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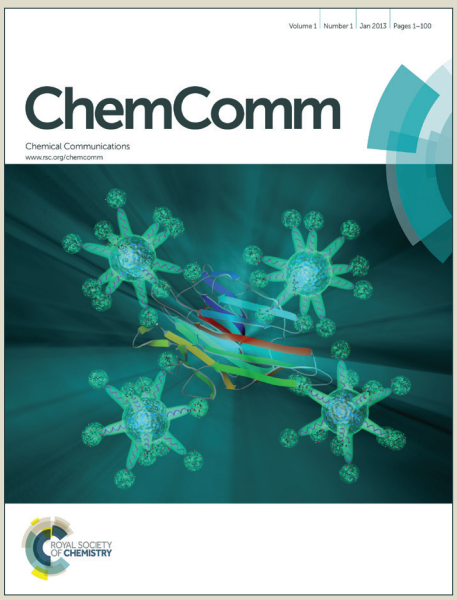

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Coordination responsive tellurium-containing multilayer film for controlled delivery

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Wei Cao, Lu Wang and Huaping Xu*

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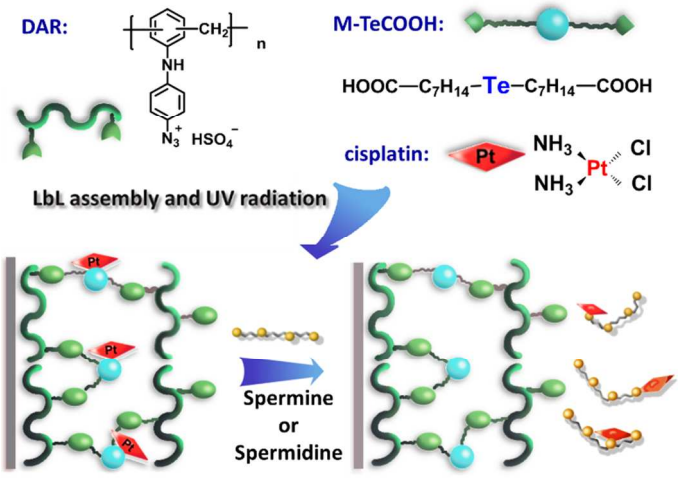
A coordination-responsive tellurium containing film was fabricated for controlled release. The coordination chemistry between telluride molecules and cisplatin was utilized for the load of cisplatin, while competitive ligands for triggered release. This work could enrich the coordination responsive system and further tune the release kinetics of cisplatin.

Smart materials which are capable of responding to the specific stimuli have been an emerging research field in the basic science and material areas due to the possibility to provide efficient drug or gene carriers for the treatment of diseases, such as cancer.[1-3] In order to achieve a better control of the drug carriers, the delivery systems have been up to now endowed with pH-,[4] redox-,[5-7] radiation-,[8-10] enzyme-responsiveness[11, 12] et al. Among them, we consider the systems with responses to the unique intracellular stimuli of cancer cells to be of great interest, since they could improve their intracellular trafficking as well as the release efficiency.[3, 13, 14] However, developing release systems adaptable to physiological environments of human body is still a big challenge.

Organotellurium compounds have been investigated as promising pharmacological agents in view of their unique biological properties such as glutathione peroxidase mimic, antioxidant activity, and thioredoxin reductase inhibition properties[15, 16] Yet compared with sulfur, the possibility of using tellurium-containing molecules for controlled delivery systems is still poorly explored. Based on the unique chemical properties of tellurium,[17, 18] we reported previously the coordination-responsive systems based on the tellurium-containing polymers for controlled delivery.[19, 20] The coordination chemistry of platinum and tellurium enabled the load of platinum drugs, whereas under mild conditions competitive coordination of other ligands could be utilized to trigger the release of platinum. The tellurium-containing polymer may provide not only regulated release kinetics but also beneficial biological effects. However, the loading capacity of the systems above is not satisfactory. Therefore, we seek to develop various systems to enrich the coordination responsive system and optimize the loading capacity.

