Highly luminescent biocompatible CsPbBr$_3$@SiO$_2$ core–shell nanoprobes for bioimaging and drug delivery
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The encapsulation of lead halide perovskite nanocrystals (PNCs) with an inert protective layer against moisture and the environment is a promising approach to overcome hindrances for their practical use in optoelectronic and biomedical applications. Herein, a facile method for synthesizing highly luminescent and biocompatible CsPbBr$_3$@SiO$_2$ core–shell PNCs with a controlled SiO$_2$ thickness, which are suitable for both cell imaging and drug delivery, is reported. The synthesized CsPbBr$_3$@SiO$_2$ core–shell PNCs exhibit bright green emission at 518 nm upon excitation of 374 nm. Interestingly, a significant increase in the photoluminescence intensity is observed with an increase in the SiO$_2$ shell thickness, which varies with the increasing reaction time. Cytotoxicity results indicate that the CsPbBr$_3$@SiO$_2$ core–shell PNCs are nontoxic, making them suitable for in vitro cell imaging using HeLa cells. Furthermore, doxorubicin physically adsorbed on the surface of CsPbBr$_3$@SiO$_2$ core–shell PNCs is efficiently released in cells when the drug-loaded perovskite nanoprobes are injected in the cells, indicating that these core–shell nanoparticles can be used for drug loading and delivery. The results of this study suggest that the CsPbBr$_3$@SiO$_2$ core–shell PNCs can pave the way for new biomedical applications and processes.

Introduction

Perovskite nanocrystals (PNCs) have emerged as promising materials for many applications, such as light-emitting diodes, laser devices, photodetectors, photovoltaic devices, and bioimaging.$^{1-10}$ Their excellent photophysical and electronic properties, such as their high photoluminescence (PL) quantum yield, free-carrier diffusion length, charge-carrier mobility, tunable bandgap, narrow and tunable emission, and relatively low fluorescence blinking, make them candidates for various optoelectronic and biomedical applications.$^1$ Owing to the facile and low-cost synthesis of PNCs under mild conditions, considerable efforts have been directed toward the development of high-quality PNCs with desirable properties for particular applications.$^{7,11-13}$ However, the low stability of PNCs in water, air, and polar solvents and the fast anion-exchange reactions in solution present significant challenges and have triggered numerous studies for developing environmentally stable PNCs.$^4$

In the past few decades, luminescent nanomaterials have attracted considerable attention as promising materials for diverse biomedical applications, such as bioimaging, drug delivery, and cancer cell therapy.$^{14,15}$ Consequently, in recent years, PNCs have emerged as new class of fluorescent probes for many biomedical applications, such as ultrahigh-resolution bioimaging, biosensing, and flow cytometry, owing to their excellent PL properties.$^{16-19}$ For example, their PL can be tuned over the entire visible spectral region by varying the halide ion and its size, and they have narrow photoluminescent emission and relatively low fluorescence blinking.$^{1,17}$ However, these perovskites have low stability against moisture, heat, and light, which limits their practical bioimaging applications. Although all inorganic PNCs (CsPbX$_3$; $X = \text{Cl, Br, I}$) have higher stability than organic–inorganic PNCs owing to the Cs$,^7$ which provides more stability than organic groups,$^{17,20}$ all inorganic PNCs undergo hydrolysis because of moisture in the atmosphere and aggregate into large particles over time.

A feasible approach to improve the poor stability of inorganic perovskites under environmental conditions involves coating the nanocrystals with a shell of environmentally inert or stable and water-resistant materials.$^{21-23}$ Although there are

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few reports on the encapsulation of PNCs with titanium dioxide (TiO₂) and aluminum oxide (Al₂O₃).³⁴,³⁵ these coatings reduce the luminescence efficiency, which limits the biomedical applications of PNCs. Polymers such as poly(methyl methacrylate), polyhedral oligomeric silsesquioxane, and polyostrene have also been demonstrated to improve the stability of PNCs.²⁶⁻²⁸

