Nano graphene oxide as drug carrier for antihypertensive agents

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ABSTRACT

Graphene oxide (GO) has a high specific surface area with many hydroxyl groups, carboxyl groups and other active groups on its surface and edges, which greatly enhance its water-solubility and biocompatibility. The skeleton of benzene rings offers large numbers of π-π binding sites, and oxygen atoms can form hydrogen bonds with drug molecules, which made GO an ideal drug carrier. The loading and release properties of three kinds of drugs: benazepril, captopril and losartan are studied. Results show good loading and release properties. Among these three drugs, benazepril can be loaded on GO via both π-π interaction and hydrogen bonds, so the highest loading capacity of benazepril is as high as 1.12 mg/mg. Dialysis release tests show the release of drugs from GO is pH-dependent.

Keywords: graphene oxide, drug carriers, benazepril, captopril, losartan

1 INTRODUCTION

Graphene oxide is an important derivative of graphene with large number of hydrophilic functional groups such as epoxy, carbonyl hydroxyl and carboxyl groups [1], wherein the epoxy and hydroxyl groups are mainly located on the surface while carbonyl and carboxyl groups are usually located at the edges of graphene oxide [2]. The graphene oxide retained some excellent characteristics of graphene, such as large specific surface area, large number of π-π binding sites and so on. Graphene oxide also has many new features, for example, the movableπ electrons were captured by surface oxygen functional groups and made the breaking of π bonds, result in the loss of the electron conduction ability. The presence of these oxygen functional groups causes the mutually exclusive between layers and the formation of hydrogen bonds in water. Compared with graphene, graphene oxide can be well dispersed in water, so the hydrophilic property is better than graphene [3].

A large number of hydrophilic functional groups makes it good wetting properties and surface activity. Large number of π-π and hydrogen bonding sites can conjunct drugs with π-π bonding and hydrogen bonding. According to another study [4], graphene oxide can't enter cells, nor presents apparent toxic effects. Cells can grow well on the graphene films, indicating graphene oxide is very safe and is very suitable as drug carrier. Graphene oxide has been reported as a drug carrier for anticancer drug DOX [5], CPT [6],SN38 [7] etc.

Now the model molecules studied are aromatic molecules with continuous benzene rings such as DOX, SN38, RB, etc. Such molecules can conjunct with graphene oxide via π-π binds, but the loading of drugs with isolated benzene rings or drugs without benzene rings is rarely reported. The antihypertensive drugs (Figure 1) were used as a model drugs to research the drug loading and release properties of graphene oxide to develop new drug carriers.

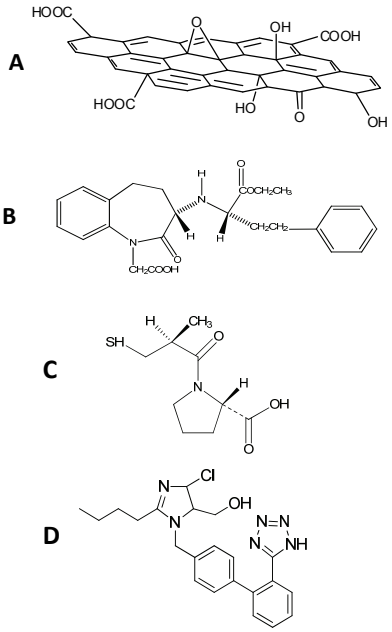

Figure 1: Schemes of graphene oxide(A), benazepril (B), captopril(C), losartan(D)

2 EXPERIMENTS

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abstract and keywords followed by the main text. It ends with a list of references.