In this study, we fabricated a competitive-coordination-responsive multilayer film for controlled release through Layer-by-layer (LbL) deposition of telluride-molecule/cisplatin complex and diazo resin (DAR, structure is shown in scheme 1) (scheme 1). LbL assembly is an attractive and powerful strategy for fabricating functional materials because of its simplicity, versatility and systematic control over the thickness and structure of the layers.[21-24] The tellurium-containing small molecules were employed to coordinate with cisplatin as delivery vehicles with an increased loading capacity of up to 40 %. As small molecules are not suitable for LbL assembly, the self-assembled aggregates were employed as polyvalent negatively-charged building blocks for the LbL film.[25, 26] Under physiologically relevant conditions, competitive-ligands such as spermine or spermidine could trigger the release of cisplatin from the films. The release kinetics could be further modulated to a great extent due to the different nature of the film with previously-reported micelles. Since spermine and spermidine are biomolecules existing ubiquitously in human body, it is highly anticipated that the new coordination responsive system may be adaptable to the physiological environment.



Scheme 1. Schematic representative for the coordination responsive tellurium-containing film for controlled delivery of cisplatin.

The telluride-containing small molecules were designed and synthesized. The design was based on the following considerations.

We first devised the telluride compound 11,11'-tellurodiundecanoic acid (denoted as m-Te11COOH) with long alkyl chains to increase the stability and simultaneously decrease the toxicity caused by the volatility. The carboxylic acid groups were utilized to increase the hydrophilicity. Yet the solubility of m-Te11COOH was poor even in pH 9.4 buffer. Then the alkyl chain was shortened by employing 8-bromooctanoic acid to react with disodium telluride to obtain 8, 8'-tellurodioctanoic acid (denoted as m-TeCOOH) with desired amphiphilicity (for details, please see the supporting information). The solubility of the compound m-TeCOOH proved to be satisfying in neutral pH. We assumed that m-TeCOOH could coordinate with cisplatin and work as a delivery vehicle with enhanced loading capacity. However, we were concerned about the coordination site of platinum, as it may also coordinate with the carboxylic acid groups on both ends.

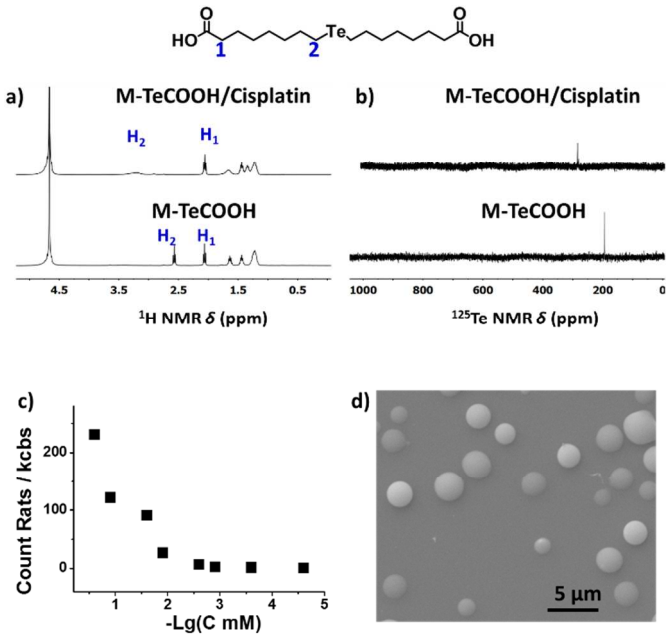


Fig 1. Evidence for the coordination between cisplatin and m-TeCOOH and the self-assembly behavior of the coordination complex. a) ^{1}H NMR spectra and b) ^{125}Te NMR for m-TeCOOH before and after coordination with cisplatin. c) The critical aggregation concentration (CAC) of the coordination complex determined by recording the concentration-dependent count rates in the dynamic light scattering (DLS) measurement of the aggregates suspension. d) Scanning electron microscopy (SEM) image for the aggregates of the coordination complex.