In a report Zhang et al. presented an approach to enhanced the stability of all-inorganic halide perovskite (CsPbX₃, X = Cl, Br, or I) nanocrystals by incorporating them in stable Zr-based metal–organic frameworks (UIO-67).²⁹ Wu and co-workers exhibited improvement in stability of all-inorganic halide perovskite by coating poly (maleic anhydride-alt-1-octadecene) polymer via postsynthetic approach.³⁰ A technique to enhance stability of CsPbBr₃ PNCs via coating mPEG-NH₂ (methoxypolyethylene glycol amine) is also demonstrated by Yan et al.３¹ Similarly, there are some other methods are also adopted to enhance the stability of PNCs by coating various materials.３²⁻³⁷ However, most of these methods are based on the fabrication of microscale colloids in which PNCs are randomly embedded, and these colloids are rarely suitable for biological applications, owing to the limited surface modification of the polymers.１,³⁸⁻⁴²

Encapsulation of PNCs with SiO₂ as a shell can serve as a facile and complementary route to improve the stability without significantly reducing the PL emission.²⁰,⁴³,⁴⁴ However, there are few reports exhibiting the use of mesoporous silica for encapsulating lead halide PNCs. Different approaches are implemented by researcher to coat SiO₂ around CsPbBr₃ PNCs to enhance stability and photoluminescence.⁴⁵⁻⁵⁰ For example, Dirin et al. demonstrated the use of mesoporous silica templates for encapsulating PNCs.３¹ Ushakov et al. showed improve stability of CsPbBr₃ PNCs by embedding in porous silica microspheres.³² The strategy to enhance the stability of CsPbBr₃ PNCs via synthesising nanocrystals in mesoporous alumina thin film is also established in a report.３³ Hu et al. investigated the enhancement in stability of CsPbBr₃ quantum dots (QDs) by embedding CsPbBr₃ QDs into waterless silica spheres.³⁴ In another report, author presented the core–shell PNCs with SiO₂ shell.³⁵ While Ding et al. used CsPbX₃/SiO₂ nanocomposites not core–shell PNCs only for bio-imaging application.２¹ However, this article with its scientific and technological originality addresses the issues which have been rarely demonstrated so far in these studies. We presented synthesis of synthesized core–shell PNCs via one-pot synthesis, application in bio-imaging and drug delivery which is not reported earlier. Additionally, we clearly demonstrated the suitability of our core–shell PNCs for both bio-imaging and drug delivery with careful study of the effect of SiO₂ shell thickness of the core–shell particles on photoluminescence (PL) properties. Consequently, SiO₂ encapsulated perovskites are biocompatible with environmental stability, making them suitable not only as bioprobes for cell imaging with their high PL but also as efficient carriers for drug delivery with their mesoporous surface.３⁵⁻⁵⁹ Present work contributes to the fascinating fields of PNCs for bio-medical applications.

Herein, we present novel biocompatible CsPbBr₃@SiO₂ core–shell PNCs with dual functions of high contrast bio-imaging and drug delivery. The CsPbBr₃@SiO₂ core–shell PNCs were successfully synthesized with SiO₂ shell thickness controlled from approximately 9 to 51 nm by varying reaction time, giving rise to the core–shell PNCs from approximately 70 to 210 nm in diameter. Interestingly, PL of the core–shell nanoparticles at the wavelength of 514–518 nm upon excitation of 374 nm was enhanced with the increasing SiO₂ shell thickness. A cell-viability test was performed to evaluate the cytotoxicity, and the results confirmed that our environmentally stable CsPbBr₃@SiO₂ core–shell PNCs are biocompatible, without toxicity arising from the hazardous Cs and Pb atoms of the nanocrystals, making them suitable for both bioimaging and drug delivery. CsPbBr₃@SiO₂-loaded HeLa cells were clearly visualized with the characteristic PL of the nanocrystals. Furthermore, doxorubicin (Dox) physically adsorbed on the surface of the CsPbBr₃@SiO₂ core–shell PNCs were efficiently delivered into the nuclei of HeLa cells.

