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ORIGINAL PAPER

Green synthesis of nanocarbon dots using hydrothermal carbonization of lysine amino acid and its application in detection of duloxetine

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Abstract

Depression is a mood disorder in which a person feels tired and bored and also unwilling to do daily activities. Duloxetine is a drug that is used to the treatment of depression and anxiety. Due to the use of different medications to treat the depression and its possible side effects, quick and accurate identification of these drugs is necessary. Also, because of the possibility of suicide in depressed people, rapid detection of drug type in drug poisoning (drug overdose) is crucial. Therefore, various sensors are used, that the most straightforward, and most accessible sensors are optical types. One of the best, simplest and safest fluorescent sensors were used for optical sensors is nanocarbon dots. In this study, a new, inexpensive and green optical biosensor was designed, and fabricated using lysine-based carbon dots to detect detection of Duloxetine. Fluorescent carbon dot was prepared by hydrothermal method. The green carbon dots were characterized by UV–visible spectroscopy, TEM, XRD and zeta sizer. Also, fluorescence of carbon dot was investigated. The CDs are spherical and the average size of the monodisperse nanoparticles was around 15 nm. The X-ray diffraction pattern represents a weak crystalline property that confirms the amorphous phase of carbon dots. The value of quantum yield for carbon dots was 31.3% to standard Quinone sulfate. The detection limit of Duloxetine was 0.002 μM. The recovery of Duloxetine was 99.2 to 101.5%, which indicates this nanosensor has a good ability to detect Duloxetine at low concentrations. The results indicate L-lysine-based CDs can be used professionally and selectively to detect of Duloxetine in real samples and human blood plasma.

Keywords Green synthesis · Nanocarbon dots · Lysine · Duloxetine

Introduction

Nowadays, drug tracking is essential in monitoring the concentration of medicine in medical centers and in measuring the amount of drugs in hospital effluents. Depression is one of the most common diseases in human binges. Duloxetine is a drug used to treat major depression, stress-induced urinary incontinence, generalized anxiety disorder and fibromyalgia. [1, 2]. Furthermore, Duloxetine can relieve nerve pain (peripheral neuropathy) in diabetic patients and chronic pain due to specific medical reasons. Although the exact function of the drug is unclear, it seems to trigger a change in the way serotonin and norepinephrine interact with the central nervous system (CNS) [3]. Due to the use of different drugs to treat the depression and its possible side effects, quick and accurate identification of these drugs is necessary. Also, because of the possibility of suicide in depressed people, rapid detection of drug type in drug poisoning (drug overdose) is very

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important. The many methods presented in recent research for the determination of Duloxetine such as UV–Visible spectrophotometric method and LC–MS/MS method [4, 5] but using of the various sensor (optical sensors, electrochemistry, surface Plasmon, piezoelectric) have been noticed due to the many advantages [6–8]. The simplest and most accessible sensors are optical types, especially the kind of fluorescence; therefore, many research is being done [9]. One of the best, simplest and safest fluorescent materials is nanocarbon dots [10]. Carbon dots (CDs) are a class of nanomaterials that are used for optical applications. The main reason for the expansion of nanocarbon dots is their very robust fluorescence; that's why these compounds are called fluorescent carbon [11–13]. Carbon nanoparticles or carbon dots are a new generation of carbon compounds containing oxygen that exhibit a variety of properties compared to other carbon-based materials [14]. Carbon dots generally contain many carboxylic acid groups on their surface, which is why they are highly soluble in water and suitable for being functionalized by various organic, polymeric, inorganic or biological species [11]. Compared to semiconductor quantum dots and organic pigments, nanocarbon dots have an increasing advantage such as high water solubility, high optical luminosity, good biocompatibility and bioavailability properties, high color stability and low toxicity [15–17]. Therefore, carbon dots are suitable to use in optical sensors to detect the different combinations, and drugs with high selectivity and sensitivity [18–22].

It can be synthesized from different materials and compounds. The use of biological and natural compounds such as plant extracts, gums, amino acids and natural carbon-rich compounds to synthesize these particles is beneficial, eco-friendly and safety [13, 23–25].

Also, several methods to synthesize these nanoparticles that hydrothermal method is suitable, eco-friendly and safe way to synthesize and grows carbon dots from different materials and compounds [26, 27]. Thus, eco-friendly CDs can be produced inexpensively and on a large scale for biological usage [14–17, 28–30].

In this research, biocompatible, safe, high water-soluble, stable and low-toxic carbon dots with high fluorescence from lysine are synthesized by the hydrothermal method. Lysine-based carbon dot was first used for the detection of Duloxetine (Fig. 1).

