Nicotinamide-Functionalized Carbon Quantum Dot as New Sensing Platform for Portable Quantification of Vitamin B12 in Fluorescence, UV–Vis and Smartphone Triple Mode

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Abstract
Development of an efficient, portable and simple nanosensor-based systems with reliable analytical performance for on-site monitoring of vitamin B12 (VB12) are still major problems and a challenging work for quality control of manufacturers. Herein, a new fluorescence, UV–Vis and smartphone triple mode nanosensors were designed for the simultaneous detection of VB12 with high sensitivity and accuracy. A novel nanosensor was synthesized through nicotinamide-functionalizing of carbon quantum dot (NA-CQDs) by an one-step microwave-assisted method with green approach. The NA-CQDs sensor showed excellent fluorescence properties and wide linear ranges from 0.1–60 µM with the detection limits of 31.7 nM. Moreover, color changes of NA-CQDs induced by the VB12 could also be detected by UV–Vis spectrophotometer and inhouse-developed application installed on smartphone as a signal reader, simultaneously. The Red, Green and Blue (RGB) intensities of the colorimetric images of NA-CQDs/VB12 system which taken by smartphone's camera converted into quantitative values by the application. A smartphone-integrated with NA-CQDs as colorimetric sensing platform displays good linear ranges (4.16 to 66.6 µM) for on-site determination of VB12 with detection limit of 1.40 µM. The method was successfully applied in the determination of VB12 in complex pharmaceutical supplement formulations without any sample pre-treatment and matrix interfering effects. The recovery results (96.52% to 105.10%) which were in agreement with the reference methods, demonstrating the capability of the smartphone-assisted colorimetric sensing platform in many on-site practical applications of quality controls.

Keywords Fluorescence · Smartphone-assisted · Colorimetric nanosensor · Vitamin B12 · Nicotinamide-functionalized CQDs · Supplements

Introduction
Vitamin B12 (VB12), also called as cyanocobalamin, plays a vital role in normal metabolism of enzymes, lipids and carbohydrates, nerve cell maintenance, DNA synthesis and red blood cell formation [1–4]. For adults, the recommended dietary allowance of VB12 are about 0.40–2.80 mg per day [5]. The excessive VB12 can resulted in liver disease, asthma, neurotoxicity and kidney disorders. Moreover, deficiency of VB12 may lead to significant public health problems like neurological degeneration, memory loss, pernicious anemia and increases the risk of heart disease [6]. Vitamin B12 is one of the essential water soluble “B complex vitamins” that cannot be produced by body cells, it can also be taken from foods like milk, meat, egg and pharmaceutical supplements in various dosage forms daily [7]. As recommended by a healthcare practitioner, the deficiency of VB12 can often be reversed by consuming supplements or by fortified foods [8]. At present, there is great attention in accurately assessing the total dietary intake of vitamins B12 from all sources, especially vitamin supplements (tablets or injections). So, the accurate and precise control of VB12 content in supplements in the laboratory is essential to control the quality of supplements.

At present, most quantification of vitamin B12 are conducted using high performance liquid chromatography
more than the others [5, 8, 19]. It should be noted that most based nanosensor using quantum dots have been reported nanosensor for quantitative detection of VB12, fluorescence-biocompatibility [17, 18]. Up to now, among developed and photo-bleaching resistance and also low toxicity and tunable photoluminescence, chemical inertness, small size materials, they are considered as promising fluorescence sens- ing platform for quantification of VB12 [15, 16]. Compared with conventional semiconductor quantum dots, carbon-based quantum dots (CQDs) offer benefits such as highly tunable photoluminescence, chemical inertness, small size and photo-bleaching resistance and also low toxicity and biocompatibility [17, 18]. Up to now, among developed nanosensor for quantitative detection of VB12, fluorescence-based nanosensor using quantum dots have been reported more than the others [5, 8, 19]. It should be noted that most of the developed fluorescent assays of VB12 for many applica- tions are still conducted with expensive instruments in laboratory and are not suitable for fast on-site detection of analytes.

