reproduce cellular oxidative stresses, thus incompatible with biological systems; insoluble in most common solvents	[29,34]
C-dots	Zero-dimensional nanocarriers with diameter <10 nm; spherical nanocrystal design; synchronized sp^2 and sp^3 hybridization	Used for targeted drug and gene delivery, tumor targeting, monitoring of cellular trafficking, and diagnostic imaging	Poor stability; difficult to maintain properties for long periods of time	[36,57,74]

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