IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 15, Issue 5 Ser. VI (Sep. –Oct. 2020), PP 40-44
www.Iosrjournals.Org

A pH-sensitive graphene oxide carrier loaded with Captopril as a sustained-release system

Tianxiong Liu, Zhouhao Wu, Ning Wang, Cheng-an Tao, Yujiao Li, Jianfang Wang*
College of Liberal Arts and Science, National University of Defense Technology, Changsha, 410073, China;

Abstract: *A novel graphene oxide (GO)-based carrier was fabricated for the sustained-release of Captopril (CAPT). A small amount of the CAPT was added to the GO solution, a nanoparticle drug-carrying composite was formed without any other chemical additives. GO–CAPT composite was prepared and the drug sustained-release was carried at different pH values: in water (pH=7), hydrochloric acid (pH=2), and sodium hydroxide (pH=10). The release kinetics indicate CAPT desorption from GO is by Fickian diffusion. The CAPT yield from the carrier amounted to 56% of the adsorbed material in a strongly acidic medium after 38 h, but only 17% in a neutral liquid. It indicates that the GO-based carrier could be a potential candidate for use in the sustained-release of CAPT in the acidic environment of the stomach.*

Keywords: *Graphene oxide; Captopril; carrier; sustained-release*

Date of Submission: 10-10-2020 Date of Acceptance: 26-10-2020

I. Introduction

Nanocarriers have been studied as vehicles for various materials, such as drugs and genes, because of their ability to increase local access to cellular targets and enhance their distribution and availability[1–4]. An important condition for designing such a carrier is to choose a suitable nanoparticle (NP) carrier. Next, the preloading material should be able to attach to the carrier and then sustained-released in the organism[5].

CAPT is an oral drug that belongs to the angiotensin-converting enzyme (ACE) inhibitor class and is responsible for converting angiotensin I into angiotensin II[6]. CAPT is widely used in the treatment of hypertension[7]. However, due to poor water solubility, CAPT has poor absorption and cellular uptake. Only about a third of the physiological dose can be systematically transported, since most of it is consumed through transformation or excretion in the body. CAPT requires repeated administration due to its short retention and release time. Therefore, the development of a new sustained-release carrier is of great significance for improving the utilization rate of CAPT and reducing the drug delivery frequency.

Graphene oxide (GO) is a very important derivative of graphene. GO consists of a single molecule sheet of graphite with a high specific surface area, surfaces and edges decorated with disordered hydroxyl, carboxyl, and epoxy Bridges, greatly enhancing its water solubility and biocompatibility. The backbone of benzene ring provides a large number of potential binding sites(π-π binding sites) for aromatic drugs. In addition, oxygen atoms on the surface of GO can form hydrogen bonds with hydrogen donors in the drug structure. The structural characteristics of GO make it a potential drug carrier with great application prospects. GO can be used directly for drug delivery without any chemical modification[8]. It has been shown that GO has good biocompatibility at low concentrations [9-10]. Lin Zhou et al. [11] investigated a potential drug-delivery system due to GO's special properties and biocompatibility. Renyun Zhang et al. [12] built a real time method for monitoring the drug load and release on GO. Liu et al. [13] studied drugs such as doxorubicin loaded on GO. Wang et al. [14] fabricated a novel GO-based hydrogel with drug. Mariagrazia et al. [15] prepared an electrically responsive GO hydrogel for use in human skin tissue and demonstrated its biological safety.

In this paper, a new drug sustained-release system with CAPT carried by GO (GO–CAPT) was developed, and the sustained-release was studied at different pH values (2, 7, 10).

II. Materials and Methods

2.1 Materials

We had bought natural graphite powder (300 mesh) from Aladdin Co. Ltd (Shanghai, China). The Aladdin supplied us with the CAPT. Other chemicals used in the experiments were purchased from regular reagent companies and used without further refinement. All the relevant solutions used in the experiment were prepared with deionized water.

2.2 Fabrication of the GO–CAPT carrier

GO was prepared from graphite powder by modified hummer's method[16]. GO and CAPT of a certain concentration were prepared respectively in ultra-pure water, and the prepared solution was mixed by equal volume, and the mixture was slowly shaken well for over 12 hours to form GO-CAPT carrier complex. Then the mixture was centrifuged at 8000 rpm for 30 min to remove free CAPT. Solvents were removed by freeze-drying. By changing the initial concentration of CAPT from 5 mg/L to 80 mg/L (saturation concentration is 30 mg/L) and keeping the carrier concentration at 10 mg/L, the effects of different initial reactant ratios on the final mixture composition were studied. The resulting mixture solution was lyophilized using an instrument (Thermo Heto PowerDry LL3000, USA) and stored in a vacuum until used.