In recent years, smartphone-based detection system inte- grated with bio/chemical sensors has shown promising pro- gress in point of care (POC)/ point of use (POU) testing approaches for various analytes. Because they are portable, ubiquitous and also produce rapid and simple quantitative results that can be interpreted by untrained personnel espe- cially in resource-limited areas [14, 20–23]. To-date, one research teams have been reported smartphone platform for POC quantification of VB12 in blood using immunoassay-based lateral flow biosensors [24]. These biosensors fabrication needs complicated antibody preparation technology and test strip assembly skill, which is not easy to achieve.

In the present study, a nicotinamide-functionalized CQDs nanosensor were designed as fluorescence and colorimetric probes for simple and portable detection of VB12 simultane- ously. NA-CQDs were synthesized by one-pot microwave-assisted hydrothermal method emploing nicotinamide as new sources of functionalized material on carbon quantum dots. Moreover, an in-house android-app on smartphone-based detection was developed to facilitate the sensing procedure in many POU testing approaches. The NA-CQDs nanosensor exhibited dual response via both fluorescence and colorimetric change for on-site monitoring of VB12, simultaneously. In the RGB-based (red, green and blue color space) software, quantitative measurement of analytes can be performed by imaging and then, selecting the measure- ment option on the software. The results display on smart- phone and data analysis and interpreting by the method was simplified. In the present study, quantification of vitamin B12 in fluorescence, UV–Vis and smartphone triple modes were evaluated to take advantage of each method such as reliability and sensitivity of fluorescence/UV–vis methods and capability of smartphone method for POU testing in VB12 pharmaceutical supplements. Therefore, the capability of fluorescence and colorimetric sensing of VB12 using the NA-CQD probes is investigated, the viability of the lat- ter allowing for arguably more convenient detection using smartphones.

**Experimental**

**Materials and Instruments**

All standards or chemical reagents used were of pharmaceu- tical and analytical grades. Nicotinamide, pyridoxine hydro- chloride (vitamin B6), thiamine hydrochloride (vitamin B1), calcium D-pantothenate (vitamin B5), and sodium hydrox- ide were purchased from Merck (Darmstadt, Germany) and cyanocobalamin (vitamin B12) and citric acid (CA) were supplied from Sigma-Aldrich.

Ultrapure water was purified with a Millipore (0.05 μS cm⁻¹) instrument. All UV–Vis absorption spectra were measured by a UV–Vis spectrophotometer (Cary 100 UV–Vis, Agilent Technologies) from 200 to 800 nm. Fluorescence spectra of VB12 standard and sample solutions were recorded from 370 to 700 nm by a fluorescence spectrophotometer (LS-55, Perkin Elmer) equipped with a Xenon lamp source and a 1.0 cm quartz cell. Surface morphology microscopy of NA-CQDs were performed using a SEM (Zeiss Sigma 500 VP Analytical FE-SEM with Oxford EDS and Mapping) and high-resolution TEM (FEI Tecnai F20 HR-TEM) microscopes. The FT-IR spectra of NA-CQDs were acquired using a Fourier transform infrared spectrometer (FT-IR Spectrum two, Perkin Elmer) from 400 to 4000 cm⁻¹. Advanced microwave system (Milestone ETHOS 1) was used for synthesis of nicotinamide-functionalized CQDs.

**Microwave-Assissted Synthesis of Nicotinamide-Functionalized CQDs**

Nicotinamide-functionalized CQDs were synthesized via a hydrothermal treatment of citric acid as C source and nicotinamide as new source of N through microwave-assisted hydrothermal method. In a typical experiment citric acid
monohydrate (1.68 g) and nicotinamide (2.92 g) were thoroughly dissolved in 10 mL of ultrapure water and stirred for 30 min. Then the solution was transferred into microwave radiation system with moderate temperature (80 W, 160 °C) for 20 min.

