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Communication

Redox-responsive polymer prodrug/AgNPs hybrid nanoparticles for drug delivery

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ABSTRACT

A drug carrier system of the hybrid nanoparticles based on the redox-responsive P[(2-((2-((camptothecin)-oxy)ethyl)disulfanyl)ethylmethacrylate)-*co*-(2-(D-galactose)methylmethacryl-ate)] (P(MACPTS-*co*-MAGP)) and AgNPs is developed to deliver the anti-cancer drug camptothecin (CPT) and monitor the drug release by the recovery of the fluorescence of CPT. CPT is linked to the polymer side-chains *via* a redox-responsive disulfide bond, attaching on the surface of AgNPs and leading to the quenching of CPT fluorescence ("off" state) due to the nanoparticle surface energy transfer (NSET) effect. Upon the exposure to glutathione (GSH), the disulfide bond is cleaved to release CPT, resulting in the recovery of the fluorescence of CPT ("on" state). The system offers a platform to track the CPT delivery and releasing in real time

Drug delivery systems have been extensively researched in recent years, and kinds of drug delivery devices have been explored to overcome the limitation of drugs including poor solubility, side effect and short blood circulation time [1–5]. However, there are still many obstacles in the application of drug delivery systems [6,7], and the releasing mechanism in tumor cells is still needed to be studied. Because the drug-loaded carriers and the released drug such as doxorubicin, camptothecin, paclitaxel display similar fluorescence, the identification of the drug-loaded carriers and the released drug become difficult [8]. Therefore, it is possible and easier to understand the mechanism behind drug release from carriers by monitoring and differentiating the drug-loaded carriers and the released drug.

Nanoparticle surface energy transfer (NSET) effect, in which an electronically excited "donor" molecule (such as fluorescent molecule) transfers its excitation energy to the nanoparticle ("quencher") surface and thus leads the fluorescence quenching of "donor" molecule, is extensively exploited in molecular probe [9–12] and drug delivery system [13–15]. There are two preconditions for NSET effect, including the overlap of the fluorescence emission spectrum of "donor" with the UV–vis spectrum of "quencher" and the close distance between "donor" and "quencher" which is less than 10 nm [16–18]. Silver nanoparticles (AgNPs), featured by high surface area, good biocompatibility, facile surface modification and adequate cell penetration ability, suitable for drug delivery systems [19–21]. Moreover, the ultraviolet absorption of AgNPs overlaps with the fluorescence emission of some fluorescent molecule (such as camptothecin), which makes AgNPs an excellent candidate as the "quencher" in NSET effect. Therefore, polymeric drug delivery systems with metal nanoparticles may give the possibility to study the releasing mechanism in tumor cells.

Here, A drug carrier system of the hybrid nanoparticles based on the redox-responsive P[(2-((2-((camptothecin)-oxy)ethyl)disulfanyl)ethylmethacrylate)-*co*-(2-(D-galactose)methylmethacrylate)] (P(MACPTS-*co*-MAGP)) and AgNPs has been established for monitoring the releasing of anti-cancer drug. Anti-cancer drug camptothecin (CPT) is linked to the side-chain of P(MACPTS-*co*-MAGP) *via* a redox-sensitive disulfide bond, being attached to the surface of AgNPs through the interaction between disulfide bond and Ag (Scheme S1 in Supporting information). The P(MACPTS-*co*-MAGP) was prepared by reversible addition-fragmentation chain transfer (RAFT) polymerization of monomers of 2-(D-galactose) methylmethacrylate) (MAGP) and 2-((2-((camptothecin)-oxy)ethyl)disulfanyl)ethylmethacrylate (MACPTS) linking with CPT. The MAGP unites containing D-Galactose structure exhibit good biocompatibility and have been widely used in medicine [22–27]. The disulfide bonds, a well-known redox-responsive structure, have been widely applied in drug delivery devices, triggering the releasing of drug [28,29] or the disassembly of the polymeric drug delivery systems [30–33]. Moreover, the disulfide

