On-off fluorescent switching of excitation-independent near-ultraviolet emission carbon nanobelts for ultrasensitive detection nimesulide in pharmaceutical tablet

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Here, we present an excellent strategy of unmodified near-ultraviolet fluorescence nitrogen doping carbon nanobelts (NFNCBs) for detecting nimesulide (Nim). After simply hydrothermal process of uric acid and hydroquinone in the DMF solvent, the NFNCB shows a shape of corroded stalactite-like composed of nanobelts aggregates, near-ultraviolet luminescence and narrowed full width at half maximum, which could improve/change the electronic properties and surface chemical active site, as result of a sensitive response to Nim. By employing this sensor, the quantitative measurement displays a linear range of 2.0 nM - 100.0 μM with a lower detection limit of 0.21 nM (3σ/k) for Nim. Our work provided a high selectivity for Nim, which may be capable for pharmaceutical sample analysis in real tablets. And the results of the recoveries (96.3%-106.2%) for real sample analysis indicate this nanoprobe might expand a good avenue to design effective luminescence nanoprobe for other biologically related drugs.

Keywords: Carbon nanobelts; Near-ultraviolet luminescence; Nimesulide; Pharmaceutical sample
Introduction

As a kind of non-steroidal anti-inflammatory drug, nimesulide (Nim, N-(4-nitro-2-phenoxyphenyl)-methane-sulphonamide) plays an important role in anti-inflammatory for the treatment of chronic rheumatoid arthritis, inflammation of otorhinolaryngological diseases, genitourinary system, postoperative pain and other inflammatory diseases [1-4]. Besides this, Nim is also widely used as metalloproteinase inhibitors, which could account for the articular molecule decomposition in the presence of free radicals [5]. However, the uncontrolled and improper use of Nim in real tablets might has a great harm to human health, such as gastrointestinal problems, liver and kidney damage, and so on [6-8]. Therefore, it is of decisive significance to detect Nim levels in real tablets for the sake of health. Thus far, a plethora of methods, including electrochemical methods [3, 9], high performance liquid chromatography-mass spectrum [10], micellar liquid chromatography [7], spectrophotometric determination [11] and fluorescence techniques [5, 12], have been used to monitor Nim. Among the above analysis methods, the luminescence sensing platform has aroused great interest due to its fast detection, simplicity, high sensitivity and selectivity, what’s more, they are not complicated pretreatment process and do not destroy biological sample.

Owing to their intriguing skeleton frame, remarkable thermal, nontoxicity, mechanical and electronic performances, especially their fluorescence emission, carbon-based fluorescent nanomaterials, as a popular luminescence nanomaterial, have aroused principal attention in the field of nanomaterial, and broad application ranging from biomedicine to living organism analysis. Recently, tuning size, shape, surface chemistry, and composition along with electrochemical and physicochemical properties, including specific active center, ground and excited state properties, are common objectives in this research field of carbon nanomaterial. During our prepared different carbon nanomaterials, namely carbon- nanodots, nanosheet, nanoflower, and nanoribbon, it has become clear that the modulation of functional nanomaterials with targeted properties can be achieved by selection the appropriate precursors, which is
an effective route to adjust the physicochemical and fluorescent properties by heteroatom inserting into the molecular skeleton. Consequently, a relatively high-output strategy to synthetize near-ultraviolet fluorescence nitrogen-doping carbon nanobelts (NFNCBs) was developed through an easy hydrothermal process of uric acid (UA) and hydroquinone (HQN) in DMF solvent, as illustrated in Scheme 1. During the hydrothermal process, the polymerization between precursors, and surface functionalization of carbon nanomaterial were achieved simultaneously, which led to the formation of the NFNCBs with superior water dispersibility and unique physicochemical properties. Furthermore, a label-free chemosensing platform for the drug of Nim detection was developed based on the nonradiative energy- or electron-transfer processes induced fluorescent quenching of NFNCBs (Scheme 1). A large number of published documents indicate that this is the first time to propose the fluorescent sensing platform for the drug molecule of Nim using efficient nonmetal doped carbon nanomaterial.