To have an exact view of its coordination mode with cisplatin, different characterizations for m-TeCOOH and the complex were examined and compared. As shown in ^{1}H NMR spectra of Fig 1a, the peaks for the key protons (H_1, H_2) are well resolved, making it convenient to identify the complexation mode. When compared with m-TeCOOH, the complex exhibited significant variation in ^{1}H NMR spectra including the disappearance of 2.70 ppm peaks and the new broad peak (3.6-3.2 ppm), suggesting that platinum coordinated with Te atoms. The observation that the chemical shift of H_1 remained unchanged after the coordination confirms that cisplatin coordinated with Te atoms on m-TeCOOH instead of the carboxylic acid moiety. In addition, ^{125}Te NMR provide more direct evidence for the coordination. As shown in Fig 1b, the chemical shift of tellurium downshifted from 191 ppm to 283 ppm as a result of the deshielding effects of platinum. To further support the formation of coordination species, ESI-mass analysis was conducted which revealed that the molecular ion peak $\{Pt(m\text{-}TeCOOH)(NH_3)_2Cl\}^+$ (*m/z*=679.11) and $\{Pt(m\text{-}TeCOONa)(NH_3)_2Cl\}^+$ (*m/z*=723.06) were the predominant species (Fig S5), indicating that m-TeCOOH and cisplatin could coordinate with 1:1 stoichiometry. Thus, the NMR and MS data supported the formation of cisplatin/m-TeCOOH coordination species.

The self-assembly behavior of the coordination complex was studied in pH 4.0 sodium borate buffer. The CAC of the coordination complex was determined to be approximately 3.2 μM by recording the concentration-dependent count rates in the DLS measurement of the aggregates suspension (Fig 1c). The aggregates are spherical with a diameter of about 2 μm (Fig 1d), as revealed by SEM and TEM images (for details, please see Fig S6). With the ratio of cisplatin to m-TeCOOH as 1:1, the loading capacity of cisplatin could reach 40 %, which is a dramatic increase compared with the previous tellurium-containing polymer micelles. The zeta potential of the aggregates was determined to be about -22.7 mV, indicating that the carboxylic acid groups were partially deprotonated and that the tellurium-containing micelles could be incorporated into the LbL thin films. The polyanion was optimized to be DAR, because DAR could be used to crosslink the film by UV-mediated photo-reaction.

The LbL assembling process was carried out and monitored by UV-Vis spectroscopy. A linear increase of the absorbance at 380 nm (Fig 2a), which is the characteristic peak for diazonium groups, was observed with the growing number of bilayers, therefore indicating a progressive and uniform deposition process. After reaching the desired layer number, the film was radiated with UV light for 10 min. Under UV radiation, diazonium groups of DAR decomposed to produce cationic phenyl groups, which reacted with nucleophile groups of carboxylate in m-TeCOOH to form carboxylate esters. As shown in the UV-Vis spectrum in Fig 2b, the peak at 380 nm for diazonium disappeared upon UV irradiation, indicating that covalently cross-linked tellurium-containing films were obtained.

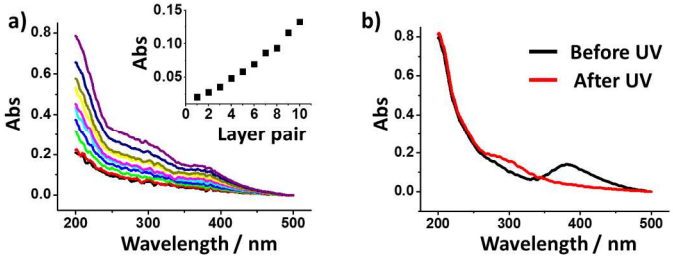


Fig 2. LbL assembly and photo crosslinking process for the fabrication of the film. a) UV-vis spectra monitoring the LbL assembly of a ten-bilayers of DAR and m-TeCOOH/cisplatin. (Inset) Absorbance at 380 nm *vs* the number of bilayers deposited. b) UV-Vis spectra of the multilayer film before and after UV irradiation.

