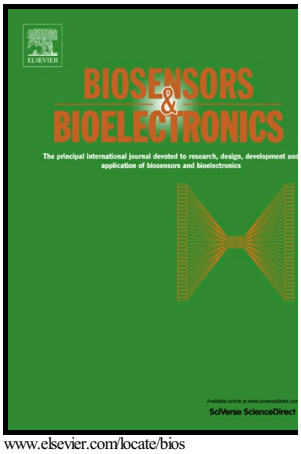

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Stimulus-response mesoporous silica nanoparticle-based chemiluminescence biosensor for cocaine determination

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Abstract

Mesoporous silica nanoparticles (MSN) based controlled release system had been coupled with diverse detection technologies to establish biosensors for different targets. Chemiluminescence (CL) system of luminol/H_2O_2 owns the characters of simplicity, low cost and high sensitivity, but the targets of which are mostly focused on some oxidants or which can participate in a chemical reaction that yields a product with a role in the CL reaction. In this study, chemiluminescent detection technique had been coupled with mesoporous silica-based controlled released system for the first time to develop a sensitive biosensor for the target which does not cause effect to the CL system itself. Cocaine had been chosen a model target, the MSN support was firstly loaded with glucose, then the positively charged MSN interacted with negatively charged oligonucleotides (the aptamer cocaine) to close the mesopores of

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MSN. At the present of target, cocaine binds with its aptamer with high affinity; the flexible linear aptamer structured will become stems structured through currently well-defined non-Waston-Crick interactions and causes the releasing of entrapped glucose into the solution. With the assistant of glucose oxidase (GOx), the released glucose can react with the dissolved oxgen to produce gluconic acid and H_2O_2, the latter can enhance the CL of luminol in the NaOH solution. The enhanced CL intensity has a relationship with the cocaine concentration in the range of 5.0-60 μM with the detection limit of 1.43 μM. The proposed method had been successfully applied to detect cocaine in serum samples with high selectivity. The same strategy can be applied to develop biosensors for different targets.

Key words: mesoporous silica nanoparticles; controlled release system; chemiluminescence; cocaine; luminol.

1. Introduction

Nanoparticles (NPs) provide versatile platforms for therapeutic applications based on their physical properties (Zhu et al. 2011). For example, NP size range is commensurate with biomolecular and cellular systems, which provides additional interactions to small molecule antibiotics. The high surface to volume ratio of NPs allows the incorporation of abundant functional ligands, enabling multivalency on NP surface to enhance the interactions to targets. Specially, mesoporous silica nanoparticle (MSN) has been used as a promising carrier system for drug delivery. Recent reports about the design of capped and gated MSN derivatives have shown

promise applications of MSNs in the generation of controlled-release systems. The systems can be trigger by different stimulus, such as temperature, pH, magnetic field, and so on. Recently, the MSN controlled release systems had been coupled with different detection technologies to develop diverse biosensors. Aptamers can recognize a wide range of targets, including proteins, small molecules, peptides, and even cells with high affinity and specificity, which has been applied to cap the channel of the MSN frequently. For examples, Zhu et al. employed aptamer-modified Au nanoparticle to close the pores of MSN, which can be opened in the presence of adenosine triphosphate (ATP) through the competitive binding. This study demonstrated that the aptamer-target interaction could be used as a stimuli-responsive mechanism in controlled-release systems (Zhu et al. 2011). He et al. also developed an ATP biosensor through the combination of the fluorescence detection method with the MSN controlled release system, ssDNA had been grafted on the pore outlets of the MSN, then the ATP aptamer had been hybridized with the ssDNA to form a sandwich-type DNA structure and block the nanochannels of MSN, the addition of ATP results in the release of $Ru(bpy)_3^{2+}$ (which had been entrapped in the channels of the MSN) from the channel and the fluorescence of the system increased (He et al. 2012). Zhang et al. developed a fluorescence biosensor for rapid, sensitive and selective detection of Hg^{2+} in aqueous solution by using of DNA-functionalized silica nanoparticles (Zhang et al. 2012). Wang et al. reported a sensing protocol for quantitative monitoring of telomerase activity based on target-responsive releasing of cargo from wrapping DNA-capped MSN by coupling a portable personal glucose

meter (PGM) with MSN (Wang et al. 2014). The target responsive cargo release from polystyrene microsphere-gated MSN had been coupled with electrochemical detection technique to develop a sensitive carcino-embryonic antigen (CEA) biosensor also (Yang et al. 2010). These studies show that the MSN controlled release system not only can be applied in the drug release systems but also can be coupled with diversify detection technologies to develop sensitive biosensors.

Chemiluminescence (CL) is the emission of light (luminescence) based on chemical reaction. CL assay owns some extremely useful analytic properties, such as simplicity and low cost of equipment, little sample needed, high sensitivity and the results are unaltered by the side reactions (Niu et al. 2012; Zhang et al. 2005). The most classical CL reaction is the oxidation of luminol with an oxidation (typically H_2O_2) in alkaline medium. The targets of this CL assay system were some oxidants or which can participate in a chemical reaction that yields a product with a role in a CL reaction. For example, ethanol-alcohol oxidase reaction produces H_2O_2 and it can be coupled to the luminol/H_2O_2 CL reaction to analyze ethanol (Danet et al. 1997). CL technique had been coupled with different techniques, such as flow-injection manifold system (Zeng et al. 2011; Lu et al. 2012), high-performance liquid chromatography (HPLC) system (Wu et al. 2012; Kodamatani et al. 2013), capillary electrophoresis system (Jiang et al. 2013; Xu et al. 2012), and so on for diverse applications. But the compounds which cannot cause effect to the CL are difficult to be detected by these strategies. So it is necessary to find some way to expand the application of CL assay.

