Functionalized MoS$_2$-nanoparticles for transdermal drug delivery of atenolol

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ABSTRACT

Molybdenum disulfide (MoS$_2$) has excellent photothermal conversion abilities, an ultra-high specific surface area, and has been extensively explored for use in biomedicine. However, the high toxicity associated with MoS$_2$ has limited its biological applications for in vivo photothermal therapy and drug delivery systems. Herein, we have developed cationic hydroxyethyl cellulose (JR400) surface-modified MoS$_2$ nanoparticles (NPs) that are responsive to near-infrared (NIR) laser irradiation as a transdermal drug delivery system (TDDS). Herein, we confirmed the preparation of hexagonal phase MoS$_2$ with robust surface modification with JR400. The flower-like morphology of the NPs had an average diameter of 355 ± 69.3 nm limiting the absorption of the NPs through the stratum corneum. With the ability to efficiently load 90.4 ± 0.3% of the model drug atenolol (ATE), where 1 g of JR400-MoS$_2$ NPs was able to load 3.6 g ATE, we assayed the controlled release capacity in vitro skin penetration studies. These JR400-MoS$_2$ NPs showed further enhancement under NIR stimulation, with a 2.3-fold increase in ATE skin penetration. Furthermore, we verified in vivo that these JR400-MoS$_2$ NPs do not cause skin irritation suggesting that they are promising new TDDS candidates for small molecule drugs.

1. Introduction

Molybdenum disulfide (MoS$_2$) is a typical transition-metal dichalcogenide with a layered structure consisting of individual S-Mo-S layers weakly bound by Van der Waals forces (Chen et al., 2015; Dhall et al., 2015; Wang et al., 2019). The remarkable physicochemical properties of MoS$_2$ has led to extensive research and applications in a wide variety of fields, including photochemistry, optoelectronics, catalysis, hydrogen storage, and biomedicine (Zhu et al., 2013; Qiao et al., 2016; Zhang et al., 2016). MoS$_2$ has been widely investigated for applications in drug delivery systems because of its ultra-high specific surface area (Liu et al., 2014; Yin et al., 2014; Wang et al., 2015; Wu et al., 2018; Zhang et al., 2018). Liu et al. used MoS$_2$ nanosheets paired with a PEG carrier to load a variety of therapeutic molecules, where the drug loading ratio of the MoS$_2$ nanosheets was superior to graphene oxide (Liu et al., 2014). Additionally, the release of the loaded drug molecules from the MoS$_2$ is inducible using 808-nm near-infrared (NIR) laser irradiation (Yin et al., 2014). The excellent photothermal performance of MoS$_2$ has inspired further use in photothermal therapies (Wang et al., 2015; Liu et al., 2016; Huang et al., 2017; Zhang et al., 2017; Fu et al., 2018). Wang et al. evaluated a MoS$_2$/Bi$_2$S$_3$ composite as a photothermal therapy agent (Wang et al., 2015). Chou et al. developed MoS$_2$-based NIR photothermal agents comprising Ce-MoS$_2$ nanosheets that offered higher photothermal performance than graphene and gold nanorods (GNRs) (Chou et al., 2013). However, the toxicity of MoS$_2$ has presented challenges for its use in photothermal therapy and drug delivery in vivo. Yu et al. found that 20 mg/L chitosan-functionalized MoS$_2$ micro-sheets exhibited cytotoxicity in the gills and liver of adult zebrafish (Yu et al., 2018). Furthermore, nano-MoS$_2$ and MoS$_2$ nanosheets exfoliated with t-Bu-Li and n-Bu-Li have been found to be cytotoxic (Chng et al., 2014; Wu et al., 2019). To date, the in vivo toxicity of MoS$_2$ remains a critical barrier for its use in biomedical applications.