2.3 Release of CAPT

The drug release kinetics of the experimental samples were studied in neutral water (pH=7), ionized HCl (pH=2) and NaOH (pH=10) solutions. The mixed solution was tested in darkness and without interference from other conditions, and the spectral absorbance of the dialyzed liquid sample was measured. The amount of released GO-CAPT was determined by UV absorbance. Three parallel experiments were carried out under different pH conditions, and the release spectrum was obtained.

2.4 Characterization

The concentration of a drug was determined by recording the UV-Vis absorption spectrum of a concentration gradient sample using an UV-1201 UV/vis spectrophotometer (China) (scanning range is 200–800 nm). The results of Raman spectroscopy were provided by an Ar 532.8nm laser using Senterra&Veate X70 Raman spectrometer. The measurement of Zeta potential is carried out by Zetasizer Nano-ZS900zeta provided by the company. Scanning electron microscope (SEM) images were obtained with a Hitachi S-4800 field emission scanning electron microscope (Japan). X-ray Diffraction (XRD) measurements were performed using a Ttr III type X-ray diffractometer (Rigaku, Japan) equipped with a conventional Cu Ka X-ray radiation(l ¼ 1.54 A) source with a scattering angle ranging between 5° and 40°.

III. Results and Discussion

3.1 Characterization of GO–CAPT carrier

GO at 10 mg/L was combined with CAPT solutions at different storage concentrations (concentration range 5–80 mg/L). **Fig. 1** shows the correlation between the loading amounts and drug concentrations. As shown in **Fig. 1**, when CAPT concentration increased from the initial 5 mg/L to 80 mg/L, the drug loading changed sharply from 0.135 mg/mg to 2.235 mg/mg. It can be concluded that when the concentration of CAPT is low, the drug loading of CAPT on GO increases significantly due to the increase of CAPT concentration. As mentioned earlier, GO has many surface sites for drug binding. The available ligands on the surface of GO decreased gradually with the increase of the free concentration of the drug. Therefore, in the range of 80 ~ 90 mg/L, the drug loading decreases gradually with the increase of CAPT concentration. However, when the concentration of free CAPT was further increased, the drug loading only increased to 2.418 mg/mg. In conclusion, when the concentration of GO is 10 mg/L, the saturation concentration of CAPT is 80 mg/L. Therefore, we use this concentration ratio in the following experiments.

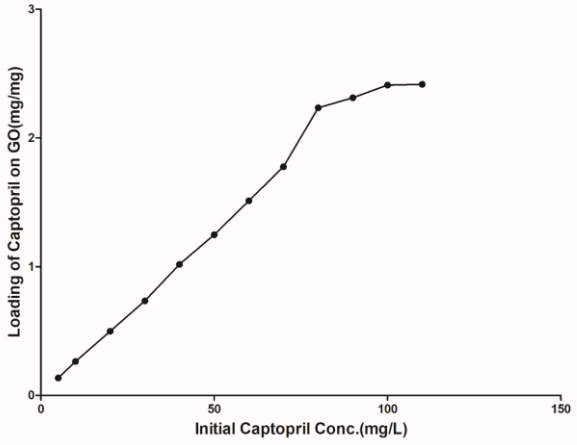

Figure 1. The curve of GO and CAPT loading.

In order to further investigate the loading law of CAPT on GO, we used XRD to characterize the structural changes of GO. In **Fig. 2**, it can be clearly observed that the main peak of GO-CAPT appears around 10°, while the main peak of GO appears around 11.74°. This indicates that after successful drug loading, the distance between the major crystallographic planes of GO was increased, and CAPT is loaded on the surface of GO.

