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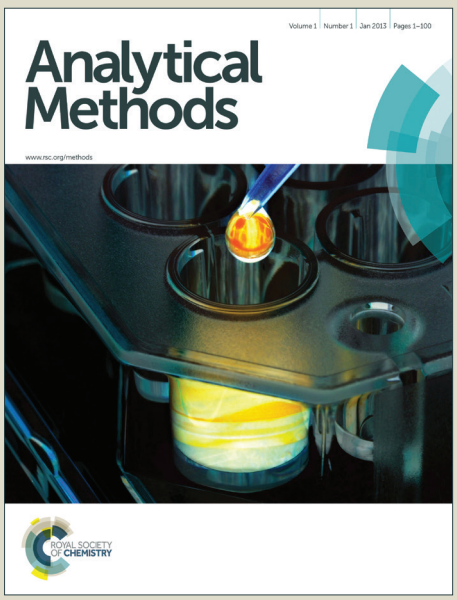

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ARTICLE

Simple and fast determination of catecholamines in pharmaceutical samples using Ag^{+}-3,3′,5,5′-tetramethylbenzidine as a colorimetric probe

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Catecholamines, generally including dopamine (DA), epinephrine (EP), and norepinephrine (NE), are important neurotransmitters and served many central nervous system functions. In this work, a simple colorimetric method for determination of the three catecholmanines is developed. The proposed method is based on the fact that Ag^{+} could oxidize 3,3′,5,5′-tetramethylbenzidine (TMB) to the oxidized TMB (oxTMB) and induce a blue color solution corresponding to an absorption peak centered at 652 nm. However, the introduction of catecholamines could cause the reduction of oxTMB which results in the fading of blue color quickly and a decrease of the absorbance at 652 nm. Based on this finding, we propose a method to quantitatively detect catecholamines with the help of UV-vis spectroscopy. The detection limit (S/N=3) for DA, EP, and NE is 50 nM, 100 nM, and 150 nM, respectively. More importantly, this method is simple, fast and without the use of complicated nanomaterials. The method has been successfully applied to the detection of catecholamines in pharmaceutical samples.

Introduction

Catecholamines, generally including dopamine (DA), epinephrine (EP), and norepinephrine (NE), are important neurotransmitters because of their involvement in various physical activities of the cardiovascular, nervous, and endocrine systems.[1] They affect the body's metabolism and their change of concentration level in biological fluid may induce many diseases, such as Parkinson's disease, schizophrenia, HIV infection, and even tumors including paraganglioma and pheochromocytoma.[2-5] Moreover, catecholamine drugs are common emergency healthcare medicine and usually used to treat anaphylactic shock, bronchial asthma, and organic heart disease.[6] Therefore, it is of great importance to develop a simple and fast method for the determination of catecholamines in pharmaceutical formulations.

To date, various analytical techniques have been developed for the quantitative determination of catecholamines, including electrochemistry,[7,8] chemiluminescence,[9,10] high-performance liquid chromatography,[11,12] capillary electrophoresis[13] and so on. Although most of these methods have high sensitivity, they suffer from the disadvantages of high cost, time-consuming sample pretreatment, and sophisticated instrument manipulation. Therefore, it is still urgent to develop a simple, fast, low-cost, and novel method for the determination of trace catecholamines.

More recently, optical sensing approaches have aroused great interest due to their intrinsic simplicity and high sensitivity among the various detection techniques.[14] Various fluorescence probes including phosphate-modified TiO_2 nanoparticles,[15] terbium ion,[16] and CdSe nanocrystals[17] have been used for the detection of catecholamine. Other luminescent nanoparticles including DNA-templated silver nanoparticles,[18] carbon nanodots,[19] quantum dots,[20] and BSA-Au nanoclusters[21] have been developed as an effective fluorescent sensing platform for the detection of DA. At the same time, colorimetric detection methods have attracted much attention due to their simplicity and low cost. Gold nanopartilces (AuNPs) are proven to be a promising colorimetric probe since they can directly detect analytes by monitoring the color change using UV-vis spectroscopy or even with naked eyes. Therefore, AuNP-based colorimetric assay for the detection of catecholamine have been extensively studied.[22-25] These colorimetric assays are based on the color change of AuNPs associated with the turnover process from dispersion to aggregation state, which can be induced by specific interactions between surface modifiers attached onto AuNPs and catecholamine. Although these AuNP-based probes displayed good selectivity and sensitivity, they are complicated due to the modification of AuNPs. Therefore, it is necessary to

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develop new methods for the determination of catecholamine without preparation of any nanomaterials.