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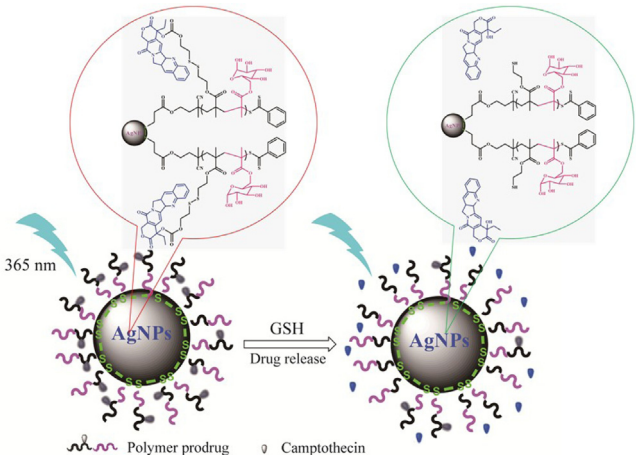

Scheme 1. The schematic illustration of fluorescence "off" and "on" with the release of CPT from P(MACPTS-*co*-MAGP)@AgNPs nanoparticles.

bonds have strong interaction with metal nanoparticles, easily being attached on the surface of metal nanoparticles. Therefore, the distance between CPT and AgNPs is close enough to satisfy the NSET effect, leading to the quenching of CPT fluorescence ('off' state). In the presence of reducing agent such as glutathione (GSH), the CPT molecule is released from the hybrid nanoparticles due to cleavage of the disulfide bond, leading to the recovery of the fluorescence of CPT ("on" state). Thus, the stimulus-responsive complex system can deliver anticancer drug and monitor the releasing of CPT by the fluorescence "turn-on" signal of CPT (as shown in Scheme 1).

The synthesis of P(MACPTS-*co*-MAGP) is depicted in Scheme S2 (Supporting information). RAFT polymerization of MACPTS (107 mg, 0.18 mmol) and 6-*O*-methacryloyl-1,2;3,4-di-*O*-isopropylidene-D-galactopyranose (MAIGP) (1.177 g, 3.6 mmol) in the presence of RAFT agent (disulfanediylbis(ethane-2,1-diyl)bis(4-cyano-4-((phenylcarbonothioyl)thio)pentanoate)) (DESCPADB) (61 mg, 0.09 mmol) and subsequent hydrolysis by trifluoroacetic acid (10 mL) to deprotect the ketal group in MAIGP unit affords the redox-responsive copolymers of P(MACPTS-*co*-MAGP). ^{1}H NMR analysis (Fig. S1 in Supporting information) was used to identify the structure of P(MACPTS-*co*-MAGP). The proton signal at δ 1.55 (Fig. S1B) was decreased, indicating that the MAIGP units convert to MAGP successfully. The drug load capacity (DLC) of the polymer prodrugs were calculated based on integral values of the aromatic proton signal at δ 7.65–9.30 and the ester methylene proton signal at δ 5.52, and were measured by UV–vis quantitative analysis (λ_{ex} = 365 nm) as well. Fig. S2 (Supporting information) shows the standard curve used for calculation of CPT content in the polymer prodrugs. The detailed results and characterization of P(MACPTS-*co*-MAGP) are listed in Table 1. Take sample 1 for example, the feed ratio of DESCPADB/MACPTS/MAIGP is 1/2/40 and the M_n of polymer prodrug is 6000 g/mol, while the DLC is 10.5% and 9.6% determined by NMR and UV–vis spectrum, respectively.