Development of RGB-Based Smartphone-App

In smartphone-assisted colorimetric sensing platform, the color intensities of the images taken by the camera are proportional to the red, green, and blue (RGB) values. For on-site image processing, in-house android-based app was developed by an algorithm similar to ImageJ software (U.S. National Institutes of Health, Bethesda, MD, USA) for quantifying color intensities and relating it to VB12 concentration. In this study, all images were taken without a flash with a 25-megapixel camera of Samsung smartphone which that positioned as close as possible to the sample container (about 6 cm away). The RGB intensities of the colorimetric images of NA-CQDs/VB12 system were converted into quantitative values by the introduced application.

Detection Procedure of VB12 and Real Sample Preparation

A stock standard solution of VB12 (1 mM) was prepared. The solutions of VB12 with different concentrations were prepared by appropriate dilution of the stock standard by ultrapure water. The NA-CQDs nanosensor were used for determination of VB12 by the following procedure. 1 mL of NA-CQDs solution (0.1 mg/mL) was added to 5 mL tube. Then, 3.5 mL of disodium hydrogen phosphate buffer solution (10 mM, pH 7) and 500 µL of VB12 solution with different concentrations were added to the above mixture solution. Fluorescence and UV–Vis spectra of NA-CQDs/VB12 system were recorded from 370 to 700 nm at excitation wavelength of 365 nm and from 200 to 800 nm, respectively. Also, the color change of NA-CQDs solution-based nanosensor upon addition different concentrations of VB12 were scanned using the smartphone camera through RGB application, simultaneously.

In order to real sample evaluation, the VB12 injection and tablet were purchased from a local pharmacy. 1 mL of VB12 injection sample, containing 333.3 µg VB12 per mL, was added to a 10 mL volumetric flask and diluted with ultrapure water to prepare the solution with concentration of 24.593 µM. A VB12 tablet, containing 200 µg VB12 per tablet, was accurately weighted and dissolved in 10 mL of ultrapure water into a volumetric flask (concentration of VB12 solution was 14.756 µM). Then, the fluorescence, UV–Vis spectra and color intensities of the real samples were recorded according the above-mentioned procedure.

Results and Discussion

Characterization of Nicotinamide-Functionalized CQDs

FT-IR

The surface chemical groups of nicotinamide-functionalized CQDs were further characterized by FT-IR (Fig. 1A). For NA-CQDs, a broad absorption band was observed at 3000–3400 cm⁻¹, which is attributed to stretching vibrations of O–H and N–H groups. Moreover, FT-IR spectrum of NA-CQDs exhibited characteristic absorption peaks at around 1659 and 1700 cm⁻¹ which are belong to C = C and C = O stretching vibrations bands. Furthermore, nicotinamide had been successfully functionalized on the carbon quantum dots due to the appearance of bending vibration of C-NH and stretching vibration of C–N at 1380 and 1550 cm⁻¹, respectively [4, 25]. The results obtained from FT-IR are in agreement with other characterization results and clearly confirm that nicotinamide-functionalized CQDs are successfully synthesized.

SEM and EDX Elemental Mapping

The morphology and elemental composition of NA-CQDs were characterized by FE-SEM apparatus which was equipped with an energy-dispersive X-ray (EDX) spectroscopy. Figure 1B, D exhibit the FE-SEM images of the NA-CQDs in different magnifications to evaluate their morphology and internal structure. The figures reveal that the synthesized NA-CQDs were all spherical in shape and fairly uniform in size.

EDX analysis and mapping were also conducted to evaluate the detailed elemental composition and distribution. The data generated from EDX spectrum of NA-CQDs showed the following atomic percentages: 67.8 wt% (C), 11.1 wt% (O) and 21.1 wt% (N). In addition, EDX mapping in the Fig. 1C, confirmed successful and uniform existence of N element in the structure of nicotinamide-functionalized CQDs.