### Experimental

#### Materials

The precursor materials—lead bromide (PbBr₂, 99.999%), cesium bromide (CsBr, 99.99%), OAm (70%), OA (90%), DMF, TMOS, and anhydrous toluene (99.95%)—were purchased from Sigma-Aldrich and used without further purification. Fetal bovine serum (FBS) (CellSera, Australia), trypsin–EDTA (Gibco, NY), CCK-8 (Dojindo, Japan), and Dox (Sigma-Aldrich, USA) were used as received.

#### Synthesis of CsPbBr₃@SiO₂ core–shell PNCs

First, 0.1468 g of PbBr₂ and 0.0851 g of CsBr were added to a solution containing 0.6 mL of OAm and 1.8 mL of OA in 10 mL of DMF. Then, the solution was kept at 100 °C until the complete dilution of PbBr₂ and CsBr. A clear solution was formed after complete dilution of PbBr₂ and CsBr. An ammonia solution (40 μL, 2.8%) was added to 2 mL of the precursor solution. Subsequently, 0.4 mL of the above final solution was quickly added to 20 mL of toluene containing 10 μL of TMOS under 1500 rpm stirring. The stirring speed was adjusted to 150 rpm after 20–25 s, and stirring was performed at this speed for 120 min. The final products were collected via centrifugation at 10 000 rpm for 10 min. Various samples were synthesized with different reaction times (1, 2, 3, 6, 12, and 24 h) in the TMOS-containing solution to examine the effect of the SiO₂ coating on the luminescence properties of the PNCs. PNCs without an SiO₂ coating were synthesized by injecting the precursor solution into 20 mL of toluene under the same conditions. Samples synthesized with reaction times of 1, 2, 3, 6, 12, and 24 h were denoted as CsPbBr₃@SiO₂–1H, CsPbBr₃@SiO₂–2H, CsPbBr₃@SiO₂–3H, CsPbBr₃@SiO₂–6H, CsPbBr₃@SiO₂–12H, and CsPbBr₃@SiO₂–24H, respectively.

#### Cell culture

HeLa cells were maintained in RPMI 1640 media (HyClone, USA) containing 10% FBS (CellSera, Australia) and a 1% (v/v)
penicillin/streptomycin solution (Hyclone, USA) in a humidified incubator at 37 °C with 5% CO₂. Cells were harvested from the subconfluent cultures using trypsin (Gibco, NY).

Cell-viability assay

The cell proliferation was assessed using a cell-counting kit (CCK-8) according to the manufacturer’s protocol. For this assay, cells were seeded in a 96-well culture plate, with 4 × 10³ cells in 100 μL of culture medium. After 24 h of cell culturing, the medium was replaced with the culture medium containing CsPbBr₃@SiO₂ core–shell PNCs at different concentrations ranging from 0 to 25 μg mL⁻¹. After 24 and 48 h of incubation, the medium was replaced with the CCK solution, followed by incubation for 3 h in the incubator. After the incubation, the absorbance at 450 nm was measured using a microplate reader (Versa Amax, USA).

Cell imaging

For bioimaging, cells were plated on a coverslip with 1 × 10⁴ cells in each well of a 24-well plate. After 24 h of incubation with the medium containing PNCs (25 μg mL⁻¹), the cells were washed with PBS (Gibco, USA) twice. Thereafter, the cells were fixed with 4% formaldehyde for 10 min and mounted using the FluoroShield mounting medium with 4’,6-diamidino-2-phenylindole DAPI (Abcam, Cambridge, MA, USA). The bioimaging was performed using a confocal microscope (Zeiss LSM 700, Germany). Z stack images were acquired by setting the thickness to 8.82 μm.