In order to get more insight into the resulting film, the morphology was studied by different means. AFM analysis revealed a relatively flat surface with a roughness of about 10 nm (see the Fig S7). As one of the building blocks is the aggregates with diameters of about 2 μm, the smooth surface may suggest the deformation of the aggregates. Attempts were also made to investigate the thickness of the films. The corresponding cross-sectional SEM showed that the 10-bilayer film has an average thickness of about 80 nm, indicating that the micelles collapsed in the film (Fig S8). It is reasoned that the deformation of aggregates is caused by two reasons. On the one hand, aggregates of telluride molecules became unstable upon dehydration. Their electrostatic attractive force with positively-charged DAR may lead to the structure change when deposited on a

solid surface. On the other hand, the chemical crosslinking process when irradiated by UV light may further induce a force to press the aggregates.

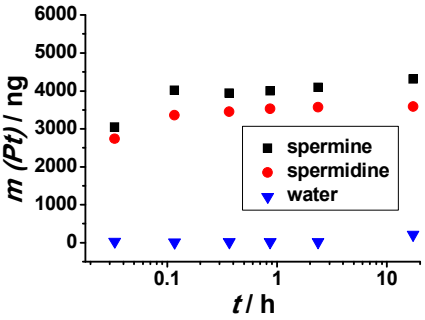


Fig 3. Controlled release profiles of cisplatin for the multilayer films.

We envisaged that release of cisplatin from the films could be triggered by the competitive ligands, for example, spermine and spermidine, which are ubiquitous polyamines in human bodies with strong biological activities. To test the hypothesis, we conducted the systematic release study of the films obtained. Upon incubation in the presence of competitive ligands, high cumulative drug release was achieved in a controlled manner. In total, 3.6×10^3 ng and 4.0×10^3 ng cisplatin were released for 5 mM spermine and 5 mM spermidine, respectively, according to the release profiles determined by the ICP-MS spectra (Fig 3), which as well corresponds with their degradation rate monitored by UV-Vis spectrum (supporting information Fig S10). Whereas for the film immersed in pure water, both the platinum release kinetics and the film degradation rate were almost neglectable, indicating the high stability of the covalently-cross-linked film. The release rate was significantly enhanced compared with the previously-reported coordination responsive tellurium-containing micelles. The reason may be that in the thin film, the cisplatin diffusion out of the film is quicker after the destruction of Te-Pt coordination interaction. To further see the effect of ionic strength on the release of cisplatin, control experiments with PBS buffer were carried out. It turned out that the release resulted from the PBS is much slower. Therefore, we conclude that competitive-coordination could also trigger the release from the telluride-containing films.

Conclusions

In conclusion, we have demonstrated the successful fabrication of a competitive coordination responsive thin film for controlled release of cisplatin via LbL approach and photo crosslinking chemistry. The film is endowed with higher loading capacity of cisplatin and could further tune the competitive ligand triggered release kinetics of the drug loaded. This approach broadens the possibility for the design of coordination responsive systems in therapeutic applications under physiological environments. If erasable-template is employed, capsules can be fabricated for delivery vehicles that can be applicable for blood transportation. Since the assembly method used is generalizable, other crosslinkers could also be used to fabricate the film. Further functionalization with low-fouling capability and targeting ligand may also be envisioned.

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Notes and references

* *Corresponding author*
Key Lab of Organic Optoelectronics and Molecular Engineering, Department of Chemistry, Tsinghua University, Beijing 100084, China.
xuhuaping@mail.tsinghua.edu.cn.

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