To the best of our knowledge, no literature which combines the merits of CL and

controlled release system has been reported yet. In this study, the frequently used aptamer based MSN controlled release system has been coupled with the luminol/H_2O_2 CL assay system for the first time to develop a sensitive biosensor for the targets other than oxidants or which can participate in a chemical reaction that yields oxidants. Owing to the instantaneous and overwhelming effects on the central nervous system and potential illegal use of cocaine, simple and sensitive detection of cocaine is very important to fight against the illegal usage of this compound (Isner et al. 1986); cocaine has been chosen as an example target in this study. The aptamer of cocaine has been used to cap the glucose in the pore of MSN, at present of the target (cocaine), the cap can be opened and the entrapped glucose can diffuses into the solution, which reacts with the dissolved oxygen in the present of glucose oxidase to produce H_2O_2 and cause the enhancing of the CL intensity of the luminol. Through cocaine itself can not affect the CL of luminol/H_2O_2 system, a sensitive CL assay method can be developed for cocaine determination.

2. Experimental Section

2.1 Chemicals and reagents

A 10 mM stock solution of luminol (3-aminophthalhydrazide) was prepared by dissolving luminol (Aladdin) in 0.1 M sodium hydroxide solution without purification. Working solutions of luminol were prepared by appropriate dilution from the stock solution. Glucose oxidase (GOx) was purchased from Sigma-aldrich (USA). Sodium hydroxide solution (NaOH), D-Glucose, 3-aminopropyltriethoxysilane (APTES),

cetyltrimethyl ammonium bromide (CTAB), tetraethyloxysilane (TEOS) and ethanol were purchased from Shanghai aladdin Biochemical Technology Co., Ltd.. disodiumsaltdihydrate (EDTA), Agarose M, 6×sucrose DNA loading buffer II, 5×TBE buffer, ethidium bromide (EB), and ssDNA (5′-GGGAGACAAGGATAAATCCTTCAATGAAGTGGGTCTCCC-3′) were obtained from Shanghai Sangon Biotech Co. Ltd. The synthetic cocaine sample solution was obtained by dissolving cocaine into distilled water. All other chemicals were at least analytical grade and used directly without further purification. Aqueous solutions were prepared with Milli-Q water (18.25 MΩ•cm^{-1}). Unless otherwise pointed out, all experiments were carried out at room temperature.

2.2 Instruments

The surface area, pore size and pore volume were collected by Micromeritics ASAP 2020 at 77.156 K. The transmission electron microscopy (TEM) images were obtained with Tecnai G2 F20 S-TWIN TEM (FEI, USA). Fourier transform infrared (FT-IR) spectra were recorded on a Nicolet 6700 (Thermo Fisher Scientific, USA) spectrometer in transmission mode. The zeta potential was recorded on Zeta PLUS (BIC, USA) zeta potential Analyzer. UV-Vis absorption spectra were measured by a Lambda 750 UV-Vis spectrophotometer (Perkin-Elmer, USA). All nanoparticles were centrifuged on a TG16-W centrifuge (Hunan, China). The CL signal was obtained using the BPCL Ultra-Weak Luminescence Analyzer (Institute of biophysics, Chinese academy of sciences).The electrophoresis was carried out on a PowerPac basic (bio-rad, USA) system and the bands were visualized by an UV trans-illuminator.

2.3 Preparation of aminated modified mesoporous silica nanoparticle ($MSN\text{-}NH_2$)

Before modification with the APTMS, MSN was synthesized according to the literature (Lai et al. 2003). Briefly, 0.5 g of CTAB was initially dissolved in 240 mL distilled water, and then 1.75 mL sodium hydroxide (2.0 M) was slowly added into the CTAB solution with vigorous stirring for 30 min at 333 K to get a clear and transparent solution. Afterwards, 2.5 mL TEOS had been dropped into the above prepared solution slowly and followed with vigorously stirring for 2 h until white precipitates obtained. The product was filtered, washed with distilled water and methanol, and then dried in air. Then 500 mg of MSN was homogeneously dispersed in 50 mL of ethanol by ultrasonication. And then, 1.5 mL of APTMS was added to the suspension and the suspension was slowly stirred for 24 h at room temperature. The mixture was collected by filtration and extensively washed with ethanol to remove the residual APTMS, and the obtained white particles were dried under vacuum at 333 K for 10 h. Finally, the aminated modified nanoparticles ($MSN\text{-}NH_2$) were centrifuged and washed with ethanol and deionized water for three times.

To remove the excess CTAB, $MSN\text{-}NH_2$ was refluxed for 10 h in the solution contains HCl (37% 1.5 mL) and methanol (75 mL), and then washed with distilled water and methanol. The resulting MSN was dried for 12 h at 333 K in vacuum to remove the remaining solvent from the pores.