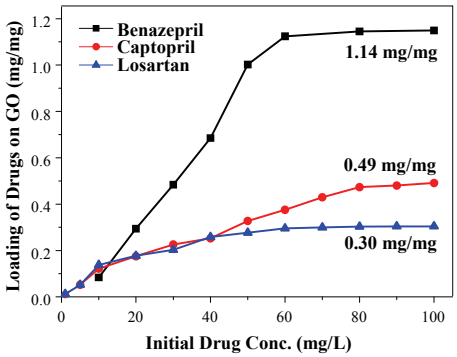

Figure 2: Plot of loading efficiency of drugs to GO

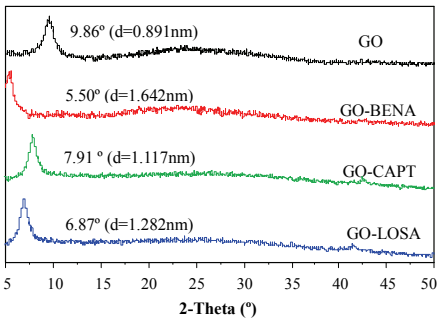

Figure 3: XRD spectra of GO-drug composites

2.1 Materials

Natural graphite (200 mesh), KMnO4, H_2SO_4, $NaNO_3$, hydrazine hydrate (50%), anhydrous ethanol, (analytical grade, commercially available) 1mol/L $BaCl_2$ solution, 5% H_2O_2 solution, 0.1 mol/L HCl solution, 0.1mol / L NaOH solution, deionized water.

2.2 Methods

Graphene oxide was prepared using improved Hummers method [8]. The maximum absorption peaks and the corresponding standard curve of each drug were measured by UV-vis. GO solutions and drug solutions were mixed and centrifuged at 8000 rpm for 30 min, then treated with freeze-drying to obtain GO-drug composites. The loaded drug amount was obtained through the initial amount minus free drug amount by UV-vis and the loading efficiency was gotten by the drug loaded amount dividing the amount of GO. GO-drug composites were dissolved in the water of different pH values and placed in dialysis bags in same pH surroundings, then taken out to detect the dialyzed free drug amount in water to analysis the drug release property. A parallel experiment was performed three times at each pH value to get release curves.

3 RESULTS & DISCUSSION

20 mg/L of the GO were mixed with drug solutions of different concentrations (concentration gradient of 1 mg/L to 100 mg/L), the loading efficiency was calculated and plotted as shown in Figure 2. The figure2 shows that the loading amount of drugs to GO is increased with the increasing of drug concentration. This phenomenon is particularly apparent when the drug concentration is lower, which is due to the large number of free surface sites available for drug molecule. With the further increase of drug concentration, more and more free surface sites were occupied by drug molecules, but the total epitope is limited, so the increasing of loading efficiency is lower and lower, finally reaching saturation. The loading amount of benazepril to GO is 1.12mg/mg, much higher than another two drugs. This is due to the appearance of benzene rings and carboxyl groups in benazepril, so benazepril can combine GO through π-π and hydrogen bonding. The interaction forces are greater than the other two drugs, therefore the drug loading amount is larger.

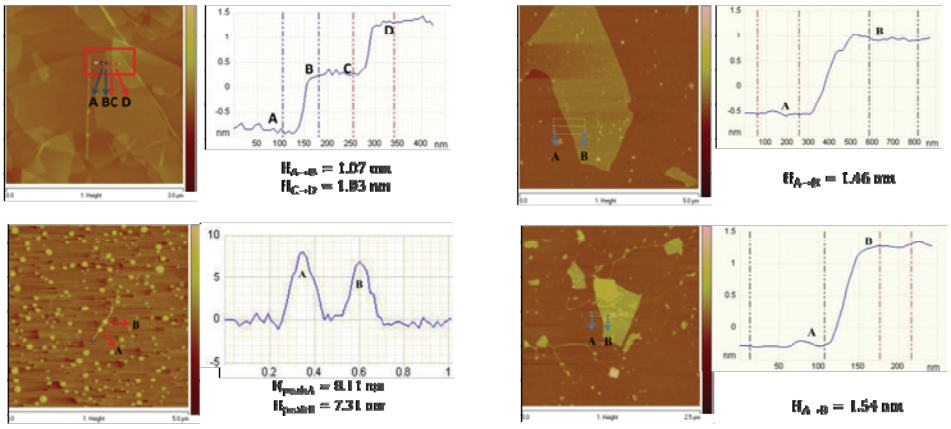

Figure 4: AFM images of GO-drug composites

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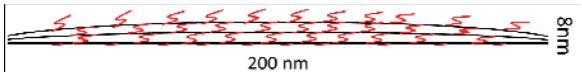