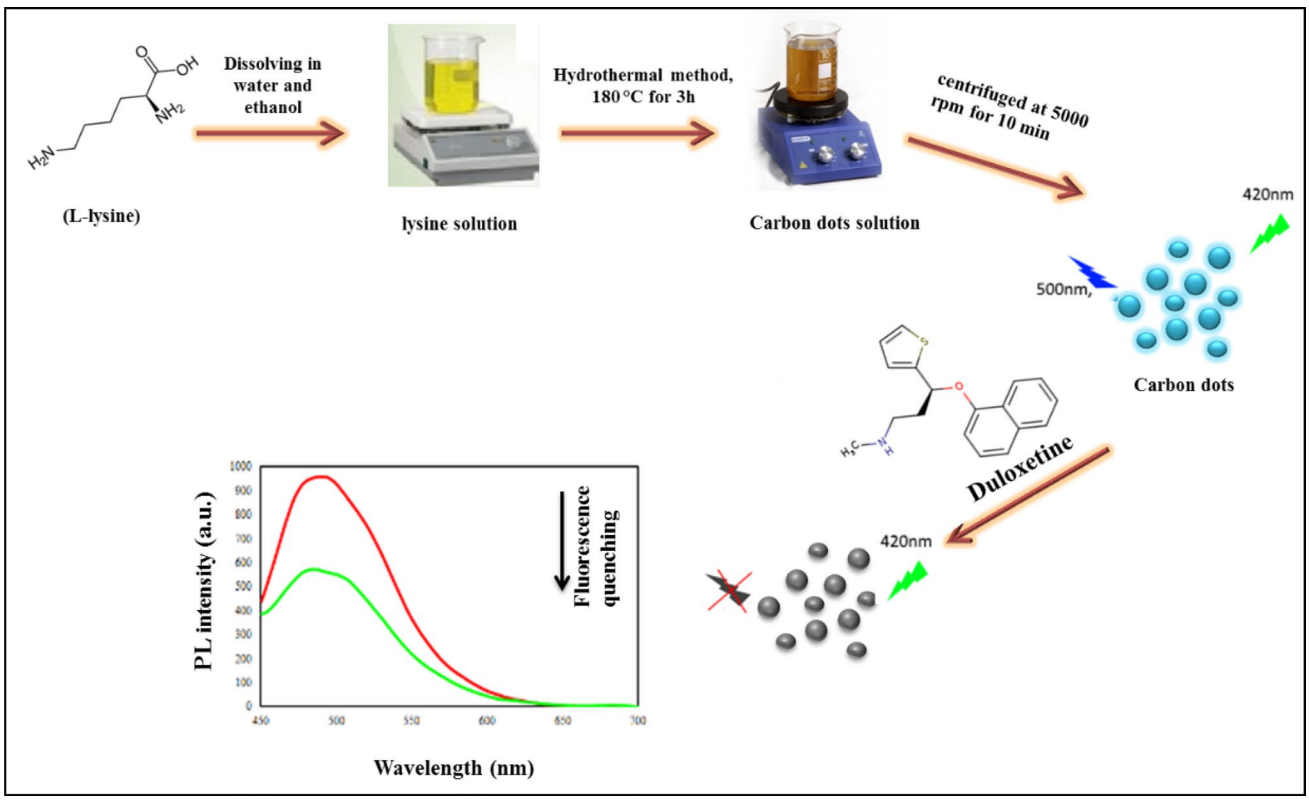

Fig. 1 The schematic synthesis of nanocarbon dots using hydrothermal carbonization of lysine amino acid and its application in detection of duloxetine

Material and methods

Reagents and solutions

0L-lysine amino acid 98%, ethanol 96%, glucose, galactose, sorbitol, sodium lauryl sulfate, citrate and ascorbic acid were purchased from Sigma-Aldrich. Duloxetine hydrochloride ($C_{18}H_{19}NOS.HCl$), hydroxyzine and Doxazosin were purchased from Nikan Exir Bakhtar pharmaceutical Company (Iran). All solvents were analytical grade and used without further purification.

Synthesis of carbon dot from L-lysine

To prepare fluorescent carbon dot by hydrothermal method, 2 gr L-lysine was dissolved in deionized water (10 mL). Then 5 ml ethanol 96% was added to the lysine solution and was shacked to obtain a homogeneous solution. The solution was transferred into a Teflon-lined stainless steel autoclave (30 mL) and was heated at 180 °C for 3 h in the oven. The color of the solution changed to dark brown that it was indicated the synthesis of carbon dots. After the reaction, the resulting mixture was passed through a 0.2-µm syringe filter and then the filtered solution was centrifuged at 5500 rpm for 10 min. Then the mixture was cooled down to room temperature naturally and was stored at 4 °C.

Characterization of nanoparticles

The green carbon dots were characterized by different data analysis such as transmission electron microscopy [1], dynamic light scattering (DLS), FT-IR spectroscopy, X-Ray Diffraction (XRD), UV–Visible spectroscopy and fluorescence spectroscopy.

