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Tellurium-Containing Polymer Micelles: Competitive-Ligand-Regulated Coordination Responsive Systems

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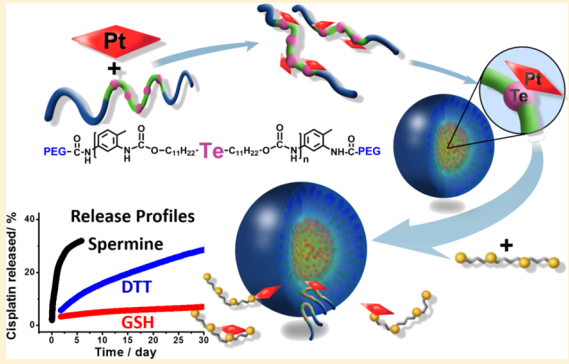
Supporting Information

ABSTRACT: Nanomaterials capable of achieving tunable cargo release kinetics are of significance in a fundamental sense and various biological or medical applications. We report a competitive coordination system based on a novel tellurium-containing polymer and its ligand-regulated release manners. Tellurium was introduced to water-soluble polymers for the first time as drug delivery vehicles. The coordination chemistry between platinum and tellurium was designed to enable the load of platinum-based drugs. Through the competitive coordination of biomolecules, the drugs could be released in a controlled manner. Furthermore, the release kinetics could be modulated by the competitive ligands involved due to their different coordination ability. This tellurium-containing polymer may enrich the family of delivery systems and provide a new platform for future biomedical nanotechnologies.



INTRODUCTION

Controlling drug release kinetics is of great significance as the efficacy and toxicity of the local therapeutics depend largely on the release kinetics.[1−4] Over the past few decades, considerable advances have been made in the fields of controllable delivery systems aimed at maintaining an adequate drug concentration in the blood or in target tissues at a desired value.[5−13] Among them, nanomaterials capable of selectively responding and adapting to specific stimuli are of interest, as this kind of approach enables well-regulated release kinetics by the programmable stimuli applied.[14−22] Different stimuli have been investigated to fabricate responsive systems, such as pH,[23−27] temperature,[28−30] radiation,[31−34] enzymes[35−37] and other chemical species.[38−40] However, developing delivery systems with multitunable release kinetics remains a scientific challenge. In this regard, different mechanisms and stimuli need to be integrated in the design.[18,41]

Competitive interactions exist widely in human metabolism process such as the function of G protein-coupled receptors.[42] G protein-coupled receptors are smart receptors on cell surfaces that enable the human body to sense its environment and adapt to new situations.[43,44] When the signal mediator binds with the G protein-coupled receptors, a conformational change will happen in the receptors, making GTP a more competitive ligand to bind with the receptor than GDP. These competitive interactions are crucial for the function of G protein-coupled receptors, since it causes the activation of the G protein and the downstream signals. Inspired by the competitive interactions, scientists have found new avenues for drug design,[43,45] while we wonder whether the response of competitive interactions can be utilized by polymer chemists to fabricate drug delivery systems. Previously, we reported a competitive coordination responsive release system based on monoselenide-containing polymer, in which the release of drugs is dictated by the competitive coordination ligands employed.[46] It is advantageous in several aspects, such as the vast kinds of competitive ligands available and the possibility to realize multidrug-cooperative therapy. To further push forward the concept of coordination release, we seek for other polymers and different biomolecules that can be employed to meet the criteria of competitive coordination response.

On the basis of the unique chemical properties and rich biological activities of the element selenium, selenium-containing polymers have attracted increasing interest as new biomaterials that can function as drug-delivery vehicles and artificial enzymes.[47−50] In contrast to the vast emerging research with regard to selenium-containing polymers, the occurrence of tellurium in biopolymers is poorly explored. Tellurium-containing organic compounds have been investigated as mimics of glutathione peroxidase (GPx), which plays an important role in protecting cells from oxidative stress.[51−53] In addition, tellurium-containing compounds are reported to be less toxic than selenium counterparts.[54,55] Although some tellurium-containing drugs are already under investigation or in clinical trials,[56] little attention has been paid to the possibility of introducing tellurium into biopolymers.