2.4 Amino group analysis

15 mg of $MSN\text{-}NH_2$ was completely dissolved in 30 mL of 0.02 M NaOH. 500 μL

of this solution was mixed with 2 mL of phosphate buffer (0.2 M, pH 8.0)； After the addition of 500 μL of fluorescamine solution (1 mM in acetone), the fluorescence spectrum was measured by excitation at 366 nm. The emission intensity at 485 nm was taken as the data point. A calibration line was prepared by using 100 μL differently concentrated solutions of APTMS in 30 mL of 0.02 M aq NaOH (containing 15 mg of the respective dissolved MSN). Repeated analysis of the same sample gave an average relative error of 2.7% (for amino contents in the range of 0.09-2.4 mmol/g) (Lai et al. 2014).

2.5 Preparation of glucose-loading MSN-NH_2 capped with cocaine aptamer

The loading of glucose into the pores of MSN-NH_2 was prepared according to the literature (Wang et al. 2014). Briefly, 5 mg of the MSN-NH_2 was initially dispersed into 500 μL phosphate-buffered saline (PBS, pH 8.0) containing 2.0 M glucose, and the resulting mixture was then gently shaken on the thermomixer for 16 h at room temperature. During this process, glucose can diffused into the pores of the MSN-NH_2. Following that, 200 μL of cocaine aptamer (100 μM) had been added into the suspension. The mixture was gently stirred for 4 h at 277 K. Owing to the interaction between positively charged MSN and negatively charged DNA, the cocaine aptamer had been attached onto the surface of the MSN-NH_2 and gated the glucose inside. Then the DNA wrapped MSN was centrifuged and washed with distilled water to remove the excess DNA strands and glucose. Finally, the DNA capped MSN loaded with glucose (designated as DNA-glu-MSN) was redispersed into PBS buffer (pH=8.0) ($C_{[MSN]} \approx 50$ μg•μL^{-1}) for further using. To evaluate the glucose-loading

efficiency, the supernatant and washed solutions were collected and the residual glucose content was measured by a personal glucose meter (PGM).

2.6 Gel electrophoresis

Firstly MSN-NH_2 nanoparticles were suspended in ultrapure water with a concentration of 50 μg•μL^{-1}. Subsequently, 10 μL of the as-prepared MSN-NH_2 suspension dispersed in 20 μL of a solution containing the cocaine aptamer in an increasing amount, the mixtures were shaken at room temperature for 2 h respectively. Finally, 10 μL MSN-NH_2/ssDNA complexes with 6/1(V/V) loading buffer were loaded on a 2.5 % agarose gel. The electrophoresis was carried out at 80 V for 30 min in 0.5×TBE buffer and the bands were visualized on a UV tran-illuminator (Radu et al. 2004).

2.7 Measurement of cocaine

5 μL cocaine aptamer capped MSN-NH_2 loaded with glucose (DNA-glu-MSN) and 5 μL different concentration of cocaine were added into 90 μL PBS buffer, then the solution was gently shaken on the thermomixer for 40 min, following that 5 μL 5 mg •mL^{-1} GOx had been added into the mixtures with an additional 30 min oscillation; Finally the 100 μL solution was taken out and mixed with 100 μL 20 mM luminol and 800 μL 0.75 mol • L^{-1} NaOH solution, and the CL signals were monitored by a PMT placed under the cell and the output signals were obtained by a computer automatically. The value of $\Delta I = I - I_0$ shown the effect of target on the CL intensity of luminol/H_2O_2 system, where I_0 stands for the signal in the absence of target and I stands for the signal in the presence of target, which was used for quantitative analysis

of target compounds.

3. Results and Discussion

3.1 **The strategy of stimulus-response MSN-based chemiluminescence biosensor**

Scheme 1 shows the principle of chemiluminescence biosensor for cocaine based on MSN based controlled release system. Firstly, the MSN-NH_2 has been mixed with glucose in the solution. The strong preferential interaction between the glucose molecules and the silica walls results in the significant concentration gradients within the pore and a noticeable amount of glucose molecules can be loaded into the pores. Then the specifically designed wrapping DNA (aptamer of cocaine) has been added into the above mentioned solution, the pores of the MSN-NH_2 can be sealed by the aptamer based on the interaction of positively charged MSN with negatively charged DNA. At this station, the MSN surface is cross covered by the flexible linear structure cocaine aptamer. Upon the addition of the target (cocaine) into the system, flexible linear structure aptamer structured will become stems structured through currently well-defined non-Waston-Crick interactions (Stojanovic et al. 2001). So the pores of MSN-NH_2 will be opened and cause the releasing of glucose into the solution. The released glucose then react with the dissolved oxygen with the assistant of GOx to produce hydrogen peroxide, which cause the enhancing of the chemiluminescence signal of the luminol system (Li et al. 2014; Zhang et al. 2014). Since the enhanced CL signal has a direct relationship with the concentration of cocaine, this principle can be applied to develop a sensitive chemiluminescence biosensor for cocaine

detection.