To determine of surface morphology and particle size of CDs, the nanoparticles were characterized by TEM. Also, the surface charge (zeta potential) of CDs was determined using Malvern Zetasizer NanoZS 90. FT-IR Shimadzu IR2 Spectrometer (Japan) was used to identify the functional groups on the carbon dots surface. The crystal structure of carbon dots was studied using X-ray diffraction (XRD) with an Inel Equinox 3000 [2], 30 kV, 20 mA, K alpha Cu: 1.54 Å. The absorption spectrum of the carbon dots was recorded using an Agilent 8453 (USA) spectrophotometer. To achieve the fluorescence spectrums of carbon dots, a PerkinElmer LS-45 (USA) spectrofluorimeter was used.

Stability of carbon dots

The examination of the fluorescence stability of prepared CDs was taken to evaluate them in different conditions. For this purpose, the fluorescence intensity of CDs was investigated at the high ionic strength, various pH values and at different times. To optimize the test conditions, incubation time and pH environment were studied to determine the best conditions for recording the CDs fluorescence signal.

Investigation of carbon dots fluorescence and fluorescence response of CDs to Duloxetine

After surveying the characterization of the synthesized carbon dots, for investigation of their capability for Duloxetine detection, a solution of carbon dots (5 µg mL^{-1}) was prepared. Then the fluorescence spectrum of carbon dots was recorded at $\lambda_{ex} = 420$ nm. The effect of increasing the amount of Duloxetine on the fluorescence spectrum of carbon dots in a PBS buffer solution (pH 7.4) was investigated. Finally, the fluorescence spectrum of carbon dots was recorded after adding of 1 µL of 1 mM solution of Duloxetine to CDs solution.

Selectivity and sensitivity analysis of the CDs for detection of Duloxetine

To evaluate the efficacy of the proposed method, the interaction effects of drugs that are prescribed with Duloxetine and also various additives that were used as excipients that formulated alongside the active ingredient of the Duloxetine were investigated. In this method, a constant concentration of Duloxetine (0.02 µM) was added to the CD solution. Subsequently, different concentrations of the materials studied (glucose, galactose, sorbitol, sugar, sodium lauryl sulfate, citrate, ascorbic acid, hydroxyzine and Doxazosin) were individually added to the system and their fluorescence was recorded. The concentration of the materials and drugs added is considered as a nuisance that causes an error of more than ± 5% in the measurement of Duloxetine.

Determination of Duloxetine in real samples

The used protocol to examine real samples is the same. To determine of the Duloxetine in plasma, first, a healthy human blood plasma sample was prepared from the Blood Transfusion Organization of Iran and stored at 20° C. 1 ml of plasma sample and 800 µL of acetonitrile were mixed and then centrifuged for 5 min in 5000 rpm, the volume of the solution reached 15 ml by PBS buffer. For example, to determine the concentration of Duloxetine at real sample *(i)* is as follows: 15 mL of human plasma sample by PBS buffer (0.1 M) reached a pH of 7.4. Then 150 µL of Duloxetine (1 mM) solution was added to the real sample. Plasma solution containing 10 µM duloxetine is considered as the stoke solution, for sample (i), we added 3 µL of 10 µM plasma solution spiked to the cell that contains CDs. Finally,

the concentration of duloxetine in the cell was reached to 1×10^{-8} M. (Note: The volume of the spectrofluorimeter cell is equal to 3 ml). These steps five times were repeated and the fluorescence emission has recorded at 500 nm. Then, by placing the recorded emission in the calibration equation, the concentration was determined. Similar to the protocol described above, this method was used for the other concentrations and samples. For determination of Duloxetine in urine, 2 mL of a fresh urine sample (healthy human) was filtered and with PBS buffer diluted to 15 mL, and like plasma samples, different concentrations of Duloxetine were added to urine samples to be evaluated by CDs spectrums.

Results and discussion

Characterization of lysine-based carbon dots

The carbon dots were synthesized by a simple and rapid hydrothermal method from L-lysine. Figure 2 shows the TEM images of lysine-based carbon dots. As the images show, the CDs are spherical, and the average size of the monodisperse nanoparticles was around 13 nm.

The zeta potential of lysine-based carbon dots is shown in Fig. 3. The zeta potential of CDs was − 8.06 mV. Carbon dots generally contain many carboxylic acid groups on their surface; for this reason, zeta potential has become negative. The results of other studies confirm the result of this study [31–33].

The FTIR spectrum of lysine-based carbon dots confirmed the presence of specific bands for several functional