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In this study, we highlight a novel tellurium-containing polymer, which possesses the ability to deliver a platinum-based drug with ligand-regulated release kinetics for different time spans. Tellurium was introduced to water-soluble polymers for the first time as drug-delivery vehicles. The coordination chemistry between platinum and tellurium was designed to enable the load of a platinum-based drug. Through the competitive coordination of biomolecules, the drugs could be released in a controlled manner. Furthermore, the release process showed a ligand-regulated manner, in which the release kinetics could be modulated by different competitive ligands. The advantage of the new coordination-triggered release is that release kinetics could be modulated widely for time spans ranging from several days to as long as a month. As a result, the goal of enhanced delivery efficiency and fewer side effects may be achieved. This tellurium-containing polymer may provide components for future biomedical nanotechnologies.

RESULTS AND DISCUSSION

An A−B−A-type tellurium-containing amphiphilic polymer was designed and synthesized. The synthesis of the tellurium-containing polymer is described in detail in the Experimental Section (please refer to the Supporting Information [SI]). Briefly, the dialkyl telluride bearing two hydroxyl groups, di-(1-hydroxylundecyl)telluride (denoted as M-TeOH), was polymerized with 2,4-toluenediisocyanate (TDI) of slightly excess amount through stepwise polymerization to obtain the polyurethane with two active isocyanate groups ends. Next, the polymer was terminated through the reaction of isocyanate groups with hydroxyl groups of PEG monomethylether. The amphiphilic block copolymer, denoted as PEG−PUTe−PEG, was yielded with a molecular weight of 3.8×10^4 g mol^{-1} as indicated by ^{1}H NMR spectrum (Figure S2 in SI).

The self-assembly of PEG−PUTe−PEG occurred spontaneously in water through the hydrophobic/hydrophilic interactions among different segments of the polymer.[57] A dynamic light-scattering (DLS) measurement for this assembly showed a size of approximately 35 nm (Figure S4 in SI). As indicated by the DLS results, the critical aggregation concentration (CAC) of the polymer was 1.4×10^{-3} g/L (about 3.7×10^{-8} M). Moreover, the structure of the assembly was investigated using transmission electron microscopy (TEM). Because of the high atomic number of the tellurium element, the self-assembled micelles could be captured under TEM without staining. The TEM image shown in Figure 1b was consistent with the hydrodynamic diameter of the micelles. Colloidal stability studies with DLS revealed that the micelles were stable against 200 mM NaCl solution and only slightly swelled to about 48 nm (Figure S5 in SI). The stability of tellurium-containing polymer micelles was also tested against 25% glycerol (volume ratio) to mimic the viscosity of serum condition and PBS to mimic the salt concentration in human bodies. As shown in Table S1 (see the SI), the micelles only swelled a little after 24 h in 25% glycerol (~55 nm) or 10 mM PBS (~46 nm). To further see whether the system can work under higher salt concentration, we treated the micelles with 50 mM PBS, and the micelles remained around 40 nm after 24 h. Thus, we believe that the tellurium-containing polymer micelles could work under biologically relevant conditions. The stable nature could be ascribed to the hydrogen bonding between urethane groups in the polymer backbone.

