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Isomer-Dependent Adsorption and Release of Cis- and Trans-platin Anticancer Drugs by Mesoporous Silica Nanoparticles

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We report on adsorption and release of the anticancer drugs cisplatin and transplatin from mesoporous silica nanomaterials, emphasizing the differences between cisplatin and its much less toxic isomer. Two types of particles, MCM-41 and SBA-15, were used, either as just synthesized or after calcination to remove the templates. The particles were characterized by TEM, nitrogen physisorption, and elemental analysis. The UV−vis spectra of cisplatin and transplatin were obtained and the intensities of several bands (205−210 nm, 210−220 nm, 220−235 nm, and 300−330 nm) were found proportional to drug concentrations, allowing their use for measuring drug concentration. To evaluate drug adsorption by nanoparticles, nanoparticles were incubated in drug solutions and removed by centrifugation, after which the supernatants were scanned by spectrometer to determine drug remaining. It was found that calcined MCM adsorbed less cisplatin or transplatin per particle than as-synthesized MCM. SBA nanoparticles adsorbed slightly more cisplatin than MCM, and slightly less transplatin. Measurements of drug adsorption as a function of time show that drug is rapidly adsorbed by all particles studied. This rapid adsorption is probably associated with adsorption of drug on the external surfaces of the particles as well as the possible physisorption within the surfactant assemblies or by replacing the surfactant molecules or ions in the case of the as-synthesized materials. For calcined SBA particles, it is followed by a slow take-up of drug, perhaps due to the internal pores. There is no slow take-up by as-synthesized SBA particles or by either as-synthesized or calcined MCM particles. Measurement of the release of platinum drugs from nanoparticles previously soaked in drug solutions showed a substantial quick release for all particles and both drugs. This was followed by a slow release of Pt species in the case of transplatin in calcined SBA.

Introduction

The tunable syntheses of functionalized nanomaterials have promised a great future for their applications in biological systems, such as drug or bimolecular delivery and medical imaging.[1−4] It has been well recognized that biocompatibility of nanoparticles depends on their physical and chemical properties. Changes in material composition, particle size, shape, surface area, or, if applicable, porosity and functional groups could induce different biological effects. The potential nanotoxicity becomes very important when nanoparticles serve as drug hosts.[5−9] Moreover, the physical properties of nanomaterials determine their capacities to load and unload guest molecules. Therefore, finding nanoparticles to serve as effective drug delivery vehicles demands efforts in reducing cytotoxicity, improving site-specific delivery, and managing drug adsorption or release properties in a controlled manner.

Since the debut of MCM-41 on the nano stage in the early 1990s,[10] mesoporous silica nanomaterials (MSN) have shown exceptional promise for biological applications, gene and drug delivery in particular, due to their large surface area and well-ordered porosity.[2−4] Because of recent achievements in size and morphology control,[11] mesoporous silica nanoparticles (MSN) offer the possibility of lodging a variety of drug molecules.[12−23] In addition, functionalized groups tethered, either inside the mesoporous channels or on the external surfaces, may facilitate drug

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adsorption and release through customized chemical affinity. Two of the most common MSN, SBA-15, and MCM-41, display well-defined arrays of pores and cylindrical mesostructures packed in hexagonal geometry.[24] The differences between MCM-41 and SBA-15-type MSN are mainly in pore dimension and to some extent in particle size and wall thickness. These nanomaterials are currently considered as promising carriers for drugs and biomolecules. We recently reported that MSN interfered with intracellular mitochondrial functions, including oxygen consumption and ATP formation, in a manner dependent on their physical properties.[9]

The nature of the transported drug may also complicate its delivery by nanomaterials. The chemical reactions of drugs (including isomerization) determine their therapeutic effect, but may also affect drug loading by nanoparticles. For instance, Δ^9-tetrahydrocannabinol (THC), a double-bond isomer of Δ^8-THC, exhibits a much higher psychotropic potency to affect central neural system than Δ^8-THC does.[25] Cisplatin, the first platinum-based chemotherapy drug, is much more cytotoxic than its geometric isomer transplatin. The isomers yield different antitumor activity and toxicity profiles, including reactivity with DNA and induction of apoptosis.[26,27] They should also differ in their adsorption and release by nanoparticles, since hydrophilicity or solubility may be different for different isomers.[25]

Here we report on the significant differences in adsorption and release properties of cisplatin and its less toxic isomer transplatin, within and from mesoporous silica nanomaterials. We first investigate, using UV−vis spectroscopy, the encapsulation of cisplatin and transplatin into two types of MSN, SBA-15 and MCM-41. We compare the two materials as-synthesized with the materials after calcination to show drug adsorption inside the mesoporous channels. We stress the effect of the difference between the isomeric platinum drugs on their adsorption by MSN. The time-dependent release behaviors of platinum drug-loaded nanomaterials are studied subsequently.