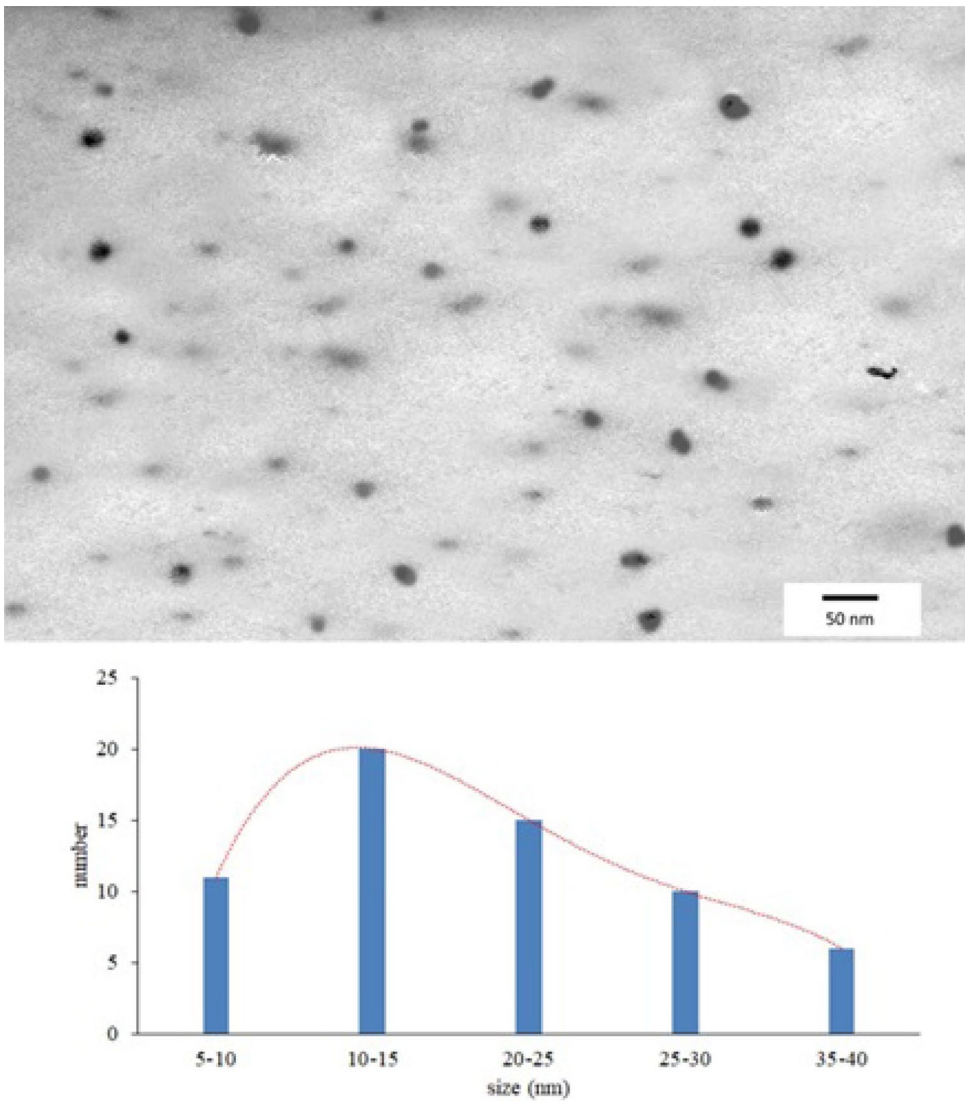

Fig. 2 TEM images of lysine-based carbon dots

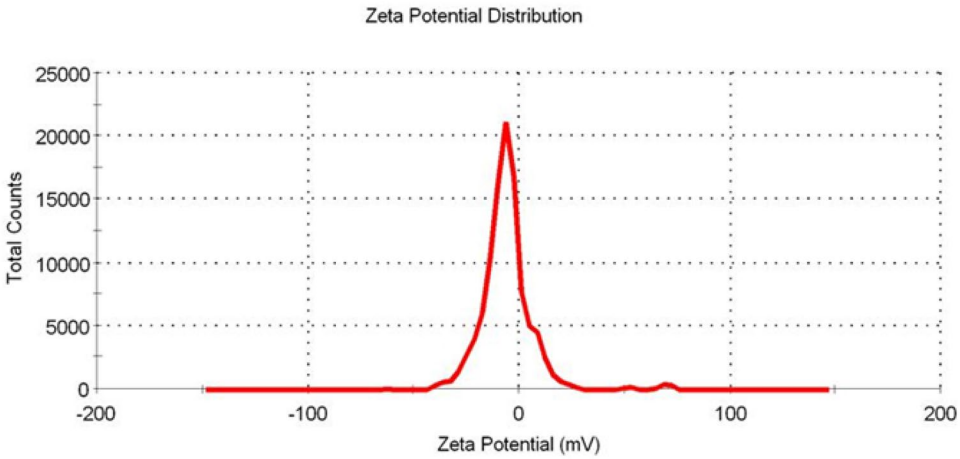

Fig. 3 The zeta potential of lysine-based carbon dots

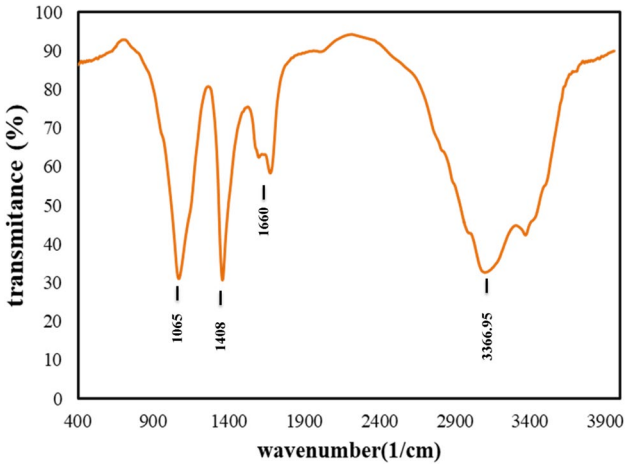

Fig. 4 FTIR spectrum of lysine-based carbon dots and the presence of specific bands for several functional groups