Previous reports have shown that Ag^+ could oxidize TMB to induce blue oxidized TMB (oxTMB), featuring an absorption peak centered at 652 nm.[26,27] Catecholamines are well-known reducing agents due to their phenol hydroxyl groups[28] which can reduce oxTMB and result in the fading of blue color and a decrease of the absorbance at 652 nm. Based on these facts, we propose a simple colorimetric method for detection of catecholamines. The proposed method is simple and fast for catecholamine detection without preparation of nanomaterials and the use of expensive instruments. Finally, the proposed method was successfully examined for the detection of catecholamines in practical pharmaceutical injection samples.

Experimental

Materials and chemicals

$AgNO_3$, TMB, acetic acid (HAc), citric acid, starch, edetic acid, and metal salts were obtained from Aladdin Reagent Company (Shanghai, China). Dopamine (DA), epinephrine (EP), norepinephrine (NE), tryptophan (Trp), tyrosine (Tyr), phenylalanine (Phe), cysteine (Cys), lactose, glucose, were purchased from Sigma-Aldrich. All of these reagents were of analytical grade and used as received. Dopamine hydrochloride injection (2mL:20mg), epinephrine hydrochloride injection (1mL:1mg), and norepinephrine bitartrate injection (1mL:2mg) were produced by Grand Pharma Co. LTD. (China). Ultrapure water produced by a Milli-Q system was used throughout this work.

Detection of catecholamine

For the detection of catecholamine, 100 μL of 1 mM TMB solution, 50 μL of 1.5 mM $AgNO_3$ solution, 340 μL of 0.2 M NaAc buffer solution (pH 5.0), and 10 μL of catecholamine solution with different concentrations were added in sequence. Subsequently, the mixture was incubated for 5 min at room temperature and then transferred for UV-vis measurements at room temperature.

To evaluate the selectivity of the proposed method, 100 μL of 1 mM TMB solution, 50 μL of 1.5 mM $AgNO_3$ solution, 340 μL of 0.2 M NaAc buffer solution (pH 5.0), and 10 μL 1.5 mM of Fe^{3+}, Cu^{2+}, Ca^{2+}, Ni^{2+}, Zn^{2+}, K^+, Na^+, lactose, glucose, citric acid, starch, edetic acid, Trp, Phe, Tyr, and Cys were added sequentially. After that, the mixture was incubated for 5 min at room temperature and then transferred for UV-vis measurements at room temperature.

UV-vis detection

UV-vis spectra were recorded using a Varian cary-300 UV-vis spectrophotometer. Absorbance at 652 nm was used for quantitative analysis.

Results and discussion

The mechanism of the sensing system

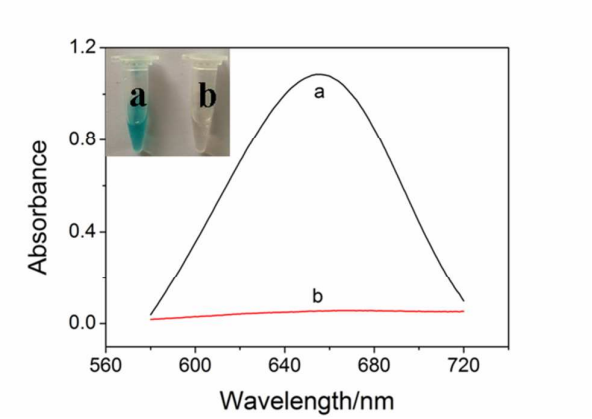
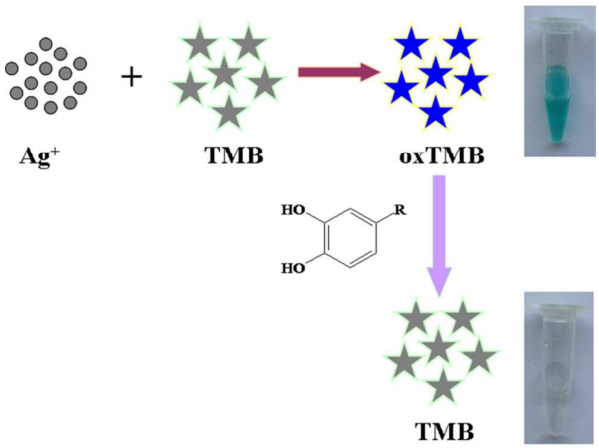