The preferred position for Scheme 1

Simple experiments had been carried out to verify our presumption. As shown in Fig.1(A), the luminol in PBS solution which contain GOx gives off weak CL signal (red column). The addition of DNA capped MSN loaded with glucose only cause little CL signal enhancement, this means the pores were blocked by the aptamer and little leakage of glucose happen (green column). But a strong CL signal can be detected if cocaine had been added into the above mentioned system (blue column). If cocaine along had been added into the luminol solution, nearly no CL enhancement had been detected (black column), these results indicated that cocaine itself cannot cause the enhancement of CL intensity of the system, but it can react with the aptamer and cause the releasing of the glucose into the system. If MSN loaded with glucose and not been gated with the aptamer had been added into the solution contains luminol and GOx, a strong CL signal enhancement had been detected since the glucose can easily diffuse into the solution (light blue column). These phenomena demonstrated the correct of our presumption.

The binding of aptamer to MSN-NH_2 nanoparticles was confirmed by zeta potential measurements and UV-vis spectra. As shown in Fig.1(B), zeta potential decreased from 15.8 mV to -12.7 mV after the binding of ssDNA to MSN-NH_2 nanoparticles; on the other hand, Fig.1(C) shown the characteristic adsorption peak at 260 nm for ssDNA disappeared in the UV-vis spectrum of MSN-NH_2/ssDNA complexes also

confirmed the bonding of ssDNAs on MSN-NH_2 nanoparticles to form MSN-NH_2/ssDNA complexes.

The preferred position for Fig.1

3.2 Characterization of the synthesized MSN materials

Fig.2(A) shows a narrow size distribution of the pores with a BJH pore diameter of 2.2 nm. The MSN-NH_2 has a BET surface area of 956 $m^2 \cdot g^{-1}$ and a pore volume of 0.42 $cm^3 \cdot g^{-1}$. TEM image in Fig.2(B) shows a typical image of the prepared MSN-NH_2, the average size of the as-synthesized MSN was 150 nm. Meanwhile, large numbers of pores on the silica nanospheres were observed and the pore size was 3.5 nm in average. Fig.2(C) shows FTIR spectra for MSNs and MSN-NH_2 nanoparticles. After MSNs were modified with amino groups, vibration peaks can be observed at 1340 and 1410 cm^{-1}, which can be assigned to the stretching bands of C-N groups. At the same time, the Si-OH band at 960 cm^{-1} in the MSN spectrum became weaker after the modification with amino groups. These results also indicated the successfully modification of amino groups on MSNs. Fluorescamine is a great reagent for the fluorometric assay to detection of the amine groups. When the non-fluorescent of fluorescamine reacts directly with amine groups can bring a strong fluorescence emission (Ex: 390nm).This character has been applied to detect the surface-grafted amine groups. Fig.2 (D) showed the calibration between the fluorescence intensity and NH_2 concentration. The quantity of amine group on the MSN was determined to be 95.58 μmol • g-1. The loading efficiencies of glucose in MSN-NH_2 and

MSN-NH_2/Glu/DNA are measured to be as high as 184 μg glucose per milligram of MSNs by PGM. After the storing of the prepared materials in the solution for 1 weak, no obvious enhancement of glucose in the solution had been detected, this means the prepared materials owns the character of good stability.

The preferred position for Fig.2

3.3 Optimization of the CL assay conditions

The sensitivity of the described protocol depends on the ratio of aptamer loaded on the surface of MSN spheres, which is tunable during the competitive aldehyde–amino coupling reaction. Increasing the ratio of aptamer in the solution would results in the increasing of amount of glucose loaded in the pore of each particle, which would affect CL signal detected. But unfortunately, more cocaine is needed to open the gate, which results in the lower sensitivity of the system. Therefore, the amount of aptamer attached on the nanoparticles need to be balanced. A gel retardation assay about the complexes of MSN-NH_2 and varying amounts of cocaine aptamer DNA had been performed (Fig. 3(A)). As shown in lane 1, the free DNA (20μg) was completely moved out of the well (line 1).The same phenomena occurred in line 2, this indicates that pure MSN cannot hold DNA. If DNA had been mixed with MSN-NH_2 at different ratios, the results indicate that MSN-NH_2 can hold DNA with high efficiency. DNA/MSN-NH_2 at lower ratio were stable under given electric field intensity (line 8 to line 5), but higher ratio (line 3 and line 4) results in the tailing phenomena, these results indicate the DNA are much more for pore block (Kim et al. 2011). The reason

lies in that more and more ssDNA been added; the surface potential of MSN sphere would turn to negative as shown in the zeta potential measurement, which cannot capture the ssDNA. So 20μg /500μg of line 5 had been chosen as the optimized coating ratio for DNA/MSN-NH_2 (Torney et al. 2007).

The pH value affects the activity of the GOx greatly, which causes effect to the amount of H_2O_2 produced and CL intensity detected. So the pH of medium for the cocaine and glucose interaction solution had been optimized since the GOx had been mixed in this solution. As shown in Fig.3(B), ΔI increased with the increasing of pH value firstly, then nearly kept a constant in the range of 6.0–8.0 and the ΔI decreased greatly if the pH was higher than 9.0. The reason lies in that the at low pH value, the activity of the glucose oxidase are low, so little amount H_2O_2 has been produced and little CL enhancement has been detected; if the pH value is higher than 9.0, the GOx lost its activity and little amount of H_2O_2 has been produced also. Therefore, pH 8.0 PBS was used in subsequent experiments. The concentration of NaOH in the CL detection system affected the CL intensity detected also. As shown in Fig.3(C), the ΔI of the system increased with the enhancing of the NaOH concentration firstly and reached the highest value at 0.6 M, and then decreased. Higher NaOH concentration is favor for the CL of the luminol system, but the background CL increased also since the interaction of NaOH and luminol can also produce some CL signal, which will results in the decreasing of ΔI. Furthermore, H_2O_2 will decompose at high NaOH concentration, which also causes negative effect to the CL intensity of the system. So a solution with 0.6 M NaOH was therefore considered to be optimal and chosen for

further work.