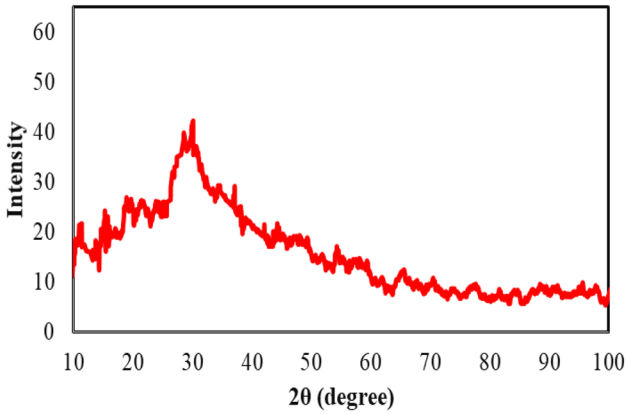

Fig. 5 XRD pattern of Lysine-based CDs. The X-ray diffraction pattern represents a weak crystalline property that confirms the amorphous phase of carbon dots

groups. As shown in Fig. 4, the peak at 3366.95 cm^{-1} in the FTIR spectrum related to O–H/N–H stretching. Also, the peaks of 1408 cm^{-1} indicate the existence of C=C aromatic structure. The peak at 1660 cm^{-1} is related to N–H bending. The band of 1065 cm^{-1} represents the C=O group.

The presence of these functional groups indicates that the carbon dots have excellent solubility in water.

The XRD pattern of CDs is depicted in Fig. 5. A broad peak at 32 degrees (2Θ values) in the XRD pattern represents the graphite plates, which are more comprehensive than normal due to many strains from amino acid side chains. In general, the X-ray diffraction pattern represents a weak crystalline property that confirms the amorphous phase of carbon dots. The results of Lu and et al. (2016) and Yang and et al. (2015) study also confirm the amorphous phase of carbon dots [34, 35].

The optical properties of prepared CDs were investigated using UV–Vis and fluorescence spectrums. As shown in Fig. 6II, the registered UV–Vis spectrums for CDs have two absorbing peaks at 310 nm and 420 nm. Respectively, these two peaks can be attributed to the $\pi \rightarrow \pi^*$ transition of $C = C$ bonds and $n \rightarrow \pi^*$ transition of $C = O$ bonds in CDs. Actually, the fluorescence spectra of CDs depend on their excitation wavelength; so, the fluorescence spectrum of L-lysine-based CDs in the different excitation wavelengths are investigated that are shown in Fig. 6II. As shown in Fig. 6I, the excitation and maximum emission wavelength for CDs are observed at 420 and 500 nm. The value of quantum yield for carbon dots was 31.3% to standard Quinine sulfate.

Stability of carbon dots

The examination of the fluorescence stability of prepared CDs was taken to evaluate them in different conditions. For this purpose, the fluorescence intensity of CDs was investigated at the high ionic strength, various pH values