Fig. 1 Typical UV-vis absorption spectra of Ag^+-TMB solution in the absence (a) and the presence of 50 μM DA (b). Inset shows the corresponding digital images.



Scheme 1 Illustration of the mechanism of the Ag^+-TMB system for sensing catecholamines.

It has been reported that Ag^+ could oxidize colorless TMB to blue oxTMB (a, inset of Fig. 1) which has a strong absorption centered at 652 nm (curve a, Fig. 1). The introduction of DA to the Ag^+-TMB system resulted in the blue color fading (b, inset of Fig. 1) and a decrease of the absorbance (curve b, Fig. 1). Similar results were obtained for both EP (Fig. S1) and NE (Fig. S2). This may be attributed to the fact that the three catecholamines have certain reducibility due to the presence of the two adjacent phenolic hydroxyl groups[25] and can reduce the blue oxTMB to colorless TMB (Scheme 1). Therefore, we provide a simple approach for the highly sensitive catecholamine detection.

Optimization of detection conditions

Herein, we investigated the effects of the experimental conditions on catecholamine detection by taking DA as an example.

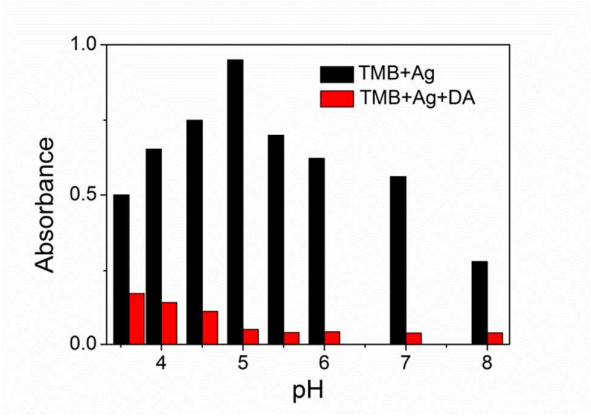


Fig. 2 Effect of pH on the absorbance of Ag^+-TMB solution in the absence (black) and the presence of 50 μM DA (red) at room temperature. [TMB]=0.2 mM; [$AgNO_3$]=0.15 mM; incubation time: 5 min.

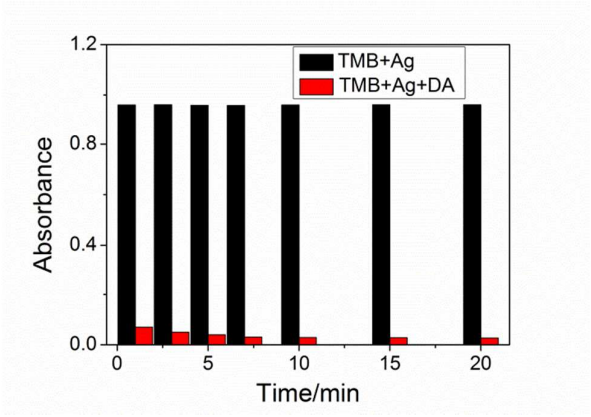


Fig. 3 Effect of reaction time on the absorbance of Ag^+-TMB solution in the absence (black) and the presence of 50 μM DA (red) at room temperature. [TMB]=0.2 mM; [$AgNO_3$]=0.15 mM; pH=5.0.