Figure 5: The pie-like structure of GO-BENA composites

XRD characterizations of GO-drug composites are shown in Figure 3. We can see the load of drugs has extended the GO sheets. We take benazepril as example, the GO peak displaces from 9.86º to 5.50º, corresponding to the layer spacing increases from 0.891 nm to 1.642 nm, indicating the introduction of benazepril stretches the distance between GO layers. This result also proves the benazepril molecules are located in the surface of GO sheets. The layer spacing of the other two drugs appears a growth of 0.226 nm (captopril) and 0.391 nm (losartan).

To further understand the drug loading mechanism, AFM observation results of GO-drug composites are shown in Figure 4. The figure4 shows that GO is single-layer of an average thickness of about 1.05nm. The thickness of GO sheets increases after drug loading. GO sheets maintain the original structure after loading captopril and losartan, but when benazepril is loaded to GO, the composite self-assembled to a pie-like structure with a diameter of about 200nm and average thickness of about 8nm, just like figure 5 shows.

The dialysis was carried out to test the release properties of GO-drug composites in different pH value, and the release curves are shown in Figure 6. The release of these three drugs are all pH-dependent, and the total amounts of drugs released are highest in acidic environment. The release speed is faster at the beginning, and gradually slows down, reaching equilibrium after 24h. We take benazepril as example, the first 10h is quick release period, during these 10 hours, the release amount is 65% to 75% of total drug released, which makes drug concentration reaching an effective concentration. The release speed slows down after 10h and reaches around zero after 24h.

The total release amount is about 58% in pH=2, which is higher than the other two drugs. The pH value of gastric juice is about 1.8, so the drug release amount GO-drug composites is large. What's more, the sustained-release time is over 24h, which is good for the drug efficacy.

4 CONCLUSION

Large specific surface area and large number of oxygen functional groups offer GO the ability of high drug loading capacity and pH-dependent release property, which makes it a excellent drug carrier. In this article, GO was found high loading capacity of three antihypertensive drugs: benazepril, captopril and losartan, especially for benazepril (as high as 1.12mg/mg). The drug release is pH-dependent, and the amount of drug released is highest in acidic environment. The sustained-release time is over 24h, so GO is very suitable for oral use of these three drugs in stomach, which makes GO a promising potential drug carrier for the three antihypertensive drugs in order to achieve better efficacy and less side effects.

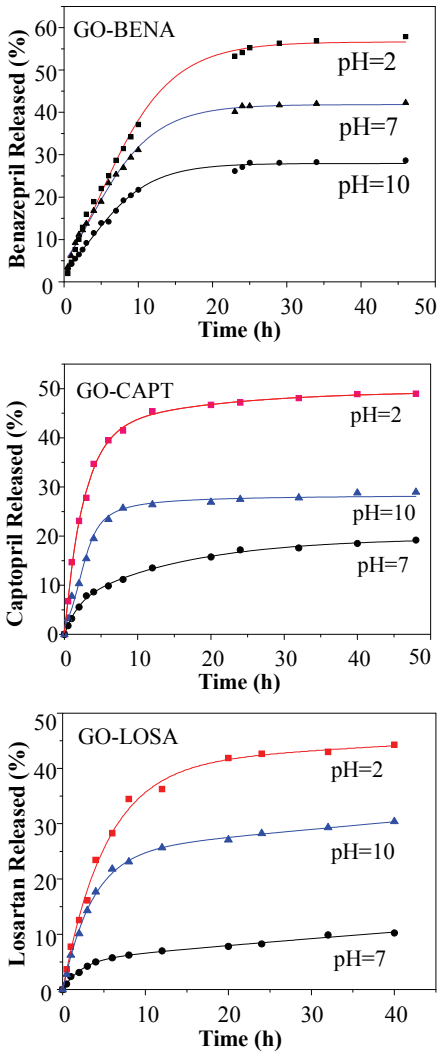

Figure 6: Release curves of GO-drug composites in different pH values

5 ACKNOWLEDGEMENTS

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