The tellurium-containing block copolymer micelles could efficiently load cisplatin. To load the platinum drug, cisplatin

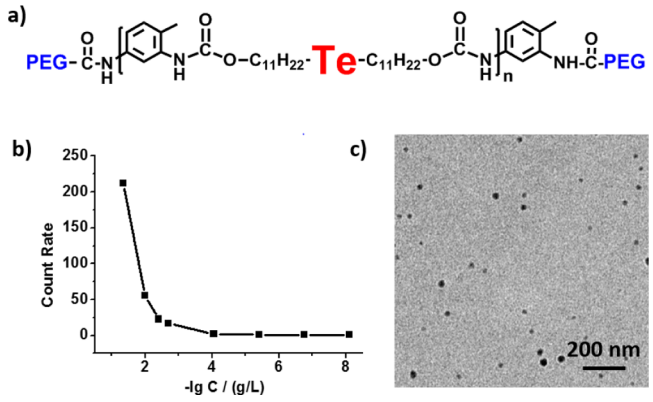

Figure 1. Self-assembly behaviors of PEG−PUTe−PEG. (a) The chemical structure of PEG−PUTe−PEG. (b) Critical aggregation concentration determined by the concentration-dependent DLS measurement. (c) TEM image obtained without staining.

was first coordinated with the polymer in DMF solution for a certain period of time. The complex solution obtained was dispersed in water followed by dialysis against water to remove the DMF and the unloaded platinum drug. The time of the coordination procedure was found to be vital for the load of platinum. As indicated by inductively coupled plasma-atomic emission spectroscopy (ICP-OES), the loading capacity showed a time-dependent manner. The ratio of Te to Pt decreased from 19:1 for only one day's coordination all the way to 6.7:1 after 5 days (Figure 2). Initially, micelles were formed

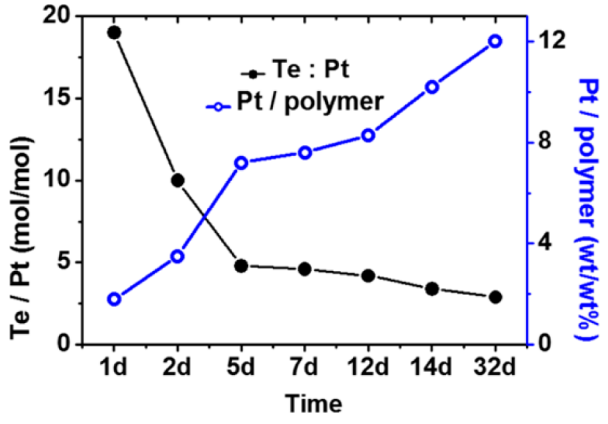

Figure 2. Load of cisplatin in PEG−PUTe−PEG micelles. The black dots are the molar ratios of Te to Pt, while the blue circles are the weight percentages of cisplatin loaded in the polymer.

with only 1.8% cisplatin in weight incorporated, while after a month, the final loading capacity increased to 12%. The reason for the phenomena may be that it took time for the telluride on the polymer chains to diffuse and coordinate with the platinum atoms of cisplatin. With cisplatin loaded, the micelles maintained the spherical morphology with a hydrodynamic diameter around 40 nm (Figure S6 in SI). The main driving force for the load of cisplatin was ascribed to the specific coordination interaction between cisplatin and tellurium.

To confirm the existence of coordination interaction between tellurium and cisplatin in the system, the complex between cisplatin and dialkyl telluride was studied in detail with M-TeOH as the model compound. First, ^{127}Te NMR data provided direct evidence for the coordination. The ^{127}Te NMR

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spectra showed that the chemical shift for M-TeOH was 233 ppm, while after complexation, the peak appeared at 754 ppm (Figure 3). The dramatic downshift should be ascribed to the

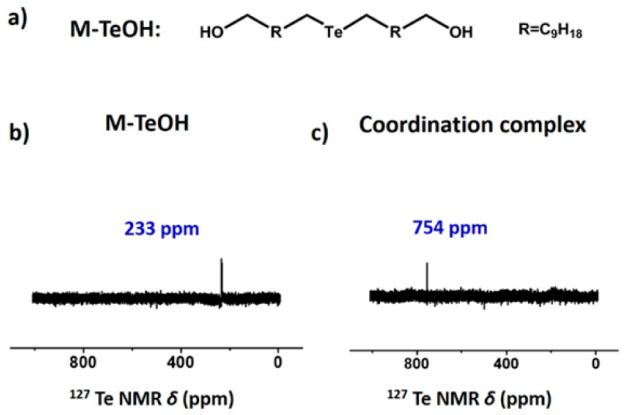

Figure 3. Evidences for the coordination of tellurium to cisplatin. (a) Structural formula of M-TeOH. ^{127}Te NMR spectra of M-TeOH (b) and the coordination complex (c).