Toxicity of MoS$_2$ can be mitigated by developing biomedical applications that can be used ex vivo. Transdermal drug delivery systems (TDDS) are an innovative approach to delivering drugs into the blood at a controlled rate via the skin. TDDS avoid the first-pass effect and improve patient compliance because they are applied topically (Laboula et al., 2011; Anselmo & Mitragotri, 2014; Pastore et al., 2015; Liu et al., 2017a, 2017b; Charoensumran & Ajiro, 2020). Materials larger than 45 nm are stopped at the stratum corneum (SC) of untreated intact human skin, allowing for sustained and controlled drug release (Laboula et al., 2011). MoS$_2$ is expected to be an outstanding TDDS material, but, to the best of our knowledge, has yet to be reported in the literature.

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Herein, we aimed to overcome the toxicity of MoS\(_2\) in biomedical applications by developing an innovative TDDS using three-dimensional (3D) flower-like MoS\(_2\) nanoparticles (NPs) produced via a simple hydrothermal approach (Zhang et al., 2015). Cationic hydroxyethyl cellulose (JR400) was electrostatically bound to the negatively charged surface of the MoS\(_2\) NPs, increasing its colloidal stability and biocompatibility (Liu et al., 2006; Ran et al., 2019). The MoS\(_2\) NPs coated with JR400 (JR400-MoS\(_2\) NPs) were further characterized using attenuated total reflection Fourier transform infrared (ATR-FTIR) spectroscopy, X-ray diffraction (XRD), and transmission electron microscopy (TEM). We chose to load the JR400-MoS\(_2\) NPs with the model drug atenolol (ATE), a \(\beta_1\)-adrenergic receptor blocking agent prescribed for hypertension. The drug load efficacy and photothermal conversion effect were evaluated, and the controlled release capacity of JR400-MoS\(_2\) NPs was demonstrated in \textit{in vitro} drug release and skin penetration assays.

2. Materials and methods

2.1. Materials

Ammonium molybdate tetrahydrate and thiourea were obtained from Shanghai Macklin Biochemical Co. Ltd. (Shanghai, PR China). Cationic hydroxyethyl cellulose (JR400, \(M_w = 8,000,000\) g/mol) was purchased from Shandong Usolf Chemical Technology Co. Ltd. (Linyi, PR China). Atenolol (HPLC grade, 98%) was purchased from Rhawn Chemical Technology Co. Ltd. (Shanghai, PR China). HPLC grade methanol and phosphoric acid were used throughout. All other chemicals were reagent grade and obtained commercially. All chemicals were used as received without any further purification. Ultrapure water was purified by a Milli-Q system (18.2 M\(\Omega\)).

2.2. Synthesis of JR400-MoS\(_2\) NPs

A facile and straightforward hydrothermal method was used to synthesize flower-like MoS\(_2\) NPs (Zhang et al., 2015). In detail, 1.24 g of ammonium molybdate tetrahydrate and 2.28 g of thiourea were dissolved in 36 mL of ultrapure water under vigorous stirring for 30 min to form a homogeneous solution. The mixture was transferred into a 50-mL Teflon-lined stainless-steel autoclave and heated at 220°C for 6 h. After unassisted cooling to room temperature, the products were collected by centrifugation and washed with ultrapure water and absolute ethanol several times, then dried in a vacuum at 60°C.

Afterward, 1.0 g of the obtained flower-like MoS\(_2\) NPs was stirred into 200 mL of aqueous containing 0.2 g of JR400. The suspension was ultrasonicated for 1 h, then heated at 80°C for 4 h. The product was separated by centrifugation and then washed with deionized water and absolute ethanol several times. After vacuum drying at 60°C for 24 h, we obtained the JR400-MoS\(_2\) NPs (black powder).