The preferred position for Fig.3

3.4 Calibration curve for cocaine detection

Different mount of cocaine had been added into the test solution to examine the CL response. Fig.4(A) shown that the dynamic enhanced CL curves increased with the increasing of cocaine concentration. In addition, Fig.4(B) shown a linear correlation (the linear equation is ΔI=2207+9859*log*C*cocaine, *C* is the cocaine concentration, *R*=0.990) existed between the enhanced CL intensity and logarithm of the cocaine concentration in the range of 5-60 μM under the optimized conditions the detection limit was calculated to be 1.43 μM (S/N=3). Seven parallel repeated experiments had been performed when the concentration of cocaine settled as 20μM. And the relative standard deviation (RSD) is calculated to be 4.7%. This result indicates that the proposed method has good reproducibility.

The preferred position for Fig.4

The analytical performance of the developed cocaine assay system has been compared with early reported methods. The detection limits of the proposed method is comparable with the early reported methods, such as aptamer-based CE (5 μM) (Deng et al. 2012), aptamer functionalized micro-cantilever sensor (5 μM) (Kang et al. 2011), fluorescence (2.1μM (Ge et al. 2012), 10 μM (Stojanovic et al. 2001)) and colorimetric methods (2 μM (Zhang et al. 2008), 50μM (Liu et al. 2006)).

3.5 Interference study and sample determination

Urate, ATP, morphine and caffeine had been chosen as the representative interferents to investigate the selectivity of the proposed biosensor. The concentration of interferents was settled as 500 μM and the target concentration was 10μM. As shown in Fig.4(C), in the of interferents cause little effect to the CL intensity of the system, but large CL enhancement had been detected in the present of relative lower concentration of target. The reason lies in that these interferents unable to combine with the aptamer, consequently cannot destroy the complexion between MSN and aptamer, so no glucose diffused into the solution and no CL enhancement had been detected. These results indicated that the proposed method owns the character of high selectivity.

Having demonstrated the ability of this method for qualitative and quantitative detection of cocaine in buffer, next we wanted to extend its application in serum which contains a variety of proteins and other interference. The recovery of cocaine by the standard addition has been tested also to evaluate the veracity of the proposed method; the recoveries are between 94.1% and 101% with the relative standard deviation of 7.3% and 5.6%, respectively (shown in Table 1). Thus, the successful detection of cocaine in biological samples as demonstrated here.

The preferred position for Table 1

4. Conclusion

In summary, chemiluminescent detection technique had been coupled with the

MSN based controlled release system successfully to detect a target which cannot cause effect on the CL of luminol itself. The system had high loading efficiency and good releasing behavior using glucose as a model guest molecule. The proposed sensor combines the advantage of CL of luminol/H_2O_2 detection system and MNS based controlled release system. Many different targets can be detected by the same strategy.

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Figures and Captions

Scheme. 1 Schematic illustration of the MSN based controlled release system coupled with luminol/H_2O_2 CL system for cocaine determination.

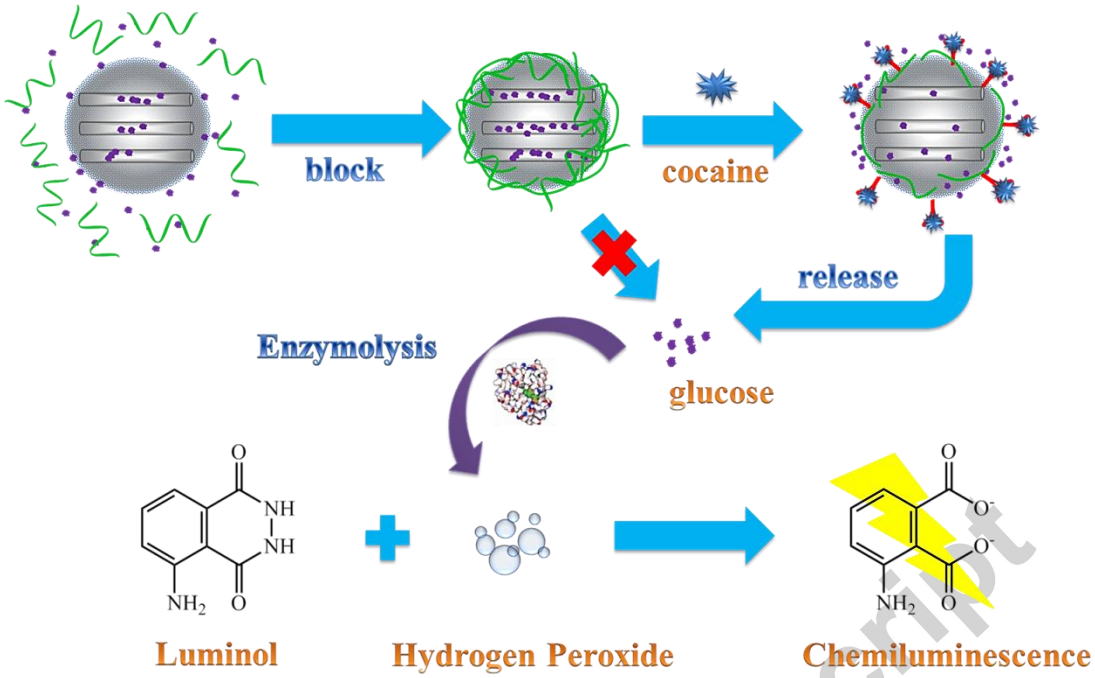
Fig. 1 (A) CL intensity of MSN-NH_2/dsDNA system before and after treatment with cocaine (50μM). Column control is MSN-NH_2 loaded glucose without DNA block. **(B)** Zeta potential of MSN, MSN-NH_2 and MSN-NH_2/ssDNA (2 mg powder dispersed in about 1 mL distilled water). **(C)** UV-vis spectrum of pure ssDNA, MSN/ssDNA and MSN-NH_2/ssDNA complexes.