Effect of pH

The effect of pH value on the detection of DA was investigated in the range of 3.5-8.0. As shown in Fig. 2, in the absence of DA, $AgNO_3$ exhibited the best oxidase-like activity in catalyzing TMB at pH 5.0. After the addition of DA to the Ag^+-TMB solution, the blue color faded quickly and the absorbance at 652 nm decreased. At pH 5.0, the ΔA (ΔA=A_0-A, where A and A_0 are the absorbance at 652 nm in the presence and absence of DA, respectively) was the maximum. Moreover, the pH being neither too high nor too low was fit for this enzyme mimetic reaction. Consequently, pH 5.0 was adopted in the following experiments.

Effect of incubation time

A previous report showed that an increase of reaction time led to an increase of the absorbance in the Ag^+-TMB system.[28] And a longer reaction time of 30 min was needed at room temperature. Therefore, different incubation times ranging from 1 min to 20 min were investigated to study its effect on the detection of DA (Fig. 3). Herein, TMB and $AgNO_3$ were mixed firstly, and then 0.2 M acetate buffer solution of pH 5.0 was added in our experiments. We found that the reaction of Ag^+ and TMB was fast. Within the first 1 min, the reaction was almost completed. With the increase of reaction time, the absorbance almost kept the same (black, Fig. 3). After the addition of DA to the Ag^+-TMB system, the absorbance decreased quickly in the first 1 min and then changed slightly with the increase of time. In view of the completed reaction, the incubation time was selected at 5 min in the following experiments.

Effect of TMB concentration and $AgNO_3$ concentration

The effects of the concentration of TMB on the detection of DA were displayed in Fig. 4. It can be seen that the absorbance of Ag^+-TMB system increased firstly and then decreased with the increase of the TMB concentration. However, after the addition of DA to the above Ag^+-TMB system, the absorbance increased gradually with the increase of TMB concentration. The effects of the concentration of $AgNO_3$ on the detection of

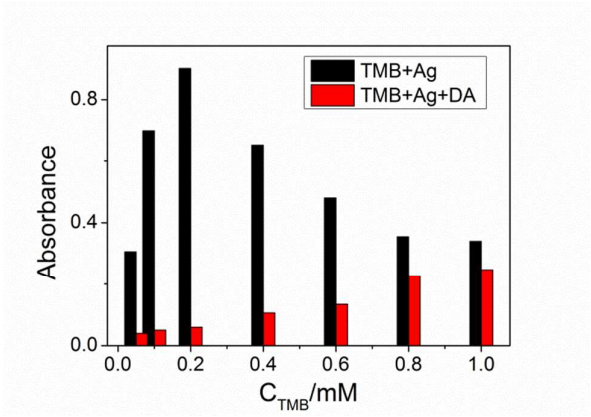


Fig. 4 Effect of concentration of TMB on the absorbance of Ag^+-TMB solution in the absence (black) and the presence of 50 μM DA (red) at room temperature. [$AgNO_3$]=0.15 mM; pH=5.0; incubation time: 5 min.