strong deshielding effect of platinum cation. Second, ^{1}H NMR characterizations (Figure S7b,c in SI) showed that, after complexation with cisplatin, 2.62 ppm triple peaks from the α protons of Te atom were absent and new broad peaks appeared downfield to 2.93 ppm with the same integral area as the 2.6 ppm peaks before complex formation. The ESI-Mass spectrum can identify the peak of 735.6 (Figure S7d in SI), which is in good agreement with the coordination fragment of $[Pt(NH_3)_2Cl(M\text{-}TeOH)]^+$ with tellurium to platinum ratio of 1:1. Therefore, we conclude that the dialkyl telluride can coordinate with cisplatin with 1:1 stoichiometry.

After the study of the coordination chemistry, we could determine whether coordination interactions are the dominant driving force for the load of cisplatin in the polymer micelles. The contribution of the coordination bonds to the load of platinum drug was further confirmed by comparing the loading capacity of the tellurium-containing block copolymer with that of a control polymer analogue. Toward this goal, PEG-PUC-PEG, ABA-type amphiphlic block copolymer without telluride, was synthesized and used as a carrier for platinum drug with the same procedure (Figure S8 in SI). The loading capacity after 20-days of coordination was still approximately 0.13%, which is much lower than that of the telluride-containing polymer. Therefore, it is assumed that the coordination interaction of platinum and tellurium contributed a lot to the incorporation of platinum in the polymer micelles.

A desirable release profile of platinum drugs could be achieved by competitive coordination. Exposure to competitive ligand, DTT (10 mM), led to the controlled release of the platinum loaded. The *in vitro* drug release profile is shown in Figure 4, where we can see that there is no burst release out of the self-assembled micelles even from the very beginning of the release process. Sustained release of platinum took place over a period of more than one month, with about 30% platinum drug released. After that, slower release kinetics was observed, lasting for another month.

The release was ascribed to the competitive coordination of DTT to platinum. Due to the more competing coordination ability of DTT to cisplatin, the thiol groups could extract the platinum from coordinating with tellurium atoms on the

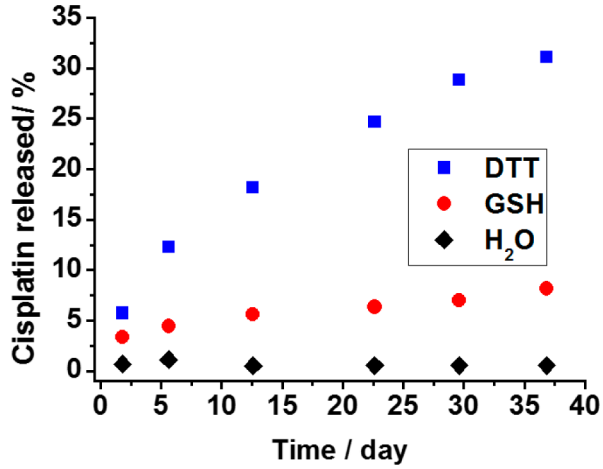

Figure 4. Competitive coordination triggered release profiles of cisplatin from cisplatin-loaded micelles in the presence of 10 mM DTT, 10 mM GSH, and water.

polymer backbone. Consequently the concentration difference between inside and outside polymer micelles resulted in the platinum release. This mechanism would lead to the formation of coordination complex of DTT and platinum. The chemical species diffused out of the dialysis bag in the release experiment and were analyzed by ESI-Mass; the coordination peak could be identified, and the structure was consistent with the literature report (Figure S9 in SI), which supported the mechanism we proposed as mentioned above. The fact that the platinum drugs loaded in the micelles need to coordinate with DTT molecules and diffuse out of the folded polyurethane chains may account for the long release-time span. Furthermore, in water control, the micelles were stable with only about 2% cisplatin release after incubation for one month (Figure 4). The much lower cisplatin release percentage in the absence of competitive ligands, in turn, suggested the coordination-triggered release mechanism proposed instead of the nonspecific diffusion release.