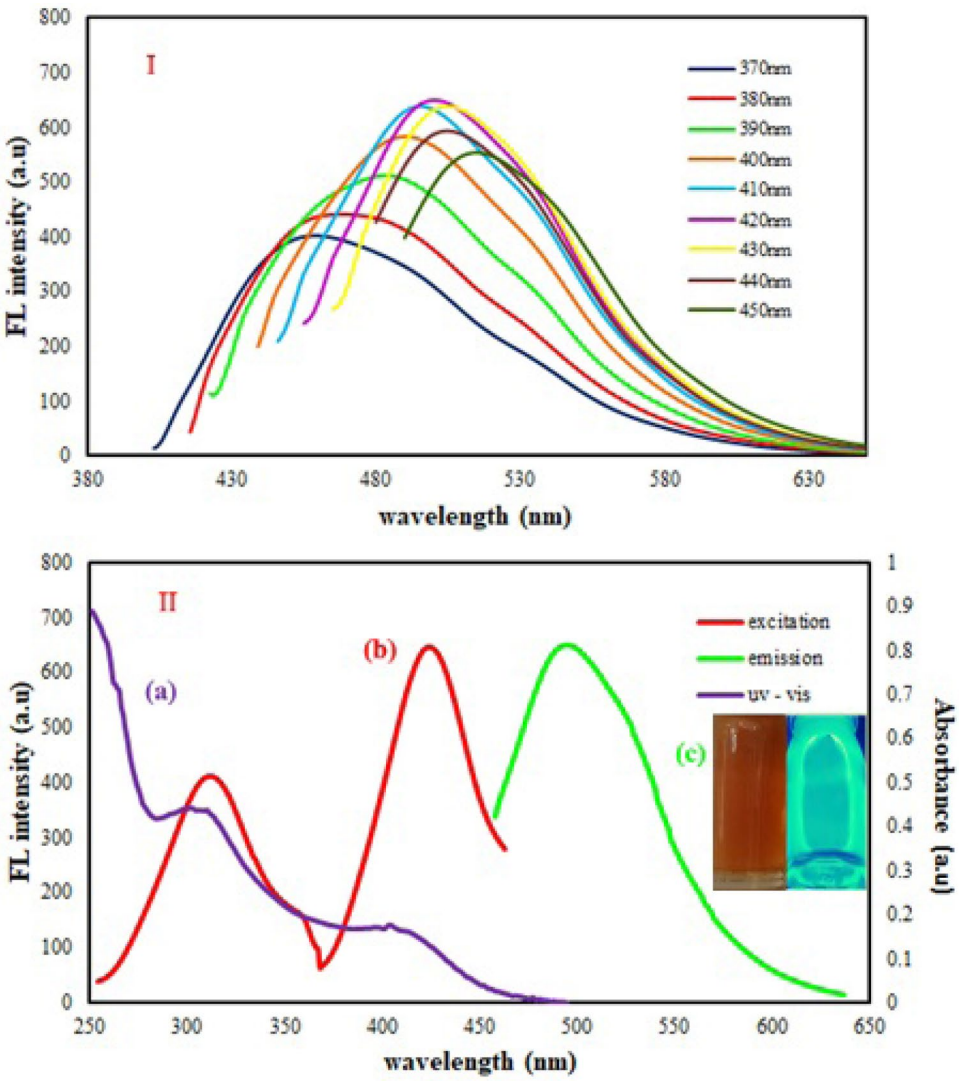

Fig. 6 (I) photo-luminescent spectra of CDs under different excitation wavelengths (the widths of the slits of excitation and emission are equal to 5 and 5 nm, respectively). (II) (a) UV–Vis absorption spectrum of CDs. (b) fluorescence excitation and (c) emission spectra of CDs

and at different times. The results in Fig. 7I show that the prepared CDs have relatively good stability over high ionic strength and will not change much in their (Fluorescence) FL intensity. The emission spectrum of CDs at various pH values are shown in Fig. 7II. As can be seen, the CDs exhibit strong and stable fluorescence in pH 7. There is some reduction in FL intensity concurrent with changes in pH that are not as significant. The good stability and intensity of the CDs in pH 7 hopes that these nanoparticles can be easily used in real samples and human blood plasma. Figure 7III shows that the fluorescence intensity did not change significantly after being placed in ambient light exposure. Also, the results show that over several consecutive days, the FL intensity of CDs decreased less than 5%. Actually, the synthesized carbon dots had high stability than the other carbon dots under different conditions. This carbon dot was more stable than other carbon dots in different studies [36–38].

Fluorescence response of CDs to Duloxetine

According to the previously mentioned and in the case of CDs stability, L-lysine-based CDs have good stability and strong emission. Therefore, these CDs were used for the detection of Duloxetine. Increasing the concentration of Duloxetine in CDs solution was caused by a significant change in fluorescence intensity and fluorescence quenching (Fig. 8I). The fluorescence quenching of the CDs can be credited to the coupling of the Duloxetine to the hydroxyl groups of CDs through an effective electron transfer process. There is a secondary (2°) amine in the structure of this drug that can react with hydroxyl groups of CD. This reaction will cause the elimination of the hydroxyl group and production of tertiary (3°) amine and, as a result, will quench the fluorescence intensity. The fluorescence spectra of CDs solution (5.0(μg)/mL, λ_{ex} = 420 nm and the widths of the slits of excitation and emission are equal to 5 and