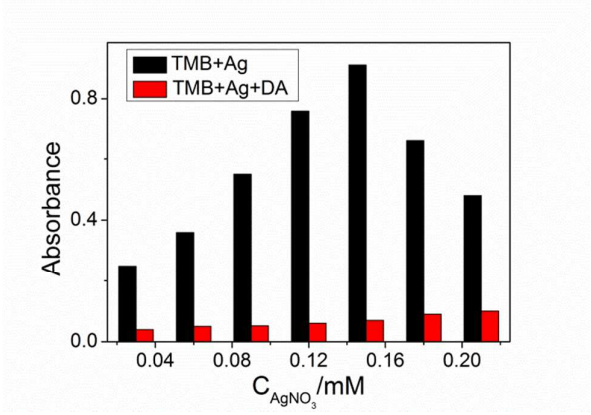


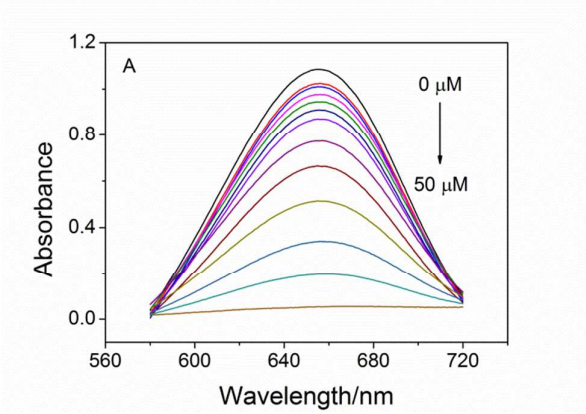
Fig. 5 Effect of concentration of $AgNO_3$ on the absorbance of Ag^+-TMB solution in the absence (black) and the presence of 50 μM DA (red) at room temperature. [TMB]=0.2 mM; pH=5.0; incubation time: 5 min.

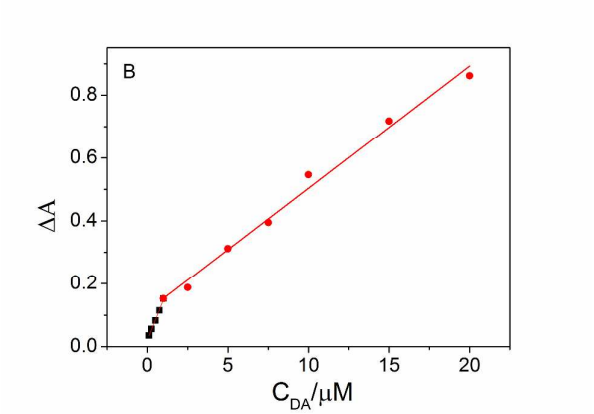
DA were also investigated (Fig. 5). Similar trends were obtained. If the concentration of TMB or $AgNO_3$ was too high, on one hand, the absorbance was low, and on the other hand, the high concentration of DA was needed to reduce the generated oxTMB, leading to low sensitivity. However, if the concentration of TMB or $AgNO_3$ was too low, the absorbance was too low to detect DA. Hence, the concentration of TMB and $AgNO_3$ being too high or too low was not suitable for DA detection. The results indicated that the highest ΔA was obtained when the TMB concentration was fixed at 0.2 mM and the $AgNO_3$ concentration was 0.15 mM. Therefore, 0.2 mM TMB and 0.15 mM $AgNO_3$ was chosen for the next experiments.

Catecholamine sensing

We next evaluated the sensitivity of the Ag^+-TMB system toward catecholamines, including DA, EP, and NE. In the absence of DA, the absorbance peak located at 652 nm was attributed to the oxidation product of TMB.[29] It was clearly seen that with the increase of DA concentration, the absorbance decreased gradually while ΔA increased systematically (Fig. 6A). The ΔA exhibited a good linear relationship with DA in the concentration range of 0.1 μM-1.0 μM and 1.0 μM-20.0 μM (Fig. 6B). The regression equation was $\Delta A=0.00249 + 0.127C_{DA}$ (μM) and $\Delta A=0.1144 + 0.0389C_{DA}$ (μM) with a correlation coefficient of 0.998 and 0.996, respectively. The detection limit can reach as low as 50 nM at a signal-to noise ratio of 3. Moreover, the color changes of Ag^+-TMB in the absence and the presence of various amounts of DA were recorded by a digital camera (Fig. 6C).The color change of Ag^+-TMB system induced by DA can be obviously visualized by naked eyes. The repeatability of the proposed method was evaluated by five repeated measurements of 0.5 μM and 5 μM DA, respectively, and the relative standard deviation (RSD) was 3.65% and 2.69%, respectively, demonstrating the reliability of the proposed method. We found the similar results could be obtained for the analysis of EP and NE (Fig. S3 and S4). The analytical parameters for the three catecholamines were summarized in Table 1.