HR-TEM

Morphological and size distribution of NA-CQDs were further obtained by high-resolution transmission electron microscopy (HR-TEM). HR-TEM image (Fig. 1E) illustrate that, the average diameter of NA-CQDs was smaller than 10 nm.
Fig. 1 (A) FT-IR spectra, (B, D) FE-SEM images of NA-CQDs with different magnification. (C) EDX elemental mapping and (E) HR-TEM image of NA-CQDs
Fluorescence Sensing Performance of NA-CQDs for VB12

The capability of NA-CQDs as a fluorescence nanoprobe for monitoring of VB12 was investigated. Figure 2A shows that as the concentration of VB12 increases, the fluorescence emission intensity of NA-CQDs is clearly decreased. Under the optimal conditions (Fig. S1), a good linear relationship of F/F₀ with concentration of VB12 was obtained in the range of 0.1–60 μM (Fig. 2B). Moreover, the linear regression was fitted based on Stern–Volmer equation (F/F₀ = 0.0294 CB₁₂ + 0.9641) with good correlation coefficients (0.9975). The limit of detection (LOD) was found to be 31.7 nM (based on the Eq. 3SD/m, where SD and m referred to standard deviation of the blank and the slope of the calibration curve, respectively. Compared with other probes based on fluorescence nanosensor for detection of VB12, the synthesized NA-CQDs nanosensor exhibit wide linear range, high sensitivity and low detection limit (Table 1).

Smartphone-Assisted Colorimetric Sensing Platform for VB12

Taking advantage of good performance of smartphone-assisted colorimetric platform for sensing analytes, the NA-CQDs/ VB12 system was utilized for on-site monitoring of VB12. As shown in the Fig. 3A, the color change of the NA-CQDs probe from blue to red induced by VB12, which were quantified through RGB profiling in the range of 4.16–66.6 μM. As revealed in Fig. 3B, a good linear regression equation (R² = 0.9959) between R/(R + G + B) intensities with respect to VB12 concentration was obtained (R/(R + G + B) = 0.0041 C₄₁₂ + 0.2949).

Table 1 Comparison of different quantum dots fluorescence based probes for the detection of VB12

| FL Probe         | Linear range | Detection limit | References |
|------------------|--------------|-----------------|------------|
| CDs              | 0.5–60 μM    | 0.1 μM          | [19]       |
| (MPA) functionalized CdS QDs | 3.69–73.78 μM | 5.10 μM        | [8]        |
| Y-CDs            | 5–200 μM     | 2.045 μM        | [4]        |
| t-CD             | 0.74–8.85 μM | 0.073 μM        | [16]       |
| CdTe QDs         | 0.74–10.33 μM| 0.110 μM        | [15]       |
| s–N-CDs          | 10–100 μM    | 2.19 μM         | [27]       |
| BCQDs            | 0.5–3 μM     | 81 nM           | [28]       |
| N-CNDs           | 0.5–35 μM    | 47.4 nM         | [5]        |
| NA-CQDs          | 0.1–60 μM    | 31.7 nM         | This work  |

The color change of NA-CQDs nanosensor upon addition different concentrations of VB12 can be observed by naked eyes under natural light. The colorimetric signal of NA-CQDs/VB12 system was captured by the smartphone camera and analyzed by in-house android-app for the total start-to-results time of less than 5 min. The results of smartphone-based sensor demonstrat the capability of smartphone-assisted colorimetric sensing platform for quality control of pharmaceutical products.
Mechanism Investigation of Fluorescence Quenching and Color Change of NA-CQDs Nanosensor

The fluorescence of NA-CQDs was effectively quenched in the presence of different concentrations of vitamin B12. For the mechanism of VB12-induced fluorescence quenching of NA-CQDs, the reasonable explanation can be inner filter effect (IFE)-based fluorescent quenching mechanism. As illustrated in Fig. 4A, the absorption spectral overlap of VB12 with the fluorescence excitation and emission peak of nicotinamide-functionalized CQDs meets the
requirement for IFE fluorescence quenching strategy for sensing of VB12. This reasonable assumption does fit well with the previous literature [18, 26].

In the present study, to more clarify color change in the NA-CQDs/B12 system, the UV–visible absorption spectra of N-CQDs in the absence and presence of VB12 were investigated and the results illustrated in the Fig. 4B. As shown in the figure, in the absence of VB12, the NA-CQDs had a characteristic peak about 334 nm. In the presence of NA-CQDs, no shift in wavelength was observed in the absorption spectrum of VB12 (33 µg/mL), but the peak at about 360 nm increases after additions of VB12 (Fig. 4B). The addition of VB12 (0–133.2 µM) into the NA-CQDs solution gradually increases the intensity of absorption band at about 360 nm, which resulted in color change of NA-CQDs nanosensor (Fig. 4C).