Drug loading

PNCs (5 mg) with different coating times of SiO₂ (1, 3, 12, and 24 h) were dispersed in 1 mL of PBS containing 1 mg of Dox (Sigma-Aldrich, USA). After stirring for 24 h under dark conditions, the nanocrystals were collected and measured using a microplate reader (Versa Amax, USA) at a wavelength of 485 nm to evaluate the Dox LE. The LE (%) of Dox was calculated as follows: LE = (initial drug – residual drug)/initial drug × 100%. The absorbance spectra of doxorubicin were determined at 485 nm. Several studies report that doxorubicin free drug and Dox-loaded PNCs for 24 h. The concentration of Dox ranged from 0 to 25 μg mL⁻¹. The cell viability was determined by performing a CCK assay. A Dox concentration of 25 μg mL⁻¹ was used for the free Dox and the loaded nanocrystals to evaluate the cell uptake after 3 h of treatment, as described in the cell imaging assay.

Results and discussion

Biocompatible and highly luminescent CsPbBr₃@SiO₂ core–shell PNCs were synthesized via the wet chemical method. A schematic of the synthesis of the CsPbBr₃@SiO₂ core–shell PNCs is presented in Fig. 1. A solution containing PbBr₂ and CsBr precursors was dissolved in N,N-dimethylformamide (DMF) in the presence of oleic acid (OA) and oleylamine (OAm). The resulting solution was quickly injected into toluene (poor solvent) at a high stirring rate (1500 rpm). As the precursor-containing solution was injected into toluene, CsPbBr₃ perovskite nanocrystal formation occurred immediately owing to the poor solubility. The colorless toluene solution became yellow upon the injection of the precursor solution, owing to the formation of CsPbBr₃ PNCs. Further, tetramethyl orthosilicate (TMOS) was dissolved in toluene to form an SiO₂ coating around the CsPbBr₃ PNCs. TMOS forms oligomers in toluene owing to the hydrolysis of TMOS. When the precursor-containing solution was injected into the TMOS-containing toluene, the TMOS oligomers (a small number of repeated units of TMOS molecules) present in the toluene solution tended to be adsorbed on the surface of CsPbBr₃ PNCs. This led to the formation of CsPbBr₃@SiO₂ core–shell PNCs. Furthermore, the thickness of the SiO₂ shell around the CsPbBr₃ PNCs increased with the reaction time in the TMOS-containing toluene solution, as shown in Fig. 1.

The crystal structure of synthesized CsPbBr₃@SiO₂ core–shell PNCs was examined by powder X-ray diffraction (XRD) (Fig. S1) [ESI†]. The XRD results of CsPbBr₃@SiO₂ core–shell PNCs are identical with those of CsPbBr₃ [JCPDS: 00-018-0364], which confirms that no change in crystal structure of CsPbBr₃ was made after SiO₂ coating. This XRD pattern also consistent with XRD pattern reported by Zhong et al. for CsPbBr₃@SiO₂ core–shell PNCs.20 Transmission electron microscopy (TEM) was performed to analyze the microstructure of the CsPbBr₃@SiO₂ core–shell PNCs. Fig. 2 shows TEM images of CsPbBr₃ PNCs and CsPbBr₃@SiO₂ core–shell PNCs. Fig. 2(a) presents an TEM image of CsPbBr₃ PNCs. As shown, the as-synthesized

![Fig. 1 Schematic of the synthesis of the CsPbBr₃ perovskite and CsPbBr₃@SiO₂ core–shell PNCs.](image-url)
CsPbBr₃ PNCs had a cubic structure. The size of the CsPbBr₃ PNCs was approximately 60–80 nm. There is some distortion (white dots) in TEM images which is due to the high energy electron beam of TEM. Further, Fig. 2(b–e) shows TEM images of CsPbBr₃@SiO₂ core–shell PNCs at various reaction times 1, 2, 3, and 24 h, respectively (in the TMOS-containing toluene solution). The TEM images in Fig. 2(b–e) indicate that the thickness of the SiO₂ shell around the CsPbBr₃ core increased from 9 to 51 nm with the reaction time which leads to increase size of core–shell PNCs from approximately 70 to 210 nm. This was due to the increase in the adsorption of oligomers on the CsPbBr₃ core over time.