In addition, we compared the characteristics of the proposed sensor with other optical DA sensors reported elsewhere. As shown in Table 2, the Ag^+-TMB system could provide better sensitivity in comparison with catecholamine-induced growth of AuNPs,[25] AHMP functionalized AuNPs,[24] carbon dots,[19] BSA-stabilized gold nanoclusters,[21] and $CuInS_2$ QDs.[30] Though, the detection limit based on DNA-templated silver nanoparticles,[18] dithiobis(sulfosuccinimidylpropionate)-modified gold nanoparticles,[31] and BSA stabilized gold nanoclusters[32] was lower than that in our method, the analysis time was much longer than that in our method. Moreover, all of them needed to prepare complicated nanoparticles while our method was nanoparticle-free. Therefore, our method was simple and fast.





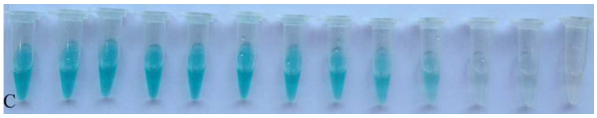


Fig. 6 (A) Typical UV-vis spectra of the proposed method in the absence and presence of different amounts of DA, from top to down: the concentration of DA is 0, 0.1, 0.25, 0.5, 0.75, 1, 2.5, 5, 7.5, 10, 15, 20, and 50 μM. (B) Relationship between the ΔA and the DA concentration. (C) Photographs of Ag^+-TMB solution in the absence and presence of different amounts of DA.

Interference study

The effects of possible coexisting compounds in catecholamine injections were investigated in order to evaluate the selectivity of this sensor for catecholamine detection. Fe^{3+}, Cu^{2+}, Ca^{2+}, Ni^{2+}, Zn^{2+}, K^+, Na^+, lactose, glucose, citric acid, starch, edetic acid, Trp, Phe, Tyr, and Cys were tested under the optimized conditions. Fig.7 showed the visual color change and the ΔA of the Ag^+-TMB system in the presence of catecholamines and other potential interferences. No obvious color changes were found after the addition of interferences, while a distinct color change could be observed in the presence of catecholamines. In addition, the ΔA in the presence of catecholamines were strikingly larger than that of the interferences. However, the presence of ascorbic acid, serotonin, and 3,4-dihydroxyphenylacetic acid severely interfered the detection of catecholamines owing to their strong reducibilities.

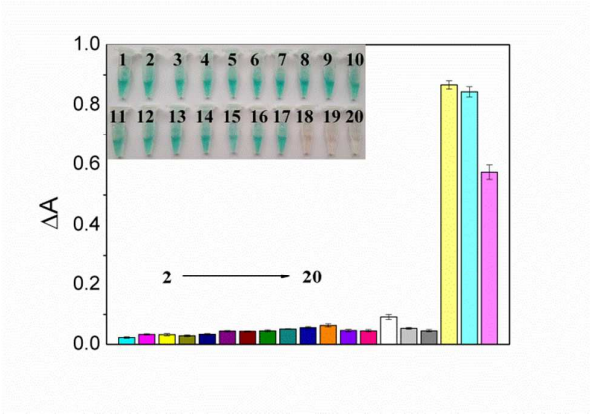


Fig. 7 The selectivity of the Ag^+-TMB detection system towards catecholamines. The concentration of each catecholamine and other interferences are 30 μM. Error bars show the standard deviations of three independent experiments. The inset shows the corresponding photographic images. From 1 to 20 is control, Fe^{3+}, Cu^{2+}, Ca^{2+}, Ni^{2+}, Zn^{2+}, K^+, Na^+, lactose, glucose, citric acid, starch, edetic acid, Phe, Cys, Trp, Tyr, DA, EP, and NE, respectively.

Sample analysis

In order to evaluate the practical utility of this method, it was applied to the detection of DA, EP, and NE in their injections respectively. Standard addition method was used for this analysis. The injections were diluted appropriately to bring them to their working concentration range, respectively. As shown in Table S1, the recoveries of known amount of catecholamines in the injections are in the range of 93.8%-110% with a RSD ranging from 2.56% to 4.12%. The results indicated that the proposed method is accurate and sensitive enough for the measurement of the catecholamines in pharmaceutical preparations.