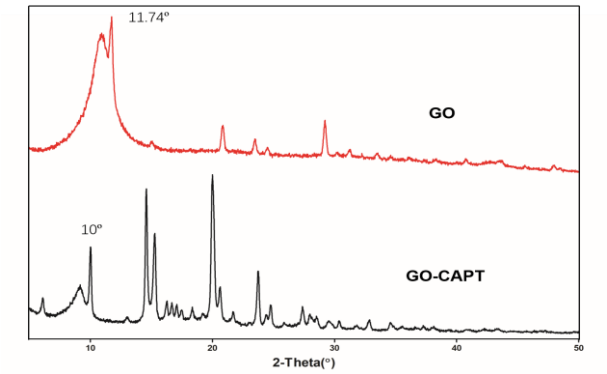

Figure 2. XRD spectra of GO and GO-CAPT.

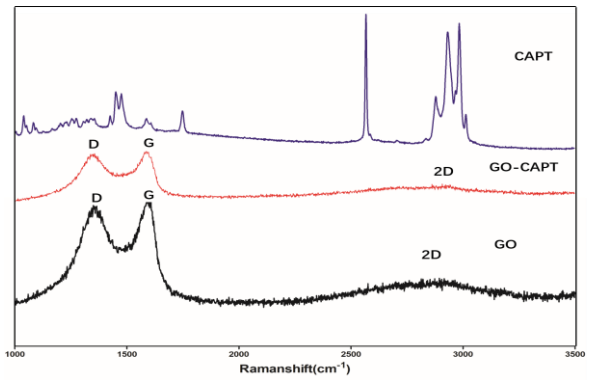

Figure 3. Raman spectra of GO, CAPT, GO-CAPT.

Raman spectroscopy is an effective method to detect the carbonic structure regions in GO and GO-CAPT. As shown in **Fig. 3**, due to the stretching vibration of C=C, we can see that the GO lattice has a G peak at 1600 cm^{-1}.While the D peak appears at the position of 1400cm^{-1}, it is generally believed that GO has undergone strong oxidation. We can see that peak D and peak G move to 1388cm^{-1} and 1611cm^{-1} respectively, so it can be inferred that CAPT has been successfully loaded on GO. In addition, the increase in ID/IG indicates that GO successfully loaded CAPT.

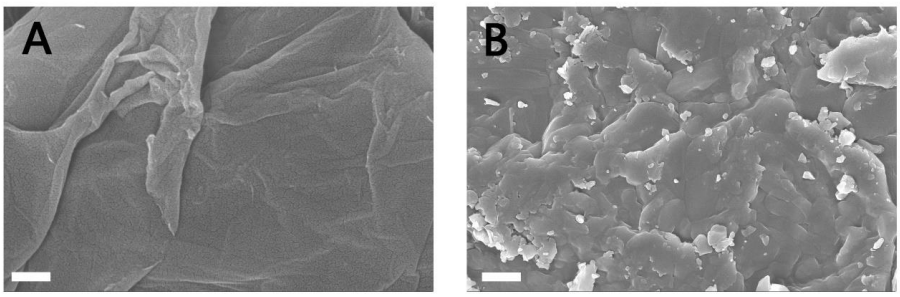

Figure 4. SEM images of lyophilized GO (A) and GO–CAPT (B). Scale bar: 1 μm.

The intuitive graphical evidence is shown in **Fig. 4**. **Fig. 4A** shows the smooth and flat morphology of GO. **Fig. 4B** shows a more distorted and rougher microstructure after loading CAPT. This suggests that the interaction between CAPT and GO distorts the chemical configuration of GO. Therefore, it can be inferred that

CAPT successfully binds to GO based on the significant morphological changes after the GO was loaded with drugs.