NFNCBs was synthesized by traditional hydrothermal synthesis technology at 180 °C for 16 h in the weak polarity of organic solvent. UA, HQN and DMF were used as the C-N sources and solvent, respectively. Based on many literatures and our previous research results, the selection of precursor and solvent/stabilizer are the decisive factors for physicochemical properties and FL quantum yield (QY) of the carbon-based nanomaterials. Therefore, the kind of precursor and stabilizer were selected as optical performance transducing unit. Compared with the pyrocatechol (PCC) as one of the precursors (Fig. S1, blue and green lines), the FL intensity of the NFNCBs using HQN as one of the precursors possess shorter emission wavelength and higher FL QY (Fig. S1, black and red lines). In addition, the FL intensity of the NFNCBs in pure DMF solvent/stabilizer possess the highest FL intensity comparing to the mixed solvent/stabilizer (C\textsubscript{2}H\textsubscript{5}OH and H\textsubscript{2}O) and other synthetic conditions (Fig. S1). From the above discussion, it is reasonable to speculate that para-position of hydroxyl could provide relatively dispersed active sites, and which could not produce intramolecular hydrogen bond and easily generate more structurally rigid plane of the carbon-based nanomaterial, resulting in increasing its FL QY. By contrary,
ortho-position of hydroxyl could form intramolecular hydrogen bond, resulting in deactivation of amounts of active sites, and which might participate reaction with a few of UA precursor and produce the flexibility of structure, as result of the weak luminescence. Besides this, the polarity of solvent is also important factor for synthetic FL carbon nanomaterial. Too strong or weak polarity of solvent would affect the internal reaction mechanism, leading to the reduction of QY of NFNCBs (Fig. S1). To date, there is still no reliable reaction mechanism for FL NFNCBs, although the above probable of several influence factor of synthesis mechanism, the practical reaction mechanism of shortwave luminescence NFNCBs remains unclear.

**Experimental**

**Materials and reagents**

Nimesulide (Nim, C\textsubscript{13}H\textsubscript{12}N\textsubscript{2}O\textsubscript{5}S) was purchased from Aladdin Chemical Reagent Co. Ltd. (Shanghai, China). Hydroquinone (HQN), pyrocatechol (PCC), captopril (Cap), histidine, tryptophan, tyrosine, and heparin were bought from Shanghai Sinopharm Chemical Reagents Co. Ltd. (Shanghai, China). Uric acid (UA) was bought from Sigma-Aldrich. N,N-dimethylformamide (DMF) was purchased from Shanghai Shanpu Chemical Co. Ltd. (Shanghai, China). All other chemicals with analytical grade obtained from commercial sources, and used directly without additional purification. Deionized water was obtained by a Millipore water purification system (Millipore Corp., Billerica, MA, USA) and used in all needed experiments.

**Apparatus**

UV-vis and fluorescence (FL) spectra were conducted at room temperature on a Shimadzu UV-2550 spectrophotometer (Tokyo, Japan) and Jasco FP-6500 FL spectrophotometer instrument apparatus (Jasco, Japan), respectively. TEM and EDX were conducted on a JEM-2100 transmission electron microscope with an operating voltage of 200 kV (JEOL Ltd.). FT-IR spectrum was taken on a Nicolet 5700 (USA) FT-IR spectrophotometer. The Thermo ESCALAB 250 X-ray photoelectron
spectrometer (USA) was used for the XPS analysis of the nanomaterial.

**Preparation of shortwave photoluminescence NFNCBs polymer**

The shortwave photoluminescence NFNCBs was obtained through simple solvothermal route. 110 mg HQN and 110 mg UA were dispersed into 5 mL DMF with ultrasonic process to prepare the mixed solution, and placed into a 25 mL poly(tetrafluoroethylene) (Teflon)-lined autoclave. Then, the mixture was treated and heated at 180 °C for 16 h in a blast drier. When the obtained suspension was naturally cooled down to room temperature, the mixture was centrifuged at 13310 g for 30 min to remove the large particles, and the NFNCBs shows shortwave luminescence.

**Photoluminescence quenching of NFNCBs by Nim**

Ten μL stock solution of NFNCBs (~1.5 mg mL⁻¹) was diluted with 50 μL pH 7.0 PBS (50 mM) in 2 mL centrifugal tube, and different amounts of Nim standard solution were separately added into the above diluted NFNCBs solutions. The selectivity of the photoluminescence sensor for Nim was assessed by mixing 100 μM of other competitive drug molecules and metal ions, including histidine, Cap, tryptophan, tyrosine, heparin, Hg²⁺, Ag⁺, Mg²⁺, Cu²⁺, Sn²⁺, Ba²⁺, Ni²⁺, Fe²⁺, Pb²⁺, Co²⁺, Cd²⁺, Cr³⁺, Fe³⁺, Zn²⁺, and Mn²⁺ instead of Nim under the same way. The total volume of the above mixtures was uniformly diluted to 500 μL with deionized water. All of the FL spectra were recorded at excitation wavelength of 300 nm.