The TEM images also reveal that the shape and size of the CsPbBr₃ PNCs changed with the increasing reaction time. This may have been due to the poor solubility of the CsPbBr₃ PNCs in the ammonium solution which required significant coating time to ensure the uniform SiO₂ shells with the targeted thickness. As shown in Fig. 2(f), the core of PNCs decreased in size with the increase of SiO₂ shell thickness with the increasing reaction time. X-Ray photoelectron spectroscopy (XPS) was performed for elemental mapping of the CsPbBr₃@SiO₂ core–shell PNCs. The EDS mapping results for the CsPbBr₃@SiO₂ core–shell PNCs are shown in Fig. S3 (ESI†). The results indicated that Cs, Pb, and Br were located at core and that Si and O were located on the shell, confirming the formation of CsPbBr₃@SiO₂ core–shell PNCs.

X-Ray photoelectron spectroscopy (XPS) was performed to analyze the surface elemental composition of the CsPbBr₃@SiO₂ core–shell PNCs. The X-ray photoelectron spectra of the CsPbBr₃@SiO₂_24H core–shell PNCs are shown in Fig. 2(g–i) and Fig. S4 (ESI†). Fig. 2(g) shows the survey scan of the CsPbBr₃@SiO₂_24H core–shell PNCs, which exhibits peaks at binding energies of 24, 68, 76, 103, 143, 155, 181, 533, and 724 eV, corresponding to Pb5d, Br3d, Cs4d, Si2p, Pb4f, Cs4p, Br3p, O1s, and Cs3d, respectively. Further, to analyze the chemical bond characteristics of the various elements in the CsPbBr₃@SiO₂_24H core–shell PNCs, such as Cs, Pb, Br, Si, and O, the bonding states of each element were investigated. Fig. 2(h, i) and Fig. S4 (ESI†) show the X-ray photoelectron spectra of Cs3d, Pb4f, Br3d, Si2p, and O1s. As shown in Fig. 2(h), the Cs3d X-ray photoelectron spectrum exhibited two peaks at binding energies of 724 and 738 eV. The Pb4f X-ray photoelectron spectrum also exhibited two peaks, at binding energies of 138.5 and 143.5 eV, as shown in Fig. S4(a) (ESI†). The X-ray photoelectron spectra of Br3d showed peaks at 68.7 eV, as shown in Fig. S4(b) (ESI†). The X-ray photoelectron spectra of Si2p, and O1s exhibited peaks at 103.5 and 532.7 eV, as shown in Fig. 2(i) and Fig. S4(c) (ESI†), respectively.

