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A comparison study of macrocyclic hosts functionalized reduced graphene oxide for electrochemical recognition of tadalafil

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ABSTRACT

The present work described the comparison of β-cyclodextrin (β-CD) and p-sulfonated calix[6]arene (SCX6) functionalized reduced graphene oxide (RGO) for recognition of tadalafil. In this study, tadalafil and two macrocycles (β-CD and SCX6) were selected as the guest and host molecules, respectively. The inclusion complexes of β-CD/tadalafil and SCX6/tadalafil were studied by UV spectroscopy and molecular simulation calculations, proving the higher supermolecular recognition capability of SCX6 than β-CD towards tadalafil. The β-CD@RGO and SCX6@RGO composites were prepared by a wet-chemical route. The obtained composites were characterized by Fourier transform infrared spectrometry, thermogravimetric analysis, atomic force microscopy, and zeta potential. The SCX6@RGO showed a higher electrochemical response than β-CD@RGO, which was caused by the higher recognition capability of SCX6 than β-CD. By combining the merits of SCX6 and the RGO, a sensitive electrochemical sensing platform was developed based on the SCX6@RGO nanohybrids. A linear response range of 0.1–50 μM and 50–1000 μM for tadalafil with a low detection limit of 0.045 μM (S/N=3) was obtained by using this method. The constructed sensing platform was successfully used to determine tadalafil in herbal sexual health products and spiked human serum samples, suggesting its promising analytical applications for the trace level determination of tadalafil.

1. Introduction

The application of artificial receptors, particularly macrocyclic hosts, in molecular recognition and sensing field has received considerable interest with the development of host–guest chemistry (Biedermann et al., 2013). The host–guest interaction is extensively used to construct nanoscale electrochemical devices in the field of molecular recognition because its recognition motifs are specific and bioorthogonal and can be used without an additional catalyst (Uhlenheuer et al., 2010; Chinai et al., 2011). Cyclodextrins (CDs), as the second class of macrocycles, are oligosaccharides composed of six, seven, or eight glucose units (α-, β-, γ-CD, respectively), which are toroidal in shape with a hydrophobic inner cavity and a hydrophilic exterior and are capable of forming inclusion complexes with a wide variety of hydrophobic guests (Guo et al., 2010; Zhu et al., 2012). Furthermore, calixarenes, recognised as the third class of macrocyclic host molecule after crown ethers and CDs, have become important receptors because they can form stable host–guest complexes with various guest molecules, which show high supramolecular recognition and enrichment capability (Mutihac et al., 2011; Dsouza et al., 2011). Water-soluble, especially, p-sulfonated derivatives have been widely investigated to develop different electrochemical sensing platforms and separation matrices due to their biocompatibility and simplicity of synthesis (Zhou et al., 2013).

Graphene is one of the most promising materials that holds great promise for potential applications in many technological fields because of its high surface area, low cost, and high conductivity (Allen et al., 2010). A major drawback of the graphene is the inevitable aggregation owing to the strong π–π stacking tendency between the nanosheets (Marcano et al., 2010). This problem has been previously resolved through large-scale production of graphene in the presence of a broad variety of protective reagents, including octadecylamine (Niyogi et al., 2006), silicone (Verdejo et al., 2008), polystyrene, poly(sodium 4-styrenesulfonate) (Stankovich et al., 2006a), 1-octyl-3-methylimidazolium (Stankovich et al., 2006b), DNA (Liu et al., 2008), large aromatic molecules (Patil et al., 2009), and didodecyldimethylammonium bromide (Su et al., 2009), *etc.* Nevertheless, in most

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cases, the presence of dispersing agents in graphene nanocomposite may be undesirable for many applications, which usually lead to poor performance (Liang et al., 2009). Interestingly, introducing a water-soluble macrocyclic host such as β-CD as functional molecule not only can effectively disperse graphene and meanwhile can bring in new and enhanced functions (Guo et al., 2010; Zhu et al., 2012; Zhou et al., 2013). Therefore, various macrocyclic hosts modified graphene organic-inorganic nanohybrids have attracted considerable attention recently in the electrochemical sensing field due to their enhanced performance by combining their individual merits and characteristics. For instance, Guo et al. (2010) reported that CDs–graphene composite could exhibit very high supramolecular recognition and enrichment capability and higher electrochemical signal toward probe molecules than unmodified graphene (Guo et al., 2010). Zhu et al. (2012) demonstrated that β-CD modified carbon nanotubes (CNTs) showed higher electrochemical response. Zhou et al. (2013) prepared p-sulfonated calixarene functionalized reduced graphene oxide (RGO) exhibit higher electrochemical sensing performance. Most recently, our previously obtained dual β-CD@Au@SiC (Yang et al., 2015a), bridged β-CD@CNTs (Yang et al., 2015b), β-CD@carbon nanohorns (Ran et al., 2015a), and disulfide linked β-CD functionalized Pd@RGO (Ran et al., 2015b) exhibit enhanced electrochemical sensing performance towards various analytes.