**Real samples**

Nim tablets, which were obtained from the Shanghai pharmaceutical Co. Ltd., were ground uniformly using the mortar, 125 mg of the above Nim powder was accurately weighted and dissolved with 1 mL NaOH solution (1 M). After ultrasonication for 30 min, the above solution was diluted using pH 7.0 PBS solution (50 mM) to form a solution of 5 mg mL⁻¹ (0.016 M). Then, the filtrate was obtained through centrifuging at 9242 g for 10 min. The standard Nim solution was separately added into the above prepared mixture for recovery measurement to assess the accuracy and practicability of the turn-off nanosensor. The corresponding calculation rules of the recovery
correspond to the later description. And the determination of recovery was repeated five times.

Results and discussions

Characterization and optical properties of the NFNCBs

The synthesized NFNCBs have been characterized with TEM and EDS to confirm the formation of the NFNCBs polymer. As shown in Fig. 1A-1C, it distinctly displays that NFNCBs are nearly ribbons-like and have a porous structure. That is, the NFNCBs are uniform and shape of corroded stalactite-like composed of nanobelts aggregates in the solid state (Fig. 1A-B), which might be ascribe to non-interacting multiple active sites of itself of UA, HQN and weak polarity solvent of DMF. The EDS spectrum indicates the NFNCBs were mainly three elements composed of C (72.88 at%), O (18.78 at%) and N elements (8.34 at%), confirming the successful synthesis of nonmetallic nitrogen doped carbon nanoprobe. And the relatively large peak at ~1.0 keV is the peak of metal copper coming from copper net (Fig. 1D). However, it should be noted that the content of N (8.34 at%) was much lower than the recently reported papers of N-doped carbon-based nanoprobes [13, 14], as result of changing of optical and physicochemical properties of NFNCBs.

The composition and surface state of NFNCBs were analyzed by XPS and FT-IR spectra. In the Fig. 2A, the full XPS spectrum displays three typical peaks at 284.9, 400.1, and 532.1 eV for C1s, N1s, and O1s [15, 16], respectively, which was consistent with the EDS result. The XPS spectrum of C1s (Fig. 2B) was deconvoluted into four peaks at 284.6, 285.7, 286.8 and 288.9 eV, which are belonged to C=C/C-C, C-N, C-O and C=O bonds [17-20], respectively. And the two peaks at 531.5 and 532.7 eV in high resolution O1s spectrum (Fig. 2C) are belonged to C=O/C-OH, and C-O-C groups [21, 22], respectively. The N1s band can be divided into three peaks at 399.8, 400.6 and 401.5 eV, which indicates the existence of C=N, C-N and -NH2 groups [19, 20], respectively. These results are consistent with the corresponding FT-IR result (Fig. S2). The FT-IR spectrum displays that the NFNCBs exists lots of polar
functional groups, for example, O-H/N-H bond at 3493 cm$^{-1}$ [21, 23], C=O bond at 1665 cm$^{-1}$ [19], C-O bond at 1062-1258 cm$^{-1}$ [24], which guarantees its excellent water-solubility in polar solvents. The broad absorption peaks at 2921 and 2851 cm$^{-1}$ are belonged to the C-H stretching vibrations, and the peak at 864 cm$^{-1}$ should be corresponding to C-H bending vibration [21, 25]. The aromatic C=N bond which presents in the rigid structure and carbon nuclei are observed in 1385-1502 cm$^{-1}$, and the stretching vibration of C-N is at 1438 cm$^{-1}$ [26, 27]. All the above results clearly suggest that our NFNCBs have large rigidity of structure with lots of oxygen/nitrogen-containing polar groups, which might produce specific optical properties and anisotropy reactivities for NFNCBs.

The UV-vis and emission of the NFNCBs were examined to evaluate its optical properties. Fig. 3A displays that the characteristic peaks of NFNCBs are mainly located at 288 nm with a wide absorption peak at approximately 370 nm, which is corresponding to $\pi$-$\pi^*$ transitions of C=C bond in the core of the NFNCBs [28, 29], while the other peak at 370 nm is ascribed to the n-$\pi^*$ transitions of the C=O, C=N and C-O/C-N bonds [30]. And the red shifts of $\pi$-$\pi^*$ transition absorption for C=C from ~230 nm to ~290 nm may be due to the incorporation of heteroatoms into the carbon skeleton [30, 31]. Different from the most reported carbon nanodots [32-34], narrowed full width at half maximum (~40 nm) and excitation-independent emission of the NFNCBs (Fig. 3B) maybe ascribe to the content of aromatic heterocyclic nitrogen of C=N and surface of N-containing groups [35], which can be regulated through selecting precursor and regulating the experimental condition during hydrothermal reactions. Varying the excitation range from 260 to 310 nm displays that the emission peaks of the NFNCBs are excitation-independent emission and the strongest FL emission peak is located at 327 nm with excitation at 300 nm. To investigate the optical stability of the NFNCBs in aqueous solution, the effects of pH, and salinity tolerance on their FL intensities were tested. The results indicate that the NFNCBs possess excellent optical stability in a wide acid-base range of pH 4-11 (Fig. S3A) and under high ionic strength (Fig. S3B), which may be inherited from the
surpassingly structural and electrostatic stabilization of NFNCBs. Because of the outstanding optical stability of luminescence, NFNCBs is a very good candidate for analysis of complex biological system as an effective probe.