2.3. Characterization of JR400-MoS\(_2\) NPs

Spectrum of JR400-MoS\(_2\) NPs was collected using the KBr pellets method with ATR-FTIR spectroscopy (Perkin Elmer 2000, Waltham, MA). The crystalline structure of JR400-MoS\(_2\) NPs was studied using Rigaku SmartLab X-Ray Diffraction with Cu K\(\alpha\) radiation. The microstructure of the samples was investigated using TEM (JEOL-2100F, Akishima, Japan), which was operated at 200 kV. The particle size and zeta potential were measured using dynamic light scattering (DLS, Melvin 2000). The colloidal stability was analyzed by zeta potential and sedimentation volume ratio. The sedimentation volume ratio was determined by the ratio of the height after \(H_a\) and before \(H_0\) the sedimentation.

2.4. Photothermal conversion performance

JR400-MoS\(_2\) NPs were suspended in water at varying concentrations from 0.1 to 1.0 mg/mL for irradiation with an 808-nm laser (0.5 W/cm\(^2\)) to measure the photothermal effects. The laser power density was also varied between 0.2 and 1.0 W/cm\(^2\). The thermal stability of the JR400-MoS\(_2\) NPs at 0.5 mg/mL was determined by NIR-stimulation (0.5 W/cm\(^2\)) for 5 min over three on-off cycles. The temperature of the solution was measured by a magnetic stirrer equipped with a temperature probe.

2.5. Drug loading

ATE was loaded onto the surface of JR400-MoS\(_2\) NPs by mixing different concentrations of the drug with 0.5 mg/mL JR400-MoS\(_2\) NPs in 5 mL of phosphate-buffered saline (PBS) (pH = 7.0). The mixture was stirred for 2 h and incubated at 32°C for 24 h. The free drug was removed by centrifugation at 5000 r/min for 10 min, and the JR400-MoS\(_2\)-ATE NPs were washed with ultrapure water three times. The JR400-MoS\(_2\)-ATE NPs were dried at 60°C for 24 h under vacuum and stored at room temperature. The drug loading was calculated by the concentration of free drug in the supernatant, as analyzed by HPLC. Drug loading efficiency and drug loading percent were calculated using the following equations:

\[
\text{Drug loading efficiency} = \frac{\text{the amount of loading drug}}{\text{the amount of NPs}} \times 100\%
\]

\[
\text{Drug loading percent} = \frac{\text{the amount of loading drug}}{\text{the amount of total drug}} \times 100\%
\]

2.6. In vitro drug release and skin permeation experiments

2.6.1. Preparation of the donor solution

A donor solution was prepared by adding 25 mg JR400-MoS\(_2\)-ATE into 50 mL PBS. In order to form a uniform suspension, the mixture was stirred for 1 h, followed by sonication for 15 min. The suspension was added into the donor
chamber of a two-chamber diffusion cell immediately after preparation.

2.6.2. In vitro drug release experiments
Drug release was assayed using a two-chamber diffusion cell separated by a 0.22-μm cellulose microporous membrane. 4.0 mL of JR400-MoS2-ATE solution was added into the donor chamber, and an equal volume of PBS (pH 7.4) containing 15% PEG400 (PBS-PEG400) was added into the receptor chamber. Both chambers were continuously stirred with a magnetic stirrer at 600 rpm and kept at 32°C. 2.0 mL from receptor chamber was collected at 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 28, 32, 36, and 48 h, and then replaced with the same volume of fresh PBS-PEG400. The donor solution was irradiated with laser (0.5 W/cm²) for 5 min after sampling.

2.6.3. In vitro skin permeation experiments
Male Wistar rats (180–220 g, 6–8 weeks old) were supplied by Liaoning Changsheng (Liaoning, China). Full-thickness skin was prepared as follows: (1) the rat was anesthetized with urethane (20% w/v, 6 mL/kg, i.p.), and the abdominal hair was shaved off. (2) Abdominal skin was excised after the rat was sacrificed. (3) The adhering subcutaneous tissues were carefully removed. All the procedures were performed in accordance with the NIH Guidelines for the Care and Use of Laboratory Animals and were approved by the Animal Ethics Committee of Shenyang Medical College.