Tadalafil is one of the three selective phosphodiesterase type 5 (PDE5) inhibitors, and it is the active compound of Cialis, a prescription drug approved by the United States Food and Drug Administration in 2003 for the treatment of erectile dysfunction (Ormrod et al., 2002; Giannitsas and Perimenis, 2009). The usage of these PDE5 inhibitors is controlled through medical supervision because of their harmful side effects such as headache, dyspepsia, back pain, rhinitis, and flu syndrome (Porst, 2004). Tadalafil has the disadvantage of poor aqueous solubility, which may cause formulation problems and lead to highly variable blood levels, and irreproducible clinical response (Badr-Eldin et al., 2008). Tadalafil is absorbed rapidly at mean C_{max} (0.973 μM for 20 mg) observed at 2 h, thereafter, concentrations declined nearly mono-exponentially with the mean $T_{1/2}$ at about 17.5 h (Demir et al., 2014). Herein, tadalafil was selected as a guest molecule, the recognition capability of β-CD and p-sulfonated calix[6]arene (SCX6) modified RGO towards tadalafil was compared. The inclusion complexes of β-CD/tadalafil and SCX6/tadalafil were studied by UV spectroscopy and molecular modeling calculations. The β-CD@RGO and SCX6@RGO composites were prepared by a wet-chemical route. The higher electrochemical signal was obtained at the SCX6@RGO modified electrode than that of β-CD@RGO due to the higher recognition capability of SCX6 than β-CD. A sensitive electrochemical sensing platform was developed based on the SCX6@RGO nanohybrids by combining the merits of SCX6 and the RGO. The sildenafil and vardenafil must be investigated in the selectivity study due to their structures are very similar with that of tadalafil. In addition, some common interferents including oxalic acid, citric acid, ascorbic acid, uric acid, Fe^{3+}, Zn^{2+}, Br^{-}, and SO_4^{2-} were also studied as they may be exist in the herbal sexual health products. The designed electrochemical sensing platform is illustrated in Scheme 1.

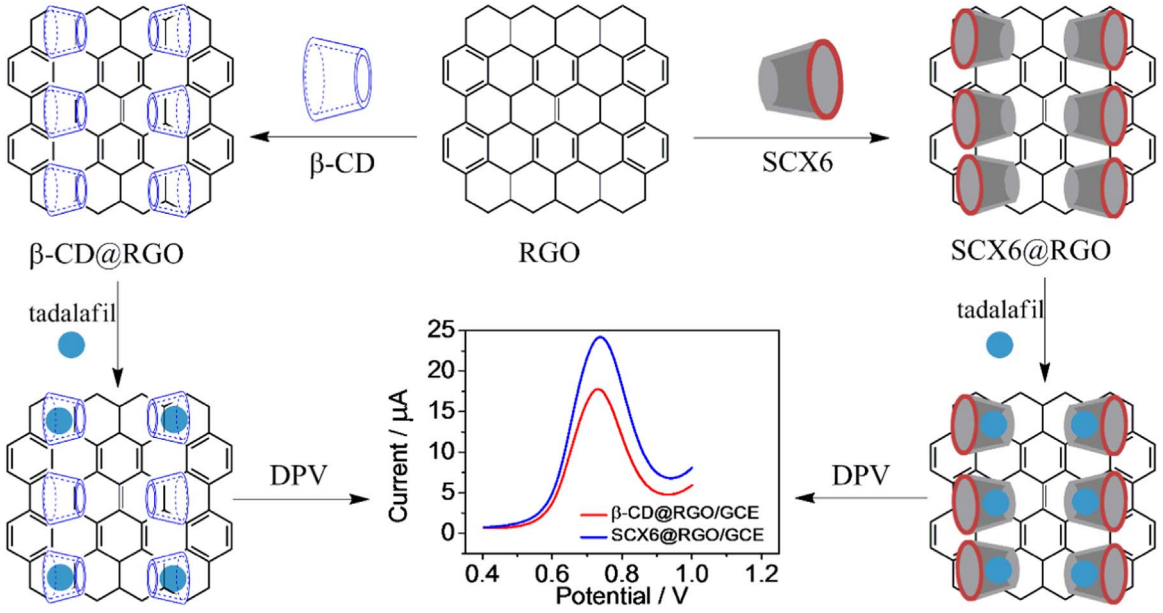
2. Materials and methods

2.1. Chemicals and materials

Graphite oxide was purchased from Nanjing XFNANO Materials Tech Co., Ltd (Nanjing, China). The β-CD was purchased from Sigma Chemical Co. (St. Louis, MO, USA). p-Sulfocalix[6]arene (SCX6) was obtained from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Tadalafil was obtained from Zhengzhou Lion Biological Technology Co., Ltd (Zhengzhou, China). Herbal sexual health products were purchased from the market. The active principle and composition are epimedium, dodder, cherokee rose, and fructus ligustri lucidi as described by the manufacturer. All other reagents were of analytical grade. Acetate buffer (0.1 M, pH 6.0) containing 40% acetonitrile was used as working solution. All aqueous solutions were prepared with deionized water (DW, 18 $M\Omega\ cm^{-1}$).

2.2. UV spectroscopic measurements

Inclusion complexes formation of tadalafil/β-CD and tadalafil/SCX6 were studied in DW using the spectral shift method. The concentration of tadalafil was kept constant at 50 μM, the β-CD concentration was 500 μM, while the SCX6 concentration was 50



Scheme 1. The illustration of the β-CD@RGO and SCX6@RGO nanohybrids-based electrochemical sensing strategy towards tadalafil.