Ultraviolet-visible (UV-vis) absorption spectroscopy and PL spectroscopy were performed to investigate the optical properties of the as-synthesized CsPbBr₃ perovskite and CsPbBr₃@SiO₂ core–shell PNCs. The UV-vis absorption spectrum of the CsPbBr₃ PNCs is shown in Fig. 3(a). A broad absorption peak was observed at a wavelength which is centered at 492 nm, which is consistent with previous reports. Thus, UV spectrum shows that the is no significant effect of SiO₂ coating on UV absorption. The emission spectrum of the CsPbBr₃ PNCs at 374-nm excitation is shown in Fig. 3(b). The CsPbBr₃ PNCs exhibited bright green emission at 518 nm. Further, the PL spectra of CsPbBr₃ PNCs and CsPbBr₃@SiO₂ core–shell PNCs synthesized with different durations of 1, 2, 3, 6, 12, and 24 h are presented in Fig. 3(c). Fig. 3(c) shows the highest emission intensities for the CsPbBr₃ PNCs and CsPbBr₃@SiO₂ core–shell PNCs, which were centered at 518 and 515 nm, respectively. The PL emission of the CsPbBr₃@SiO₂ core–shell PNCs increased significantly with the increasing thickness of the SiO₂ shell around the CsPbBr₃ PNCs. The change in the PL emission intensity with respect to the SiO₂ coating time is presented in Fig. 3(d). After more than 24 hours, the resulting CsPbBr₃@SiO₂ core–shell PNCs were settled down due to colloidal instability of the particles. PL measurement was hardly done with the suspension of such large particles. There are various reasons for the increase in the PL emission intensity of the CsPbBr₃@SiO₂ core–shell PNCs: (1) surface passivation of the CsPbBr₃ PNCs due to the coating of the silica on the CsPbBr₃ (i.e., surface traps and defects) which was well observed and explained in many previous reports; (2) the reduction in the size of the PNCs (as revealed by TEM), which may have increased the PL emission because the crystal-size reduction favored exciton recombination due to dielectric confinement; and (3) another reason of increase in PL intensity may be the numerous CsPbBr₃ PNCs formed by decomposition due to NH₄OH. NH₄OH can possibly decompose large particles with an extended reaction time; thus, the number of CsPbBr₃ PNCs with a reduced size increased, increasing the PL intensity. (4) The
dipole ordering of A-site cations affected by the crystal orientation can also influence the PL efficiency. The size of the CsPbBr₃ perovskite was initially large, and it decreased with the increasing reaction time, as discussed above, which may have resulted in CsPbBr₃ perovskite with a preferred orientation. Further, the photoluminescence quantum yield (PLQY) of PNCs were measured via FP-8500 spectrophotometer with integrated sphere at excitation wavelength of 365 nm, whereas rhodamine B was used for excitation spectrum correction prior to measurement. The PLQY obtained for CsPbBr₃ PNCs and CsPbBr₃@SiO₂ core–shell PNCs were 0.42% and 10.2%, respectively. It was observed that the PLQY of CsPbBr₃ PNCs low. Our pristine CsPbBr₃ PNCs were synthesized at room temperature by a relatively simple and easy process, based on anti-solvent treatment while various PNCs have been frequently synthesized by hot injection method for high quality crystallinity and performance. In the hot injection methods, PNCs surfaces are readily modified with surface ligands, resulting in securely passivated nanocrystals with high crystallinity. On the other hand, in the case of the anti-solvent method we employed at room temperature, highly crystalline PNCs are resulting in securely passivated nanocrystals with high crystallinity. Moreover, the blue shift in the emission spectrum may have been due to the lattice distortion of the Pb–Br bonds in the CsPbBr₃ perovskite nanocrystal caused by the grain-size reduction. Fig. 3(e) shows photographs of CsPbBr₃ PNCs and CsPbBr₃@SiO₂ core–shell PNCs at different reaction times of 1, 2, 3, 6, 12, and 24 h under 365 nm-wavelength light. The figure clearly indicates the significant improvement in the green emission of the CsPbBr₃ perovskite with the increasing thickness of the SiO₂ shell or reaction time in TMOS. Fourier transform infrared (FTIR) spectroscopy was performed to analyze the chemical bonding of the CsPbBr₃@SiO₂ core–shell PNCs. The FTIR spectrum of CsPbBr₃@SiO₂ core–shell PNCs synthesized with a reaction time of 24 h because they had the highest photoluminescent emission intensity and water stability and the best mesoporous structure among the samples synthesized in this study. Before the toxicity of the CsPbBr₃@SiO₂ core–shell PNCs was tested, the water stability was examined. The PL emission spectrum of the CsPbBr₃ PNCs in water at 374 nm excitation is shown in Fig. 4(a). A photograph of CsPbBr₃@SiO₂ core–shell PNCs dispersed in water (1 mg/3 mL) under normal daylight and UV light (365 nm) is presented in inset of Fig. 4(a). As shown, the CsPbBr₃@SiO₂ core–shell PNCs were stable in water and exhibited a bright green color under UV light. Fig. S7(a) shows photographs of core–shell PNCs dispersed in water under UV light after 24 h, respectively. The PL emission spectra of core–shell PNCs dispersed in water and after 24 h is illustrated in Fig. S8 (ESI†). The obtained results reveal that PL emission did not decrease much (remain ~80% of initial PL intensity). These results divulge that the core–shell PNCs were highly stable in water.