The two-chamber diffusion cell was used for the permeation experiments. The skin was mounted between the two chambers with SC facing the donor solution and epidermis facing the receptor solution. Sample collection and drug concentration measurements were performed in the same manner as drug release study, except that sample collection was conducted at 2, 4, 6, 8, 12, 24, 28, 32, 36, and 48 h with NIR-stimulation after every sampling. The cumulative drug skin penetration amount was calculated using the drug concentration in the receptor solution, taking the effect of sampling into account.

2.6.4. HPLC analysis of the drug
The drug concentration was determined by Hitachi HPLC (Tokyo, Japan), which consisted of a Pump L-2130, AutoSampler L-2200, UV-detector L-2420, and C18 reversed-phase column (200 × 4.6 mm, 5 μm, ODS-2 Waters, Milford, MA). The mobile phase for the ATE was a mixture of methanol, water, and phosphoric acid solution (70:30:0.1, v/v). The column temperature was 25°C, the flow rate was set at 0.7 mL/min, and the free drug was detected at a wavelength of 275 nm.

2.7. In vivo skin erythema study
A Mexometer® (MX 16, Courage & Khazaka Co., Cologne, Germany) was used to measure the biocompatibility of JR400-MoS2 NPs by measuring the erythema index (EI) of the skin. Rabbits were used to assess potential skin irritation caused by JR400-MoS2 NPs compared with a 10% (w/v) aqueous solution of sodium dodecyl sulfate (SDS) as the positive control. The dorsal skin of the rabbits was shaved and divided into three separate sections, each with an area of 2.5 cm × 2.5 cm. The initial EI values of the chosen sections were measured as a baseline value (EI0) before topical application of 500 μL of PBS, JR400-MoS2 NPs, or 10% SDS in their respective sections. The application sites were covered with double-layer gauze in order to prevent perturbation. After 8 h, the excess solutions were removed, and the predefined sections were gently cleaned with cotton wool swabs. The EI was measured at set intervals and ΔEI was calculated by subtracting EI0 from EI. This experiment was performed in quadruplicate.

2.8. Statistical analysis
Results are reported as the mean ± SD. The data were subjected to analysis of variance (ANOVA) using the SPSS 16.0 software (SPSS Inc., Chicago, IL). Significance levels are reported for p < .05.

3. Results and discussion
3.1. Synthesis and characterization of JR400-MoS2 NPs
Flower-like MoS2 NPs were synthesized using a previously reported hydrothermal process using ammonium molybdate tetrahydrate and thiourea precursors to produce polyacrylamide (PAM) modified MoS2 NPs (Wang et al., 2019). NPs were subsequently surface modified with JR400 (Figure 1), a water-soluble cellulose derivative that is currently used in skincare products (Li et al., 2012).

The JR400 surface modification was evaluated using ATR-FTIR spectroscopic analysis (Figure 2). The peaks present at 2875 cm⁻¹, 2974 cm⁻¹, and 3409 cm⁻¹ were attributed to the symmetrical stretching vibrations of the C–H bond, asymmetrical stretching vibrations of the C–H bond, and stretching vibration of the O–H band from the JR400 molecule, respectively, indicating that the MoS2 NPs were readily surface-modified with JR400.

The XRD patterns exhibited five well-resolved diffraction peaks at 2θ = 14.4°, 32.7°, 39.5°, 49.8°, and 58.3°, which can be assigned to the (002), (100), (103), (105), and (110) diffraction planes, respectively (Figure 3). These planes correspond to the hexagonal phase of MoS2 (JCPDS no. 37-1492) (Tang et al., 2013). No other diffraction peaks were observed; thus, a hexagonal phase of MoS2 was prepared.