To take the concept of coordination release a step further, we demonstrated that other mercapto biomolecules, such as GSH, could also work. The intracellular concentrations (mM) of GSH are reported to be much higher compared to the extracellular value (μM), which can be the inspiration for designing GSH-responsive delivery systems for therapeutics and genetic materials.[58] As shown in Figure 4, for the PEG−PUTe−PEG system, the release triggered by 10 mM GSH is relatively slow but remains continuous over about 30 days. However, synergy effects in biological systems could be expected as other biological molecules could also take part in the competitive coordination,[59] while in the action of platinum anticancer drugs, Pt does not end up bound at the competing S-donor ligand. It is generally accepted that DNA platination is the ultimate event in spite of the Pt−S interactions.[60] Therefore, we believe that this coordination response system also works under physiological environments and that it may have the potential to be used as drug-delivery vehicles with long durations.

The release system is versatile and also works on other platinum-based drugs. To demonstrate its versatility, oxaliplatin was employed as another model drug. The incorporation of oxaliplatin increased the hydrodynamic diameter to 80 nm and the contrast under TEM observation was enhanced because of

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the heavy metal inside the micelles (see Figure 5). The amount of oxaliplatin in the micelles was determined by ICP-MS to be

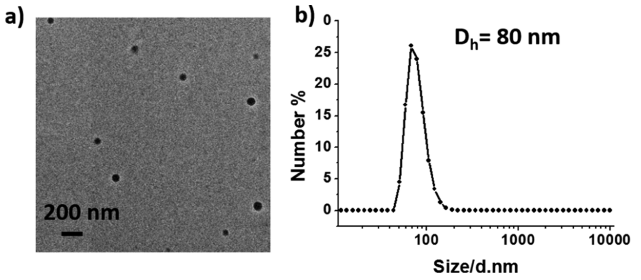

Figure 5. Self-assembly behaviors of oxaliplatin-loaded PEG−PUTe−PEG micelles. (a) TEM image. (b) DLS plot of oxaliplatin-loaded micelles of PEG−PUTe−PEG.

8.5 wt % of the polymer. The release plot revealed that the release kinetics of oxaliplatin was similar to that of cisplatin, with about 30% platinum released after one month against DTT (Figure S10 in SI). This suggested that the tellurium-containing polymer can serve as a delivery vehicle for different kinds of platinum-based drugs.

Apart from the conventional mercapto ligand, we demonstrated that other biomolecules, such as spermine, can work in the above systems and the release kinetics could be modulated by the competitive ligand. Polyamines are ubiquitous regulators of cell growth and proliferation, maintenance of which is the function of all normal cell types. As one of the natural polyamines with the strongest biological activity, spermine is involved in regulating cell growth and differentiation and is found in all eukaryotic cells. In the presence of 10 mM spermine under similar conditions, the release rate was accelerated to great extent compared to that of DTT. The release percentage of cisplatin reached only about 25% after 2 days, whereas oxaliplatin release increased to about 40% after 2 days. After the initial stage, the process slowed down and reached about 35% and 50% for cisplatin and oxaliplatin, respectively, after about 10 days. This release kinetics is suitable for controlled release, since effective therapeutic concentration could be achieved by the initial rapid release and the maintenance dose could be supplied by the following slower release. In comparison to the release in the presence of DTT, the enhanced release should be ascribed to the stronger coordination ability of spermine to platinum drugs, possibly due to the multivalent nature of spermine and the resulting chelating effects. Additionally, the system worked under biologically relevant conditions, particularly in serum conditions. Similar procedures were carried out in PBS containing 10% fetal bovine serum (FBS) with 10 mM spermine to monitor the release behaviors under serum conditions. As shown in the Figure S12 in SI, both cisplatin and oxaliplatin could still be released in a controlled manner with similar release kinetics (see also Figure 6). It has been reported that elevated spermine concentration is indicative of the presence of rapidly growing malignant tumors.[61] Therefore, the spermine-responsive release may have potential in targeting delivery. The spermine-triggered release not only verified the coordination response mechanism, but also demonstrated the possibility of ligand-regulated release kinetics.