Conclusions

In conclusion, we have developed a simple, fast, and sensitive colorimetric assay for the quantitative detection of catecholamines using TMB as an indicator. In the absence of catecholamines, Ag^+ could oxidize TMB to generate blue oxTMB, while the introduction of catecholamines induced the decrease of absorbance and the color gradually became lighter with the increasing addition of catecholamines. Compared with other methods, the proposed method is sensitive, simple, and fast. More importantly, the method does not need to prepare complicated nanomaterials. The proposed method shows a detection limit of 50 nM, 100 nM, and 150 nM for DA, EP, and NE, respectively, with the help of UV-vis spectroscopy. Moreover, this method is successfully applied to the detection of catecholamines in their pharmaceutical formulations.

Table 1 Summarized analytical characteristics of the catecholamines based on Ag^+-TMB system.

catecholamine	Linear range (μM)	Regression equation	R	LOD (nM)
DA	0.1-1.0 1.0-20.0	$\Delta A=0.00249+0.127C_{DA}$ (μM) $\Delta A=0.1144+0.0389C_{DA}$ (μM)	0.998 0.996	50
EP	0.25-20.0	$\Delta A=0.0731+0.0319C_{EP}$ (μM)	0.994	100
NE	0.25-50.0	$\Delta A=0.0596+0.0139C_{NE}$ (μM)	0.997	150

Table 2 Comparison of different optical sensors for DA detection.

Probe	Mode	Linear range	LOD (nM)	Time (min)	Reference
DNA-Ag NPs [a]	Fluorimetry	0-200 nM	3	180	[18]
Carbon dots	Fluorimetry	0.1-10 μM	68	30	[19]
adenosine capped QDs [b]	Fluorimetry	0.1-20 μM	29.3	20	[20]
BSA-Au NCs [c]	Fluorimetry	0-3.5 μM	100	5	[21]
$CuInS_2$ QDs	Fluorimetry	0.5-400 μM	200	6	[30]
DTSSP-AuNPs [d]	Colorimetry	0.02-0.8 μM	10	30	[31]
BSA-Au NCs	Colorimetry	0.01-1μM	10	30	[32]
AHMP-AuNPs [e]	Colorimetry	0.2-1.1 μM	70	30	[24]
AuNPs	Colorimetry	2.5-20 μM	2500	2	[25]
Ag^+-TMB	Colorimetry	0.1-1.0 μM 1.0-20.0 μM	50	5	This Work

[a] DNA-Ag NPs: DNA-templated silver nanoparticles
[b] adenosine capped QDs: adenosine capped CdSe/ZnS quantum dots
[c] BSA-Au NCs: BSA stabilized gold nanoclusters
[d] DTSSP-AuNPs: dithiobis(sulfosuccinimidylpropionate)-modified gold nanoparticles
[e] AHMP-AuNPs: 4-amino-3-hydrazino-5-mercapto-1,2,4-triazol (AHMT) functionalized gold nanoparticles

Acknowledgements

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Graphical Abstract:

Simple and fast determination of catecholamines in pharmaceutical samples using Ag^{+}-3,3′,5,5′-tetramethylbenzidine as a colorimetric probe

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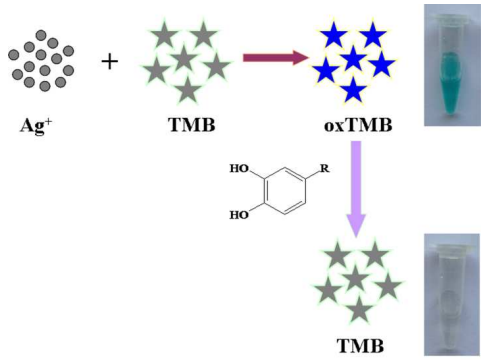

For the first time, a colorimetric method for catecholamine detection is developed based on their reducibility towards blue oxidized 3,3′,5,5′-tetramethylbenzidine oxidized by Ag^{+}.