The grain size, morphology, and structure of the JR400-MoS2 NPs were investigated using scanning electron microscopy (SEM), TEM, and high-resolution TEM (HRTEM) (Figure 4). The SEM images indicated that the JR400-MoS2 NPs formed via irregular curling and winding of the thin MoS2 nanosheets (Figure 4(a)). The structure was studied in more detail using TEM and HRTEM. TEM revealed the NPs had a flower-like morphology (Figure 4(b)), consistent with the SEM images. HRTEM showed that the NPs were made from overlapping MoS2 nanosheets, matching previous reports in the
The lattice spacing of the MoS$_2$ (002) plane was observed in the enlarged HRTEM image (Figure 4(c)), where the 0.63-nm lattice spacing was consistent with the XRD results.

The JR400-MoS$_2$ NPs had an average diameter of 355 ± 69.3 nm (PDI = 0.259), as obtained by DLS, similar to the size obtained by HRTEM image (Figure 4(c)). Generally, particles larger than 45 nm are stopped by the SC of skin (Labouta et al., 2011). Thus, the potential in vivo toxicity of JR400-MoS$_2$ NPs is significantly reduced as it cannot translocate into the bloodstream. Furthermore, the JR400-MoS$_2$ NPs could be used in TDDS for the controlled release of the drug across the SC.

The colloidal stability of JR400-MoS$_2$ NPs and MoS$_2$ NPs was explored using zeta potential, sedimentation volume ratio, and dispersion times. The zeta potential of the MoS$_2$ NPs was measured to be $-14.64 \pm 1.72$ mV, while the zeta potential of JR400-MoS$_2$ NPs was found to be significantly more negative at $-25.52 \pm 2.15$ mV, indicating that the JR400 functionalization increases the stability of the particle (Khafaji et al., 2019). After five days of sedimentation, the $H_2/O_2$ of JR400-MoS$_2$ NPs and MoS$_2$ NPs were 0.95 ± 0.03 and 0.22 ± 0.12, respectively (Figure 5). The results were probably related to hydroxyl groups in JR400, which could form hydrogen bond with water. Overall, modifying the surface of the MoS$_2$ NPs with JR400 made them more stable in water.

### 3.2. Photothermal conversion performance study

The photothermal properties of NP drug carriers have been reported to have a substantial effect on drug release (Yin et al., 2014). Previous studies have shown MoS$_2$ exhibits...
absorption at 808 nm (Yang et al., 2018). The conversion efficiency of the JR400-MoS2 NPs was studied by changing the power density of the laser and concentration of the MoS2 NPs. The temperature of the 1.0 mg/mL JR400-MoS2 NP solutions increased rapidly to 86.6°C during the 5 min of irradiation, while the control samples exhibited minimal changes under the same conditions (Figure 6(a)). The temperature increase was dependent on the concentration of NPs, as well as the power density of the laser (Figure 6(a,b)). Considering the enhanced effect on drug release and overall skin irritation, an NP concentration of 0.5 mg/mL and a power density of 0.5 W/cm² were used for the in vitro experiments. The conversion stability was confirmed by conducting three on-off cycles (Figure 6(c)). Overall, the JR400-MoS2 NPs exhibited outstanding photothermal conversion ability.

3.3. Drug loading

MoS2 nanosheets have been used as drug delivery systems, but the multilayer structure has led to compromised drug loading efficiency. The porous structure of the 3D flower-like MoS2 increases the number of drug loading sites (Yang et al., 2018). Using ATE as a model drug, higher drug concentrations yielded greater loading, with a 4:1 mass ratio of ATE to JR400-MoS2 NPs led to optimal drug loading efficiency (Figure 7). At this ratio, 1.0 g of JR400-MoS2 NPs was able to load 3.6 g of ATE, resulting in a drug loading efficiency of 361.6 ± 1.0% with 90.4 ± 0.3% of the initial drug loaded onto the NPs. An optimized concentration of 0.5 mg/mL JR400-MoS2 NPs with 2.0 mg/mL ATE was selected.