The biocompatibility of the CsPbBr₃@SiO₂ core–shell PNCs was evaluated via a cytotoxicity test. The cytotoxicity of the CsPbBr₃@SiO₂ core–shell PNCs to HeLa cells was investigated by performing a CCK-8 assay. The cells were treated with CsPbBr₃@SiO₂ core–shell PNCs at concentrations ranging from 0.01 to 25 µg mL⁻¹. Fig. 4(b) presents the cell viability in this concentration range. As shown, there was no difference in the cell viability after 24 and 48 h of treatment compared with the untreated group. Thus, the cytotoxicity test revealed that the synthesized CsPbBr₃@SiO₂ core–shell PNCs had low cell toxicity at concentrations up to 25 µg mL⁻¹. Consequently, these nanocrystals can be used for biomedical applications.
applications. Cellular permeability without toxicity is critical for the fluorescent nanomaterials. The confocal fluorescence image indicated that the nanocrystals induce endocytosis to cells. A schematic of the proposed mechanism whereby the core–shell PNCs induce endocytosis to cells is presented in Fig. 4(c). The fluorescence-imaging capability of the nanocrystals was evaluated via cellular-uptake experiments using HeLa cells. The cells were analyzed using a confocal microscope. The nanocrystal-treated HeLa cells exhibited green fluorescence with the excitation of 488 nm light. According to the merge images, the nanocrystals were internalized by the HeLa cells and localized in the cytoplasm (Fig. 4(d)). The confocal z-stack of HeLa cells also confirmed the internalization and localization of nanocrystal in the cytoplasm (Fig. S9, ESI†).

The application of nanoparticles as drug carriers is a promising method for enhancing the delivery efficiency of the drug-delivery system and reducing the side effects of the drug.69,70 To demonstrate the drug-delivery application of the CsPbBr3@SiO2 core–shell PNCs, doxorubicin (Dox) (broad-spectrum antitumor anthracycline antibiotic) was used as a drug. CsPbBr3@SiO2 core–shell PNCs synthesized with different reaction times (1, 3, 12, and 24 h) were loaded with Dox. The drug loading efficiency (LE) of the CsPbBr3@SiO2 core–shell PNCs synthesized with different reaction times (1, 3, 12, and 24 h) is presented in Table 1. The drug LE increased with an increase in the SiO2 (shell) thickness around the CsPbBr3 PNCs owing to the increase in the surface area of the core–shell nanocrystals (Table 1). The loading efficiency was the highest (42.1%) for the CsPbBr3@SiO2 core–shell PNCs with a synthesis time of 24 h. Therefore, the CsPbBr3@SiO2 core–shell_24H PNCs were used for the drug-release study. The cumulative release profile of the drug (Dox) from drug-loaded CsPbBr3@SiO2 core–shell PNCs in phosphate-buffered saline (PBS, pH of 7.4) is illustrated in Fig. 5(a). As shown, 18% of the Dox was released within 2 h, and the release slowed over time. The release of drug absorbed on the surface of nanoparticles includes the steps of the surface absorption and diffusion of drug, followed by the erosion of the nanoparticles. The rapid drug release from the nanoparticle is called “burst release”, often observed in the initial time period.71 The burst release is attributed to the drug which is weakly bound to the outer surface area. In our experiment, doxorubicin drug was loaded on the surface of perovskite nanocrystal which showed 18% burst release in the initial phase, followed by the substantial release for two weeks.72–75