Fig. 2 (A) Nitrogen sorption isotherms of the as-prepared amino-MSN measured at 77.156 K. and the BJH pore distribution curve based on the adsorption isotherm. **(B)** TEM images of MSN-NH_2. **(C)** FTIR spectra of MSN with surfactant, MSN and NH_2-MSN (from top to bottom). **(D)** The calibration curve between the fluorescence intensity and the NH_2 concentration.

Fig. 3(A) Gel retardation assay of the MSN with different amount of DNA (aptamer). **(B)** The effect of pH of medium for the cocaine and glucose interaction solution on the enhanced CL intensity of the system. (C) The effect of the concentration of NaOH on the enhanced CL intensity of the system.

Fig. 4 (A) The CL dynamic curves for the system contains different cocaine concentration. **(B)** The relationship between ΔI and logarithm of cocaine concentration. **(C)** Selectivity of the proposed aptamer-based sensor method for cocaine detection (the concentrations of analytes were 10μM and others are 500μM).

Scheme 1



The pore size is not related to the real scale.

Figure 1

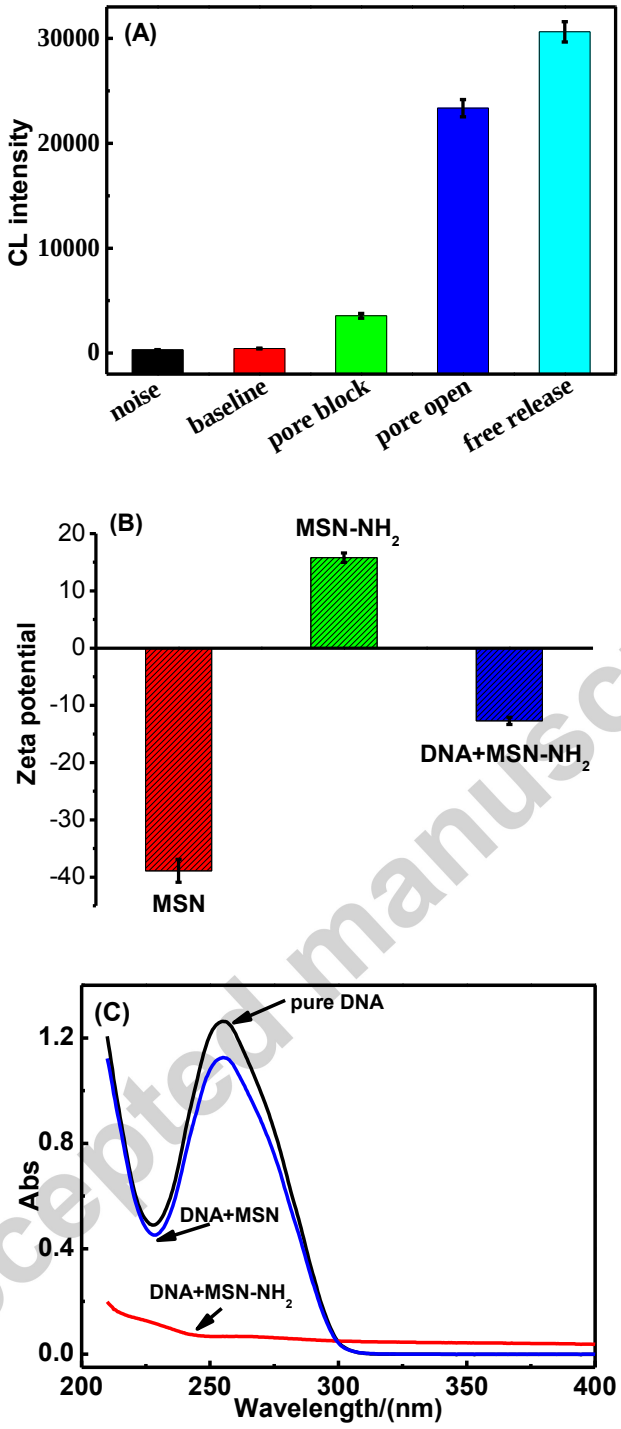


Figure 2

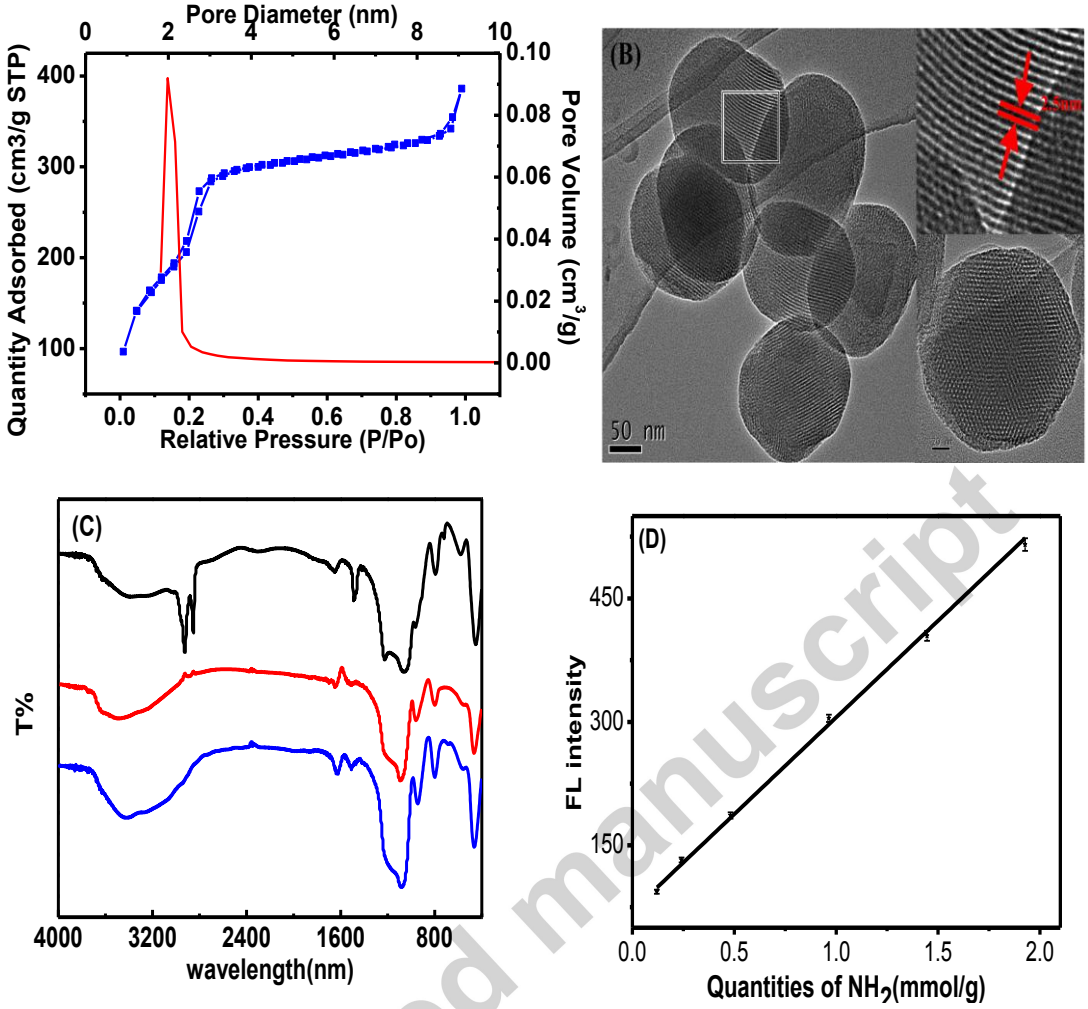


Figure 3

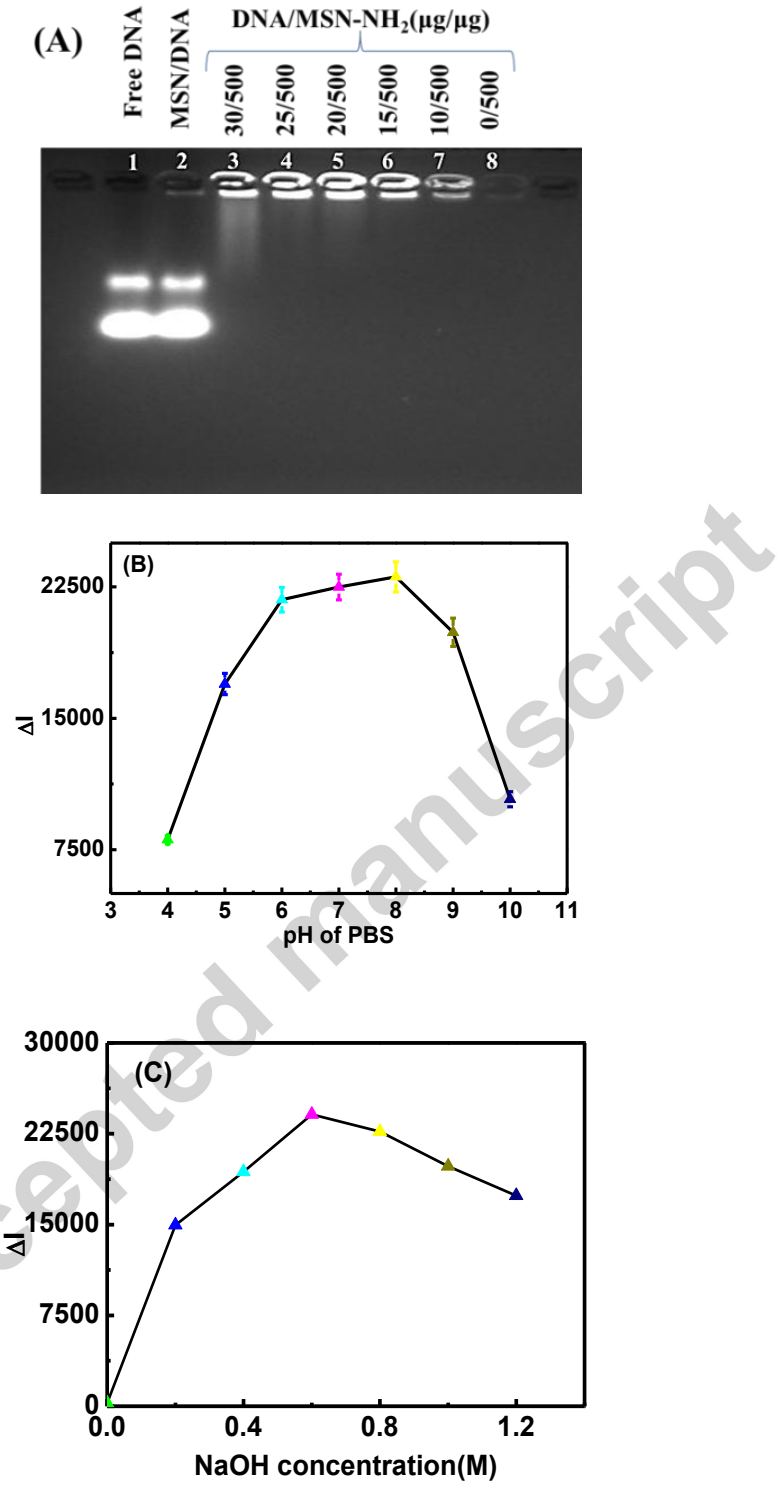
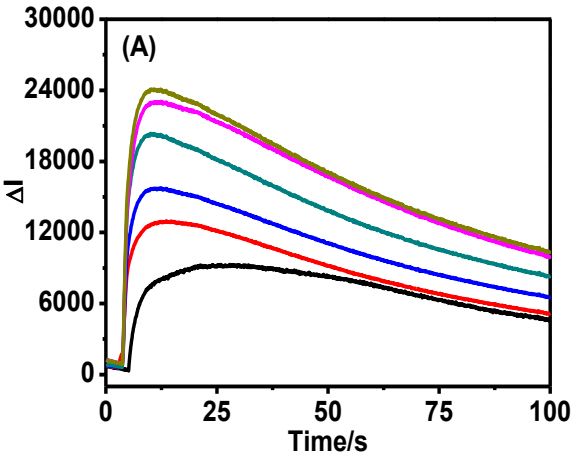
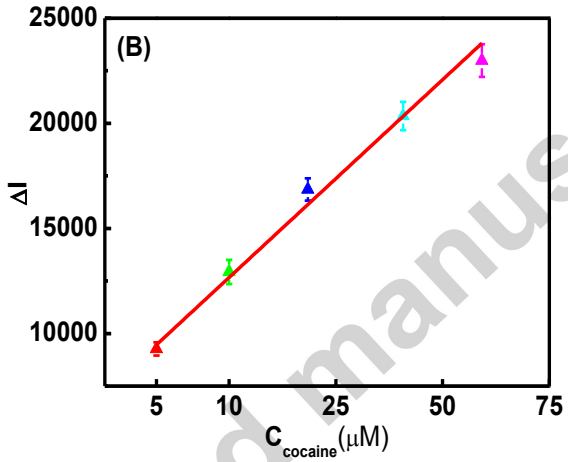


Figure 4





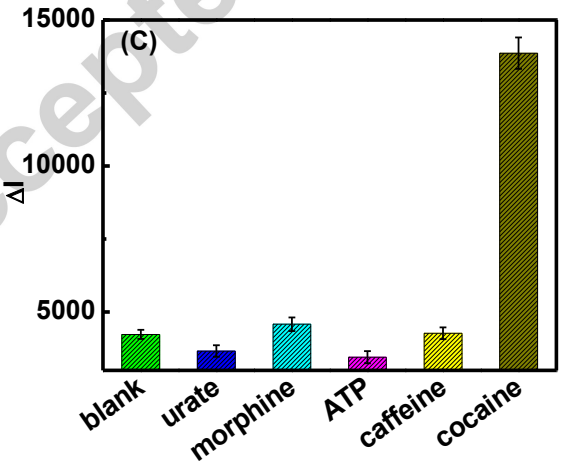


Table 1 Detection results of cocaine in 20% human serum samples using the proposed sensor(n =7).

Sample number	Found in sample (μM)	Added (μM)	Total found (μM)	Recoveries (%)	RSD (%)
1	0	20.0	20.2	101	5.6
2	0	16.0	15.3	95.6	6.1
3	0	32.0	30.1	94.1	7.3

Highlights

- Chemiluminescent detection technique had been coupled with mesoporous silica-based controlled released system for the first time.
- The sensor had been used to detect target which does not cause effect to the chemiluminescence system itself.
- The detection limits for cocaine is 1.43 μM and the linear range is 5.0-60 μM.
- The sensor has been applied to detect cocaine in serum samples.