3.4. Drug release experiments

The release of ATE from the JR400-MoS2 NPs was investigated using a classic transdermal drug release study with a two-chamber diffusion cell (Sun et al., 2012). Without NIR irradiation of the JR400-MoS2 NPs, only 139.4 ± 18.17 μg/cm² ATE was released within 48 h (Figure 8(a)). However, NIR-stimulation at 0.5 W/cm² for 5 min caused a significant increase releasing 340.12 ± 17.84 μg/cm² of the drug, indicating that NIR stimulation was beneficial for the release of ATE. Moreover, the use of NIR-stimulation significantly increased the release of ATE in 36 h. These results demonstrate the potential for a controllable JR400-MoS2 NP drug delivery system.

Nanoparticle drug delivery systems commonly use NIR stimulation to facilitate drug release. Shao et al. presented a polymeric microcapsule drug delivery system involving water-soluble antitumor drug encapsulation and GNR functionalization, where low power NIR radiation was applied to trigger the release of the drug (Shao et al., 2015). Similarly, Koning et al. developed a thermosensitive liposome drug delivery system that released the drug upon hyperthermia (Koning et al., 2010). The drug loading capacity of the JR400-MoS2 NPs was high in comparison with these other reported NPs and is expected to allow for a more sustained release of drugs.

3.5. Skin penetration study

An in vitro skin penetration assay is one way to predict drug penetration in vivo and has been validated by in vitro–in vivo correlation studies (Elmowafy et al., 2019). The amount of skin penetration in the NIR-stimulated group was 125.11 ± 8.58 μg/cm², which was 2.3 times higher than the control, indicating that JR400-MoS2 NPs are suitable for TDDS applications (Figure 8(b)).

Transdermal penetration of small molecule drugs involves two critical steps: (1) drug release from the matrix and (2)
percutaneous absorption. JR400-MoS2 NPs were not able to pass through the intact skin because of their relatively large particle, but they can easily control drug released into the matrix. Intercellular lipids of the SC are the main barrier to the penetration of drugs across the skin. The diffusion coefficient of intercellular lipids of SC could be increased by rising temperature of the skin, which could increase the mobility of the intercellular lipid (Liu et al., 2017). JR400-MoS2 NPs showed excellent photothermal conversion ability and an increased diffusion coefficient for both the drug and the intercellular lipids, resulting in increased percutaneous drug absorption (Haine et al., 2017; Teodorescu et al., 2017).

3.6. In vivo skin erythema study

Visual observation of erythema is widely used to evaluate the skin irritant potential of substances. However, this method has been criticized as imprecise and subjective. A noninvasive in vivo skin erythema measurement was used to monitor irritation caused by the JR400-MoS2 NPs. As shown in Figure 9, the ΔEI increased significantly after the topical application of 10% SDS, serving as an established positive control. Application of the JR400-MoS2 NPs suspended in water did not increase ΔEI, indicating high biocompatibility.

4. Conclusions

JR400-functionalized MoS2 NPs were synthesized as a TDDS for ATE, a β1-adrenergic receptor blocking agent prescribed for hypertension. The ultra-high specific surface area of the JR400-functionalized MoS2 NPs allowed for efficient binding of ATE with 90% loading efficiency. NIR stimulation enhanced drug release and facilitated drug skin penetration. The application of JR400-MoS2 NPs as a TDDS shows the potential to mitigate issues associated with the toxicity of MoS2 use in vivo and allows for the controlled release of ATE. To our knowledge, this is the first demonstration of a functional MoS2-based TDDS. The promising results showed herein warrant further studies to evaluate the in vivo application of JR400-MoS2 NPs based TDDS.
Ethical approval

All the procedures were performed in accordance with the NIH Guidelines for the Care and Use of Laboratory Animals and were approved by the Animal Ethics Committee of Shenyang Medical College.

Disclosure statement

The authors declare no competing interests.

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