Selectivity and Interference Studies for the Detection of VB12

Various common substances in VB12 supplements formulation may interfere with the accuracy of B12 detection. Therefore, Vitamin B1, B5 and vitamin B6 were applied as competitive vitamins for selectivity studies of the NA-CQDs nanosensor in various supplements. To evaluate the selectivity of the NA-CQDs nanosensor, VB12 was detected in the presence of other competitive vitamins including vitamin B1, B5 and vitamin B6. Figure 5A shows the quenching effect of the NA-CQDs/VB12 (B12, 30 µM) system in the presence of vitamins B1 (3000 µM), B5 (3000 µM) and B6 (3000 µM). The results indicated that, even 100-fold concentrations of competitive vitamins have no obvious effect on the B12 detection.

To further confirm the IFE quenching mechanism and the selectivity of NA-CQDs nanosensor, several UV–vis absorption spectra of different vitamins, including vitamins B1, B5 and vitamins B6 and B12 are also displayed in Fig. S5. It is obvious that only the UV–vis absorption spectrum of VB12 have the significant overlap with the excitation (366 nm) and emission spectra (444 nm) of NA-CQDs.

Neurobion is a brand of supplements that contain a combination of B-complex vitamins. Based on summary of product characteristics of European medicine agency guidelines for Neurobion injection and Tablet, possible interferes which related to excipients of different pharmaceutical formulations, were also evaluated. Moreover, As shown in Fig. 5B,
it was obvious that these coexisting excipients did not interfere with the detection of vitamin B12 (fluorescence change < 2%). Therefore, the results demonstrate that the selectivity of nanosensor toward VB12 and the possibility of practical application of NA-CQDs nanosensor for determination of VB12 in various pharmaceutical supplements formulation (injection and tablet) is good.

### Real Samples Evaluation

The applicability of the NA-CQDs nanosensors for quantitative detection of B12 were evaluated in pharmaceutical VB12 supplements in various dosage forms (injection and tablet) as real samples. Table 2 indicates the results obtained by the fluorescence, UV–Vis and smartphone-integrated colorimetric sensing platform for on-site quantification of VB12 in the B12 injection and tablet, respectively. The recovery values of VB12 by the NA-CQDs nanosensors in the real samples are in the ranges 96.52–105.10% with RSD between 1.32% and 3.44% (n = 3). These results were in agreement to their label/manufacturer’s claims which determined by the reference method (USP 42 vitamin oral solution for analysis of VB12, HPLC chromatograms in Figs. S2, S3 and S4).

### Conclusion

A triple mode detection of B12 via novel nicotinamide-functionalized CQDs nanosensor with benefit of advantages of universal fluorescence and UV–Vis methods and smartphone-assisted colorimetric sensing platform as new generation of analytical tools for bio/chemical detections was successfully designed. The satisfied recovery results (96.52% to 105.10%) which are in agreement with the reference method in various dosage forms of VB12 supplements like an injection and tablet were obtained which demonstrates that the capability of new sensing platform for on-site monitoring in quality control of pharmaceutical manufactures. Excellent optical properties, high sensitivity, good selectivity, rapid response time, portability, wide linear range and simplicity of data analysis/interpreting were the advantages of the new designed sensing platform. Besides the promising fluorescence sensing performance of NA-CQDs, the introduced smartphone-assisted colorimetric sensing platform could also afford experience for designing neotype sensing strategy for point of care (POC)/point of use (POU) testing in many practical applications.

### Supplementary Information

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### Authors’ Contributions

SD designed and performed the experiments and analyzed the data, and also write the manuscript. AM designed the experiments, interpreted the data and edit the manuscript. AJ checked the data and manuscript. AM developed the smartphone application was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

### Declarations

**Ethics Approval** Not applicable.

**Consent to Participate** Not applicable.

**Consent for Publication** Not applicable.

**Conflict of Interest** The authors declare that they have no conflict of interest.

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