**Fluorescence response of NFNCBs to Nim**

Currently, optical sensing has become one of the most popular analysis techniques in chemical sensing because of its simplicity, obviousness, and convenience. In order to obtain better selectivity and sensitivity of the sensor, it is very important to choose the type of buffer solution and the pH value of buffer. From the Fig. S4, it clearly shows that the cushioning effect of PBS is much better than Tris-HNO₃ buffer, in which organic compounds of Tris might have some influence on the detection of Nim molecule. Therefore, PBS buffer of pH 7.0 was selected as the optimum reaction environment for Nim determination. Under the optimized conditions, Fig. 4A displays that a gradual decline in the FL intensities of NFNCBs at 327 nm was discovered with the concentration of Nim from 0 to 500 μM. From the Fig. 4A, the diagram of the kinetic reaction between relative fluorescence intensity of \([FL_0 - FL]/FL_0\) and the concentration of Nim from 0 to 500 μM was obtained (Fig. 4B). The FL₀ and FL were the FL intensities of NFNCBs at 327 nm in the absence and presence of Nim, respectively. And the proportional value of \([FL_0 - FL]/FL_0\] versus the concentration of Nim in the linear range of 2.0 nM - 100.0 μM (correlation coefficient 0.985, n=5) was plotted in the inset of the Fig. 4B. The detection limit of Nim was calculated to be 0.21 nM (3σ/k), which is lower than the previously reported sensors (Table S1), illustrating that the FL detection of Nim can be easily achieved using NFNCBs as a nanoprobe. Considering that the NFNCBs sensor may be applied to the detection of Nim in the biological and drug detection analysis, the selectivity of the NFNCBs sensor for Nim was assessed. As illustrated in Fig. 5, the influence of these biological small molecule or metal ions on the specificity of our sensor for Nim is negligible. The experimental results indicate that the NFNCBs nanoprobe is capable of discerning between Nim and the interfering substance. All these results validate the fact that the NFNCBs probe for high selectivity detection of Nim make NFNCBs as a
good candidate for analysis Nim in real samples.

Detection of Nim in pharmaceutical samples

The NFNCBs sensor was applied to the analysis Nim in a pharmaceutical Nim samples to verify its practicability in the real sample analysis. And analysis of Nim in one pharmaceutical sample by standard addition method was conducted, the experimental data are presented in Table 1. It was verified that the measured concentration of Nim (9.78 μM) used our method was very close to the theoretical concentration of Nim (10 μM). The recoveries were calculated based on the following formula:

\[
\text{Recovery} \, (\%) = \frac{C_{\text{founded}}}{C_{\text{initial}} + C_{\text{added}}} \times 100\%
\]

The recoveries of Nim are in the range 96.3-106.2%, illustrating that this FL assay might be applied to the analysis of Nim in real samples.

Mechanism of Nim detection by the NFNCBs

To know the detection mechanism of NFNCBs to Nim, UV-vis and FL spectra before and after the addition of Nim were studied. The UV-vis of NFNCBs showed no any change in the presence of Nim compared to the pure NFNCBs solution (Fig. 6A, curve a, b), suggesting that Nim cannot influence the frame structure of the NFNCBs. Furthermore, the FL intensity at 327 nm of NFNCBs dramatically reduce in added the Nim (Fig. 6B, curve a, b), which indicate that the NFNCBs can act as effective nanoprobe and highly sensitive detection of Nim. Meanwhile, the above results confirm that the normally recognized Meisenheimer complex can not produce by the delocalization p-π/π-π conjugation between Nim and the NFNCBs [36], while the most probable reason for the quenching mechanism of NFNCBs in the presence of Nim, is based on the electron/energy transfer process [37]. That is, it is known that Nim structurally possesses a strong electron withdrawing group of nitro, which might accept electrons from containing -NH₂ and -OH groups of the excited state of NFNCBs in the appropriately spatial location, leading to a strong electron or energy transfer and the FL decreasing of NFNCBs. And it should be noted that the FL of
NFNCBs show no evident change in the presence of metal ions such as Ag\(^+\) and Hg\(^{2+}\) ions (Fig. 5), indicating that spatial arrangement of -NH\(_2\) and -OH groups in the surface of the NFNCBs is not suitable for binding these metal ions (Fig. 5). This is also one of the reasons for the high selectivity of NFNCBs to drug Nim. Therefore, the appropriately spatial location of -NH\(_2\) and -OH groups of NFNCBs plays important roles in the detection of Nim.