The biocompatibility of the tellurium-containing polymer was also tested. An *in vitro* cytotoxicity study with the PEG−PUTe−PEG micelles was performed with two different cell

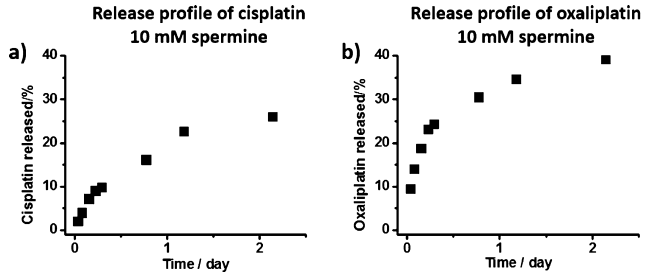

Figure 6. Release profile of cisplatin (a) and oxaliplatin (b) in the presence of 10 mM spermine.

lines (Hep G2 cells and L-02 cells) (Figure 7). The viability of the cells was more than 90% after exposure to the micelles for

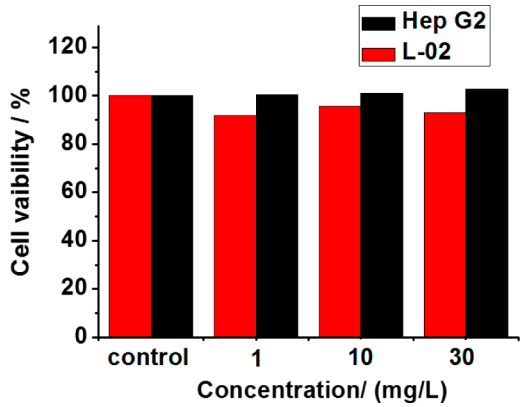

Figure 7. MTT assays for PEG−PUTe−PEG of varied concentrations based on L-02 and HepG2 cells. The cells were incubated with micelles for 24 h.

24 h and similar to that of the untreated control, indicating the good biocompatibility of the polymer micelles. In addition, polyurethanes are materials with good biocompatibility and biodegradability, which also facilitate its potential for future *in vivo* biomedical application. Our preliminary studies have shown that the platinum drug-loaded polymer micelles, e.g. oxaliplatin-loaded micelles, could indeed kill cancer cells to some extent.

CONCLUSIONS

In summary, we present here a successful demonstration of a competitive ligand-regulated responsive system based on a tellurium-containing polymer. The incorporation of tellurium into water-soluble block copolymers enables a novel drug delivery vehicle. Competitive coordination of biomolecules could trigger the release of the drugs loaded. In addition, ligand regulation of the release kinetics was also shown in the system. Other metal-containing drugs could potentially also benefit from this approach. Considering that other polyamines such as spermidine, arginine, and S-donor ligands such as biomolecules containing methionine and cysteine residues can also take part in the competitive coordination, the *in vivo* release may be enhanced to a large extent. Tellurium-containing polymers may provide new components for future biomedical nanotechnologies.

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■ ASSOCIATED CONTENT

Supporting Information

Detailed characterization of PEG−PUTe−PEG polymer and the cisplatin/M-TeOH complex; chemical structure for the control polymer PEG−PUC−PEG; release profile of oxaliplatin. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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