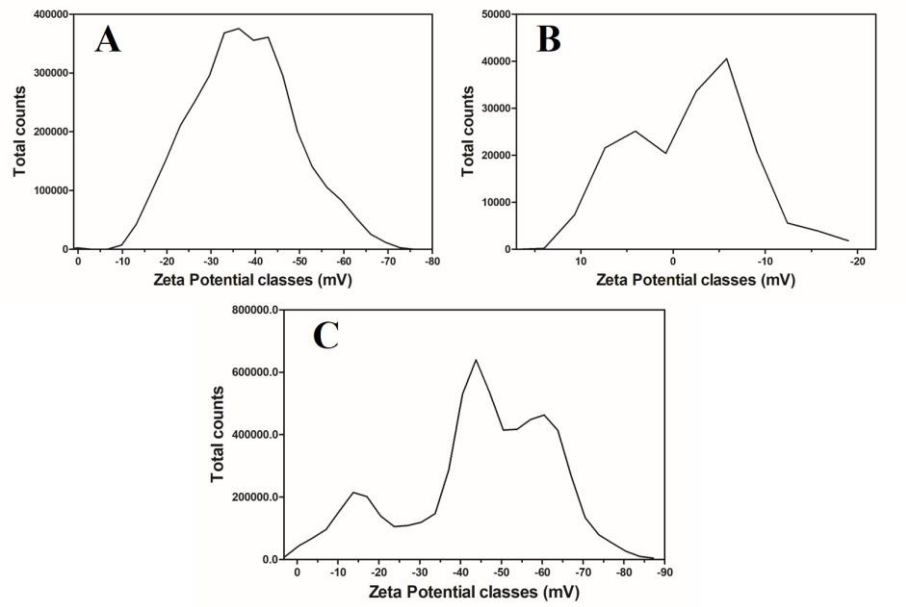

Figure5. Zeta potential of GO(A), CAPT(B) and GO-CAPT(C).

The Zeta potentials of GO, CAPT and GO-CAPT are shown in **Fig. 5**. The zeta potential of CAPT is 6.3 and that of GO is -36.5 within the tested pH range. This indicates that the surface charges of CAPT and GO are positive and negative respectively. At the same time, it can be observed that the Zeta potential of GO-CAPT is between the two substances, indicating that the loading of CAPT neutralizes the surface charge of GO.

3.2 Sustained-release of GO-CAPT

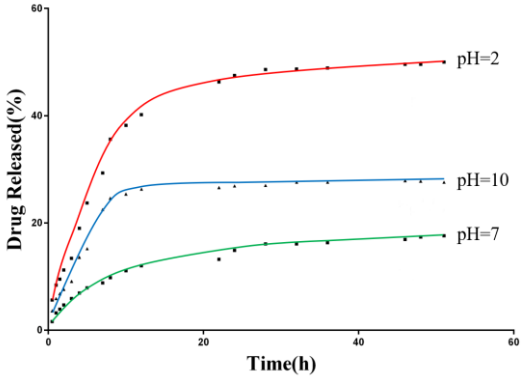

Figure 6. Yields of drug released from freeze-dried carrier at different pH values.

Fig. 6 shows the release pattern of CAPT in solution under different pH values. CAPT release time process is similar in different pH environments, but the drug release time point to the maximum concentration is different. During the first 12 hours, the drug release concentration changes rapidly. The curve in **Fig. 6** shows that the drug release rate gradually slows from 12 hours to 38 hours after the drug release reaches its maximum level. CAPT released the largest amount in acidic solution, up to 56% of the total adsorbed drugs. However, in neutral and alkaline solutions, the maximum drug release was only 17% and 23% of the total drug amount, respectively. Meanwhile, in the human body, the pH of gastric juice is about 2. Therefore, we can infer that the drug delivery from this drug carrier can reach the optimal level during oral administration, and the duration of the drug is more than 38 hours.

In order to further infer the drug release law, we fit the drug release data obtained from the experiment into the following empirical equation:

$$\frac{M_t}{M_\infty} = kt^n$$

In this formula, k is a rate constant related to the diffusion coefficient and binding energy of the drug M_t and M_∞ are the after equilibrium has been reached and cumulative drug release yield at sampling time, respectively, and n is the release index representing the transport mechanism. For a diffusion model, $n = 1$ infers that itis II model (relaxation control) diffusion, $n > 0.5$ infers irregular diffusion and $n < 0.5$ or less infers Fickian diffusion. We plotted $\log(\frac{M_t}{M_\infty})$ vs. log(t), to obtain the values of n, k and the proportion of the variance in the dependent variable (M_t/M_∞) that is predictable from the independent variable (t) (coefficient of determination R^2). Based on the calculated data, we can infer that $n < 0.5$ under the three pH solutions, indicating that CAPT release conforms to the Fickian diffusion model (see Table 1).

Table 1 Release characteristics of encapsulated GO-CAPT carrier under different methods at different pH values.

Specimen	*k*	*n*	*R*	Diffusion mechanism
pH=2	27.85±1.04	0.23±0.05	0.9321	Fickian
pH=7	35.11±1.09	0.32±0.01	0.9522	Fickian
pH=10	27.19±1.01	0.39±0.03	0.8781	Fickian

IV. Conclusions

In summary, we have fabricated a novel graphene oxide-based carrier with drug molecules. CAPT hydrochloride was utilized as a model drug and was added to GO to form a composite by supramolecular fabrication. The resulting composite had pH-sensitive performance and the samples had different drug release profiles in neutral, alkaline, and acidic media. The samples were found to be capable of sustained-release of drugs in the strongly acidic environment of the stomach. We have successfully obtained pH-sensitive GO-CAPT supramolecular carriers as sustained-release system.