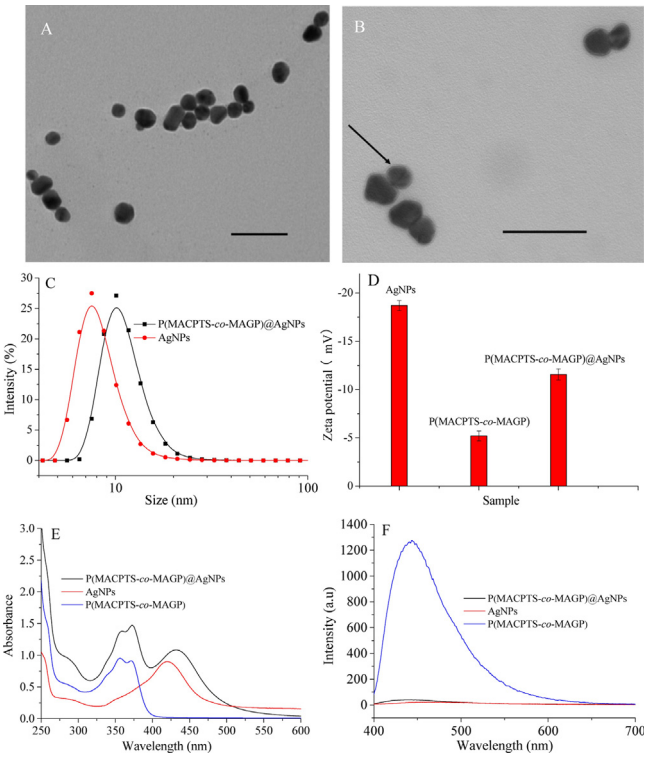

Fig. 1. The characterization of the P(MACPTS-*co*-MAGP)@AgNPs nanoparticles. TEM images of AgNPs (A) and P(MACPTS-*co*-MAGP)@AgNPs (B). Scale bar is 100 nm. (C) DLS data of AgNPs before and after covering with P(MACPTS-*co*-MAGP). (D) Zeta potentials of AgNPs, P(MACPTS-*co*-MAGP) and P(MACPTS-*co*-MAGP)@AgNPs. (E) UV–vis spectra of AgNPs, P(MACPTS-*co*-MAGP) and P(MACPTS-*co*-MAGP)@AgNPs. (F) Fluorescence emission spectra of the AgNPs, P(MACPTS-*co*-MAGP) and P (MACPTS-*co*-MAGP)@AgNPs.

We employed the reaction between AgNPs (1.45 mmol/L, 4 mL) and disulfide bond to link P(MACPTS-*co*-MAGP) onto the surface of AgNPs [34] to yield the target hybrid nanoparticles. The characterization of the P(MACPTS-*co*-MAGP)@AgNPs hybrid nanoparticles was shown in Fig. 1. The TEM images (Fig. 1A and B) show that AgNPs were coated by P(MACPTS-*co*-MAGP) and the combination of AgNPs and P(MACPTS-*co*-MAGP) was realized. The DLS data (Fig. 1C) show that the average hydrodynamic diameter of AgNPs increased about 5–10 nm after reacting with P (MACPTS-*co*-MAGP). The variation of zeta potential (Fig. 1D) and the UV–vis spectra (Fig. 1E) of hybrid nanoparticles combine the characteristic absorption of P(MACPTS-*co*-MAGP) and AgNPs, illustrating the successful linking of P(MACPTS-*co*-MAGP) onto the surface of AgNPs. Moreover, calculated from the TGA curve of the P(MACPTS-*co*-MAGP)@AgNPs as shown in Fig. S4 (Supporting information) approximately 1.38×10^{-20} mol polymer coated on the surface of each sliver nanoparticle.

As a drug delivery system, the drug loading ability in normal environment and drug releasing in nidus is very important. The

Table 1
The preparation and characterization of the P(MACPTS-*co*-MAGP).

Sample	Feed ratio (R/C/M)[a]	Con[b] (%)	$Mn_{(NMR)}$[c]	Ratio in polymers (R/C/M)[d]	$DLC_{(NMR)}$[e]	$DLC_{(UV)}$[f]
1	1/2/40	40	6000	1/1.07/14.5	10.5%	9.6%
2	1/2/40	39	3300	1/1.15/5.9	20.8%	19.0%

[a]R, C and M respectively represent DESCPADB, MACPTS and MAIGP monomers with various feed molar ratios.
[b]Con refers conversion, which was calculated based on decrease of vinyl proton signal in the ^{1}H NMR spectra of reaction mixture.
[c,d]Measured by ^{1}H NMR method.
[e,f] DLC refers drug load capacity, which was calculated based on the CPT content in the copolymer and measured by NMR spectra (NMR), UV–vis absorbance spectra (UV), respectively.

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