**Conclusions**

In short, we used a simple and economic route to prepare excitation-independent near-ultraviolet emission NFNCBs with narrowed peak widths. The results indicate that the type of precursor and solvent are generally considered to be very important for the anisotropy and shape of the NFNCBs. The prepared NFNCBs exhibits good specificity for Nim relative to other competitive biological small molecule and metal ions. Under the optimal conditions, the fluorimetric route shows a relatively low detection limit of 0.21 nM for Nim, which is much superior to lots of constructed platforms via fluorimetric method. Furthermore, the recoveries (96.3-106.2\%) of Nim in pharmaceutical tablets detection and standard deviations demonstrated the high specificity and usefulness of the method. Finally, we hope that our work could provide a possibility for design and establish a promising FL sensing platform in hard conditions.

**Conflicts of Interest**

The authors declare no conflict of interest.

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### Table 1 Analysis of Nim in tablets by the NFNCBs sensor.

| Sample | Standard value (µM)a | Founded (µM)a | Recovery (%) (n=5) | RSD (%) (n=5) |
|--------|-----------------------|---------------|------------------|--------------|
| Tablet | 0                     | 9.78          | 97.8             | 2.41         |
| 1#     | 10                    | 21.23         | 106.2            | 1.87         |
| 2#     | 25                    | 33.72         | 96.3             | 3.65         |
| 3#     | 40                    | 52.31         | 104.6            | 2.89         |

The real samples were prepared to the linear range of 2.0 nM - 100.0 µM before analysis.

aThe data were obtained from the average of five parallel determinations.
Figure Captions

Scheme 1 Schematic diagram of synthesis of NFNCBs and the mechanism of the detection of Nim by the NFNCBs.

Fig. 1 TEM images (A, B, C) at different magnification, and EDS (D) of the fluorescent NFNCBs.

Fig. 2 (A) XPS, (B) C1s, (C) O1s, and (D) N1s spectra of the NFNCBs.

Fig. 3 (A) UV-vis (curve a) and emission (curve b, λex=300 nm) spectra of the NFNCBs. (B) FL spectra of the NFNCBs at different excitation wavelengths from 260 to 310 nm; both the excitation and emission slit widths were 3 nm, respectively.

Fig. 4 (A) FL emission spectra of NFNCBs in the presence of different concentrations of Nim (0 to 500.0 μM, top to bottom, excitation at 300 nm). (B) Plot of the increased FL signals [(FL0-FL)/FL0] versus Nim concentration. Both the excitation and emission slit widths were 3 nm, respectively.

Fig. 5 Selectivity of the NFNCBs-based detection system. The concentration of Nim was 100 μM, and those of the other disturbing substances was 100 μM, respectively.

Fig. 6 UV-vis (A) and FL (B, λex=300 nm) spectra of free NFNCBs (curve a), and NFNCBs in the presence of Nim (curve b), respectively. The final concentration of Nim was 100 μM.
Scheme 1

[Diagram showing chemical reactions and structures, labeled with conditions: 180 °C, 16 h, λex=300 nm, λem=327 nm, and resulting structures labeled as NFNCBs and NFNCBs@Nim]
Fig. 1
Fig. 2

A

B

C

D

Intensity/a.u.

Binding Energy/eV

Intensity/a.u.

Binding Energy/eV

Intensity/a.u.

Binding Energy/eV

Intensity/a.u.

Binding Energy/eV

C 72.88 at%
N 8.340 at%
O 18.78 at%

C-C/C=C
C-N
C-O
C=O

pyridinic/pyrrolic
-like N

-C=O
-C-OH
Ols

-NH2

-NH2
Fig. 3
Fig. 4
Fig. 5

The graph shows the ratio of (FL - FL₀)/FL₀ for various substances. The substances are labeled on the x-axis, and the y-axis represents the ratio. The bars indicate the change in fluorescence intensity for each substance.
Fig. 6

(A) Absorbance spectra (Abs) at different wavelengths (nm) for samples a and b.

(B) Fluorescence intensity (FL Intensity/a.u.) spectra at different wavelengths (nm) for samples a and b.