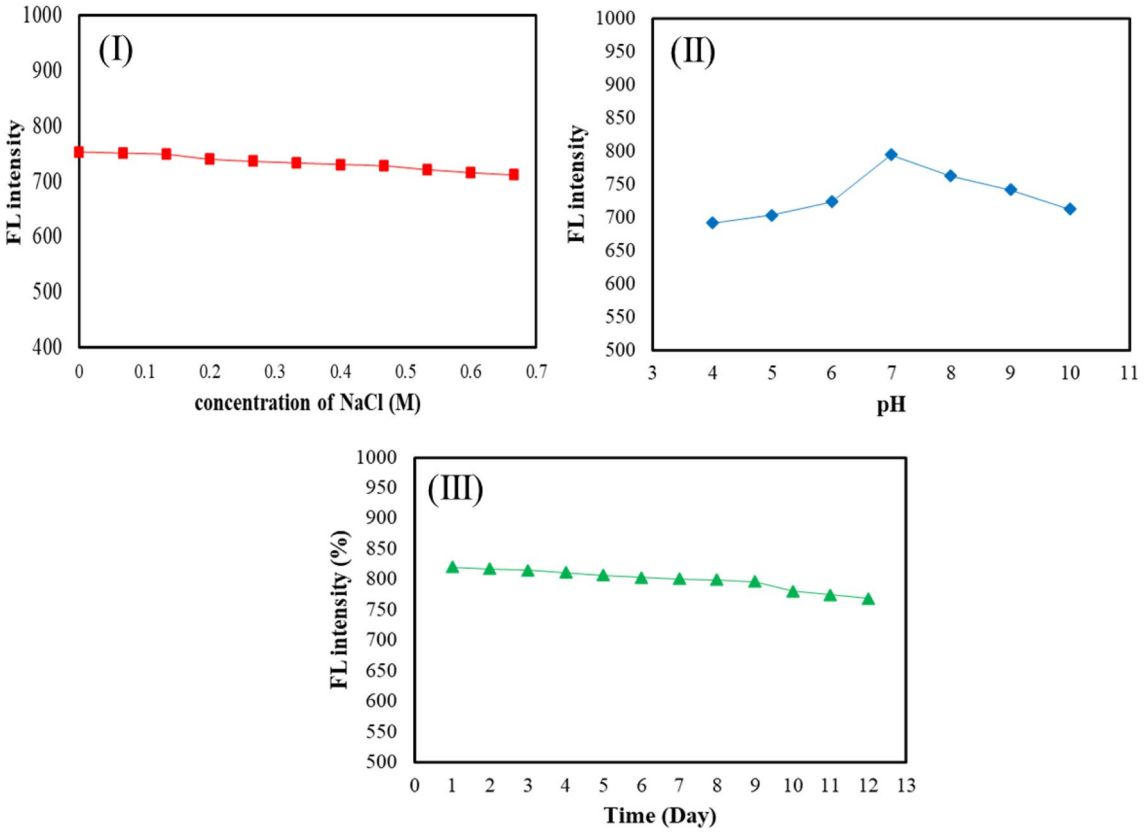

Fig. 7 Investigation of fluorescence intensity stability of CDs at the (I) high ionic strength (II) various pH values and (III) different time

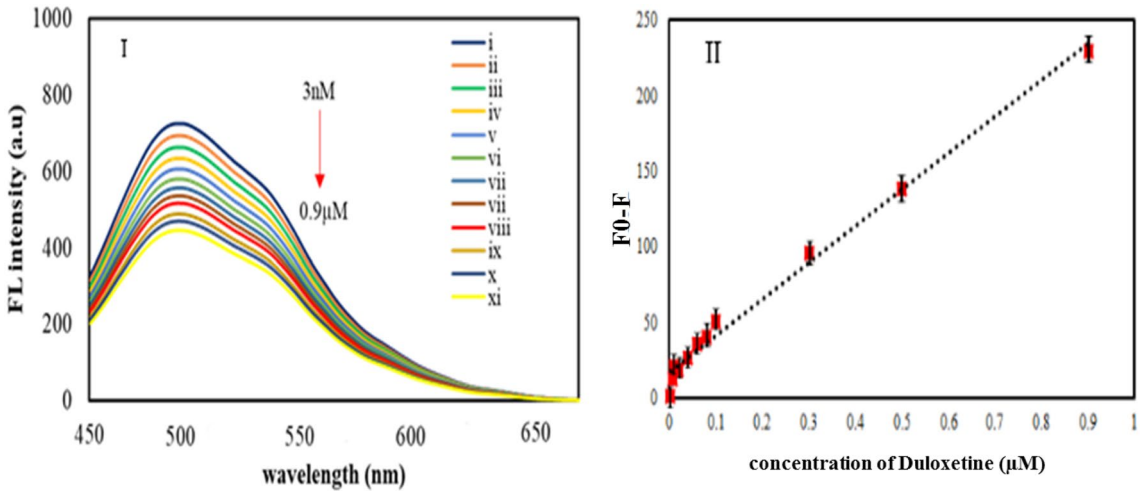

Fig. 8 (I) The Fluorescence response of CDs to Duloxetine at the various Concentrations (3 nM-0.9 μM), (II) The calibration curve of fluorescence intensity versus Concentration of Duloxetine in the range of 3 nM – 0.9 μM

5 nm, respectively), in pH 7.4 of PBS Buffer, were recorded after the increase of Duloxetine concentrations. Figure 8II shows the linear relationship between variations in fluorescence intensity of CDs and the increasing of Duloxetine concentrations (0.003–0.9 μM). The regression equation obtained as: $\Delta F = 241.64[Q] + 16.68$ (μM) with a correlation coefficient of 0.98 and a limit of detection = 0.002 μM based on S/N = 3 and the relative standard deviation (RSD)

for the detection of 0.01 µM of Duloxetine ($n=3$) is 2.8%. This method has the advantage over the methods presented in recent research to determine Duloxetine, such as UV–Visible spectrophotometric method and LC–MS/MS method [4, 5]. This type of sensor has a lower detection limit than the other methods and it is more applicable for the accurate determination of Duloxetine.