Experimental Section

Materials and Reagents. Phosphate-buffered saline (1x PBS, without Mg^{2+} and Ca^{2+}, pH = 7.4) was purchased from Mediatech (Herndon, VA). Cetyltrimethylammonium bromide (CTAB), tetraethylorthosilicate (TEOS) and poly(ethylene oxide)-*block*-poly(butylene oxide)-*block*-poly(ethylene oxide) (Pluronic P123 or P123, MW = 5800) were obtained from Sigma-Aldrich. Cisplatin and transplatin (yellow powder, m.w. 300.05) were obtained from Sigma-Aldrich and dissolved in PBS before experiments. Cisplatin (1 mg/mL for injection, ~3.3 mM in 154 mM NaCl) was purchased from American Pharmaceutical Partners (Schaumburg, IL).

Synthesis and Characterization of SBA-15 and MCM-41. Mesostructured MCM-41 and SBA-15 type nanomaterials (or labeled here as MCM and SBA) were synthesized by previously reported procedures with minor modification,[1−5] both followed by calcinations to remove the surfactants. The particles were used as-synthesized (SBAsyn and MCMsyn) or further calcined (SBAcal and MCMcal). Nitrogen physisorption measurement was then carried out for all the nanomaterials at 77 K after outgassing the samples at 433 K for 2 h, using a Micromertitics Tristar 3000 volumetric adsorption analyzer. The characterizations also yielded total BET surface area and pore size distributions for each sample. Besides, elemental analysis was employed as well to measure the C, H, and N contents in all the particles by weight.

Correction of UV−Vis Spectra. Absorption spectra of solutions of cisplatin or transplatin were measured between 190 and 800 nm. In order to eliminate the effect of instrumental errors, each spectrum obtained was corrected as follows: The measured absorbance intensities for wavelengths between 800 and 500 nm were fitted to a line. Since the drugs do not absorb in this region, these small intensities represent an instrumental artifact. The linear function, extended to the spectral region from 500 to 200 nm, was subtracted from the original absorbance readings. The resulting subtracted intensities were utilized in all calculations throughout this study.

Adsorption of Platinum Compounds by Nanomaterials. Cisplatin and transplatin were dissolved in PBS immediately before the experiments. One of four different nanoparticles, MCMsyn, MCMcal, SBAsyn, and SBAcal, was added into the drug solution and soaked with constant stirring. After the desired time period, 2 mL solution was removed from the container and centrifuged at 5585*g* for 10 min to remove the nanoparticles. The resulting supernatant was carefully collected and the residual concentration of platinum compounds was then determined spectroscopically, using a Lambda 950 UV−vis spectrophotometer (PerkinElmer). However, it was found that centrifugation did not suffice to completely remove silica from solution. The residual nanoparticle fragments (and possibly, template) scattered light at the wavelengths used for measuring drug concentration, which appeared as absorption. To correct this, we measured the apparent absorption spectrum of the supernatant from solutions containing no drug, in which nanoparticles had been soaked. This spectrum was subtracted from the absorption spectrum of the supernatant obtained by centrifuging a drug solution containing nanoparticles at the same concentration.

HPLC Analysis. We used HPLC to show any possible drug-surfactant chemical interaction was absent. The possible interaction between platinum drugs and P123 or CTAB in the solutions was studied by a Beckman reversed-phase HPLC system, which consisted of an automated injector (model 507e) and a pump (model 125). The column, 4.6 × 250 mm Beckman Ultrasphere IP column, was operated at room temperature (25 °C) at a flow rate of 0.5 mL/min. The run time was 30 min and the mobile phase was 1% (v/v) methanol in dH_2O. Here, 1 mM samples of cisplatin and transplatin in PBS were incubated with or without 10 mg/mL CTAB or P123 for 16 h. Then a 40 μL solution from each condition was diluted in 2 mL of dH_2O, and 10 μL injections were run on HPLC. The detection wavelengths were fixed at 210 and 300 nm, respectively. A single peak was observed at retention time ~5 min in all the samples and the area of this peak was evaluated. The variation of peak area in all conditions was $< 5.1\%$. In each condition measurements were performed again 48 h later. The interday variations of peak areas for the same injection were found to be between 0.1% and 5.9%. Thus, it is clear that the solution of platinum drugs is stable and there is no chemical reaction between platinum drugs and templating chemicals (CTAB or P123).

Results and Discussion

The syntheses of the MCM-41 and SBA-15 types of MSN were carried out by supramolecular self-assembly techniques, following the reported procedures with minor modification[10,28−31] (see Supporting Information for details). The nanomaterials as synthesized were labeled SBAsyn and MCMsyn, respectively.