Moreover, the cytotoxic effects of the drug-loaded CsPbBr3@SiO2 core–shell PNCs were tested. The results indicated that the cytotoxic effects increased with the concentration of free Dox. The amount of Dox adsorbed onto the CsPbBr3@SiO2 core–shell PNCs was identical to the amount of free Dox, and their cytotoxicity was compared. The results indicated that the activity of the Dox-loaded CsPbBr3@SiO2 core–shell PNCs was similar to that of the free Dox (Fig. 5(b)). The cellular internalization mechanisms differed between the free Dox and the nanocrystals. The Dox-loaded CsPbBr3@SiO2 core–shell PNCs were internalized through endocytosis, whereas the free Dox was internalized through passive diffusion, which is a quick process compared with endocytosis.56,76 A schematic of the proposed mechanisms of drug loading and release using the CsPbBr3@SiO2 core–shell PNCs is presented in Fig. 5(c). The electrostatic interaction between the positively charged Dox molecules and the negatively charged nanocrystals may be the reason for the drug loading on the nanocrystals.20 It is well known that the SiO2 surface exhibits porosity.77,78 Therefore, another possible reason for the drug loading on the CsPbBr3@SiO2 core–shell PNCs is the adsorption of Dox molecules into the pores of the nanocrystals.

The electrostatic interaction between the positively charged Dox molecules and the negatively charged nanocrystals may be the reason for the drug loading on the nanocrystals.20 It is well known that the SiO2 surface exhibits porosity.77,78 Therefore, another possible reason for the drug loading on the CsPbBr3@SiO2 core–shell PNCs is the adsorption of Dox molecules into the pores of the nanocrystals.

### Table 1. Drug LE of the CsPbBr3@SiO2 core–shell PNCs

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adsorption–desorption isotherm of the CsPbBr₃@SiO₂ nanocrystals, which indicates that the CsPbBr₃@SiO₂, 24H nanocrystals had a mesoporous characteristic. The obtained BET results are presented in Table S1 (ESI†). These results indicate that the average size of the mesopores in the CsPbBr₃@SiO₂ nanocrystals was ~3 nm. The zeta (ζ) potential of the CsPbBr₃@SiO₂, 24H core–shell PNCs is shown in Fig. S12 (ESI†). It was found to be −19.38 mV. The zeta-potential measurement indicated that the CsPbBr₃@SiO₂, 24H core–shell PNCs had a negatively charged surface. The SEM, BET, and zeta-potential results supported the proposed drug-loading and release scheme (Fig. 5(c)).

The slower release of the drug from the CsPbBr₃@SiO₂ core–shell PNCs could be advantageous, as it increases the bioavailability of the drug, improving the cell cytotoxicity. The uptake of Dox-loaded CsPbBr₃@SiO₂ core–shell PNCs was examined via confocal imaging. After 3 h of incubation, red fluorescence signals from Dox molecules were observed mainly in the cytoplasm, suggesting that Dox was loaded in the CsPbBr₃@SiO₂ core–shell PNCs and that endocytosis of the HeLa cells occurred.

The observed bright red dots were related to the aggregated carriers in the cytoplasm, whereas the homogeneous red fluorescence in the nuclei corresponded to the free Dox molecules (Fig. 5(d)). The comparison between some of previous study and our present experiment is shown in Table S2 (ESI†). Hence, the encapsulation of the PNCs with SiO₂ increased their water stability and biocompatibility, which is beneficial for biomedical applications.

**Conclusion**

We developed CsPbBr₃@SiO₂ core–shell PNCs with improved stability via a rapid injection method at room temperature. The formation of the SiO₂ shell around the CsPbBr₃ PNCs enhanced the stability of the perovskite. The CsPbBr₃ and CsPbBr₃@SiO₂ core–shell PNCs exhibited green emission at 518 and 515 nm, respectively, under excitation of 374 nm. Further, via the proposed approach, the PL emission of the PNCs was enhanced with the increasing thickness of the SiO₂ shell around the nanocrystal core. A cytotoxicity test indicated that the CsPbBr₃@SiO₂ core–shell PNCs were biocompatible, making them suitable for biomedical applications. The CsPbBr₃@SiO₂ core–shell PNCs were also investigated as fluorescent nanoprobes for in vitro bioimaging using HeLa cells and for drug-delivery applications. The results of this study indicate that the CsPbBr₃@SiO₂ core–shell PNCs are suitable for novel biomedical applications.

**Conflicts of interest**

There are no conflicts to declare.

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**Notes and references**


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