References

[1]. Xiaojiao Y, Ian T, Muqing R, et al. Design of nanoparticle-based carriers for targeted drug delivery[J]. Nanomater. 2016, 6(9):1-15.
[2]. Hillaireau H, Couvreur P. Nanocarriers' entry into the cell: Relevance to drug delivery[J]. Cell Mol Life Sci. 2009, 66:2873–2896.
[3]. Kumari P, Ghosh B, Biswas S. Nanocarriers for cancer-targeted drug delivery[J]. Drug Target. 2016, 24:179–191.
[4]. Ruiz-Gatón L, Espuelas S, Larrañeta E, Reviakine I, Yate LA, Irache JM. Pegylated poly (anhydride) nanoparticles for oral delivery of docetaxel[J]. Eur J Pharm Sci. 2018, 118:165–175.
[5]. Kang EJ, Baek YM, Hahm E, Lee SH, Pham X-H, Noh MS. Functionalized β-Cyclodextrin Immobilized on Ag-Embedded Silica Nanoparticles as a Drug Carrier[J]. Int J Mol Sci. 2019. 20(2):315-322.
[6]. Ying Chen, Chih-Hsueh Lin, Mei-Jy Jeng. Effects of intratracheal captopril on severely meconium-injured piglet lungs[J].J Chin Med Assoc. 2019, 82(6):505-509.
[7]. Swathi N, Jayaprakash D. Formulation Development and Evaluation of Captopril Mouth Dissolving Films[J]. International Journal of ChemTech Research. 2019, 12(3):17-27.
[8]. Yang XY, Zhang XY, Liu ZF, Ma YF, Huang Y, and Chen YS. J. High-Efficiency Loading and Controlled Release of Doxorubicin Hydrochloride on Graphene Oxide[J]. Phys Chem C. 2008, 112(45):17554-17558.
[9]. Pahlevanzadeh F，Bakhsheshi-Rad HR，Hamzah E. In-vitro biocompatibility, bioactivity, and mechanical strength of PMMA-PCL polymer containing fluorapatite and graphene oxide bone cements[J]. Journal of the Mechanical Behavior of Biomedical Materials. 2018, 82:257-267.
[10]. Moré S, Yaimara，Panella G，Fioravanti G, et al. Biocompatibility of composites based on chitosan, apatite and graphene oxide for tissue applications[J]. Journal of Biomedical Materials Research Part A. 2018, 106(6):1585-1594.
[11]. Zhou L, Wang W, Tang J, Zhou J, Jiang H, and Shen J. Graphene Oxide Noncovalent Photosensitizer and Its Anticancer Activity In Vitro[J]. Chem Eur J. 2011, 17(43):12084-12091.
[12]. Zhang RY, Hummelgard M, Lv G, and Olin H, Real time monitoring of the drug release of rhodamine B on graphene oxide[J]. Carbon. 2011, 49(4):1126-1132.
[13]. Liu CC, Zhao JJ, Zhang R, et al. Multifunctionalization of graphene and graphene oxide for controlled release and targeted delivery of anticancer drugs[J]. Transl Res. 2017, 9(12):5197-5219.
[14]. Tao C-a, Wang J, Qin S, Lv Y, Long Y, Zhu H, Jiang Z. Fabrication of pH-Sensitive Graphene Oxide-Drug Supramolecular Hydrogels as Controlled Release System[J]. Journal of Material Chemistry. 2012, 22(47):24856-24861.
[15]. Di Luca, M，Orazio V，Cirillo G, et al. Electro-responsive graphene oxide hydrogels for skin bandages: the outcome of gelatin and trypsin immobilization[J]. International Journal of Pharmaceutics, 2018, 1–2(546): (50-60), 30.
[16]. Marcano DC, Kosynkin DV, Berlin JM, A. Sinitskii Z, Sun A, Slesarev L, Alemany B, Lu W, and Tour JM. Improved Synthesis of Graphene Oxide[J]. ACS Nano. 2010, 4(8):4806-4814.