Selectivity and sensitivity analysis of the CDs for detection of Duloxetine

To evaluate the efficacy of the proposed method, the interaction effects of drugs that are prescribed with Duloxetine, and also various additives that were used as excipients were investigated. In this method, a constant concentration of Duloxetine (0.02 µM) was added to the CDs solution. Subsequently, different concentrations of the materials studied (Ca^{2+}, K^{+}, Na^{+}, Mg^{2+}, cysteine, glutathione, glucose, galactose, sorbitol, sugar, sodium lauryl sulfate, citrate, ascorbic acid, hydroxyzine and doxazosin) were individually added to the system and their fluorescence was recorded. The concentration of the materials and drugs added is considered as a nuisance that to causes an error of more than ± 5% in the measurement of Duloxetine. The results of recovery of Duloxetine in this study are presented in Table 1, which shows that the possible disturbances have been low at high concentrations of glucose, galactose, sorbitol, sugar, sodium lauryl sulfate, citrate, ascorbic acid, hydroxyzine, Doxazosin, and so on. They had little effect on Duloxetine detection by CDs. Therefore, L-lysine-based CDs can be used to detect duloxetine in real samples and human blood plasma.

Table1 Recovery of Duloxetine (0.02 µM) from different interferences

Additive species	Tolerance limits (fold)	Recovery (%)
Ca^{2+}, K^{+}, Na^{+}, Mg^{2+}	200	99.8
Cysteine	50	100.2
Glutathione	50	98.7
Glucose	100	99.4
Galactose	100	98.2
Sorbitol	20	97.5
Sugar	100	98.5
Sodium lauryl sulfate	10	99.3
Citrate	10	101.3
Ascorbic acid	10	98.6
Hydroxyzine	10	97.8
Doxazosin	50	98.4

Determination of Duloxetine in blood plasma samples and urine

To confirm the validity of the proposed method for detection of Duloxetine, in real conditions, the system was examined using the blood plasma samples and urine spiked by four amounts of the drug. As indicated in Table. 2, the recovery of Duloxetine in 8 samples was 99.2 to 101.5%, which indicates this nanosensor has a good ability to detect Duloxetine at low concentrations.

Conclusion

In this study, the potential use of carbon dots prepared from the amino acid lysine as a fluorescent sensor for the detection of Duloxetine was confirmed. L-lysine-based CDs were synthesized simply, fast, cost-saving, stable, and with high fluorescence. The fluorescence quenching of L-lysine-based CDs was investigated in the presence of the basic medicine material and other drugs prescribed in concomitant with Duloxetine, such as hydroxyzine and Doxazosin. The possible disturbance has been low at high concentrations of hydroxyzine and Doxazosin and they had little effect on Duloxetine detection by CDs. The detection limit was 0.002 µM and also the recovery of Duloxetine in 8 samples was 99.2 to 101.5% which indicates this nanosensor has a good ability to detect Duloxetine at low concentrations. A comparison of the method with previously reported techniques for determining of Duloxetine is provided in Table 3.

Table 2 Precision and accuracy of the method under optimum conditions

	Duloxetine present (M)	Duloxetine found (M)	RSD%($n=5$)	Recovery%
Plasma	6.00×10^{-9}	6.03×10^{-9}	2.80	100.5
	1.00×10^{-8} **(i)**	1.01×10^{-8}	1.06	100.3
	7.00×10^{-8}	7.11×10^{-8}	3.32	101.5
	5.00×10^{-7}	5.06×10^{-7}	1.3	101.2
Urine	6.00×10^{-9}	5.98×10^{-9}	2.68	99.6
	3.00×10^{-8}	3.01×10^{-8}	1.13	100.3
	7.00×10^{-8}	7.04×10^{-8}	2.75	100.5
	5.00×10^{-7}	4.96×10^{-7}	2.5	99.2

Table 3 List of different methods for determine Duloxetine

Method of detection	Liner Range (ng/mL)	LOD (ng/mL)	LOQ (ng/mL)	RSD%	Refs.
GC-FID	5000–50,000	110	340	200	[39]
Spectrofluorimetric	20–400	3	10	2	[40]
HPLC	2–1500 ($\times 10^3$)	800 ($\times 10^3$)	–	4	[41]
Colorimetric	2–20 ($\times 10^9$)	0.25 ($\times 10^9$)	4 ($\times 10^9$)	1.02	[42]
Capillary electrophoresis	2.5–150	1.0	2.5	6.7	[43]
solid-phase extraction	2–2500	0.5	2	3.5	[44]
This work	0.8–267.67	0.59	0.8	2.8	[45]

The linear range, LOD and, LOQ of this sensor were better than the other methods.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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