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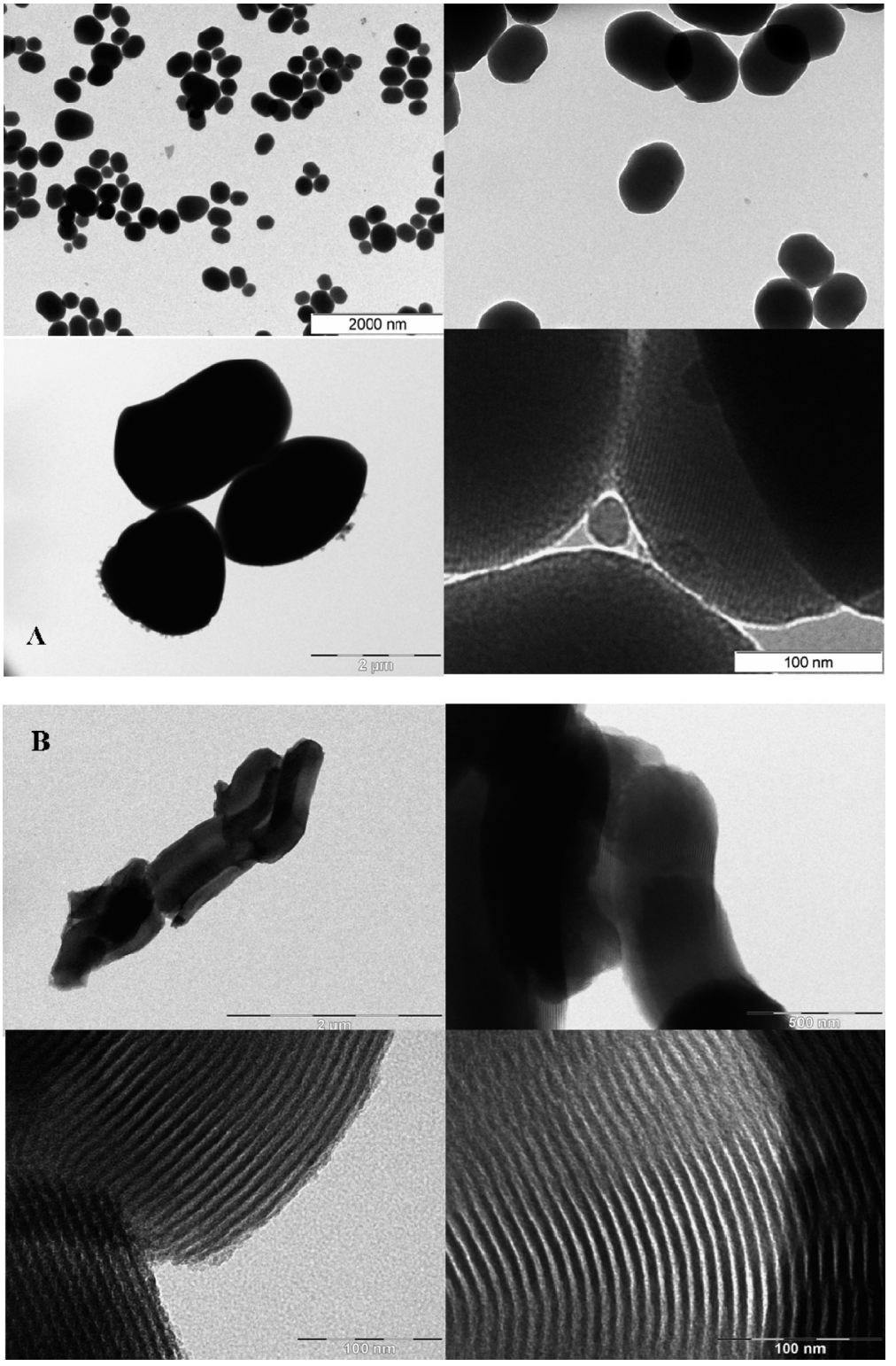

Figure 1. TEM images of calcined MCM-41 (A) and SBA-15 (B) that are labeled as MCMcal and SBAcal, respectively.

In both cases, synthesis was followed by calcination to remove the template, resulting in the formation of MSN, denoted as MCMcal and SBAcal, respectively. The transmission electron microscopy (TEM) images (Figure 1) show that the calcined MCM-41 materials are rather regular spherical or oval shaped particles (~350 nm in diameter), while the calcined SBA-15 materials are irregularly shaped particles spanning a larger size range (300−650 nm). The TEM images also indicate that the materials have highly hexagonally ordered mesoporous structures. The materials were further characterized by surface area measurements using nitrogen physisorption. The mesoporous nanoparticles show Type IV isotherms with steep capillary condensation steps (see Supporting Information, Figure S1), confirming the presence of uniform mesopores with large surface areas.

The adsorption of cisplatin or transplatin by SBA and MCM-type nanomaterials was derived from the decrease in concentration of platinum drug in the solution after exposure to the nanomaterials. For calibration purposes, the platinum drugs were

dissolved in PBS (pH = 7.4) and the solutions were measured spectroscopically. The wavelength was scanned from 800 to 190 nm. UV−vis spectra of 1.0 mM cisplatin and transplatin in PBS are shown in Figures 2A and 2C, respectively. Each spectrum was corrected by background subtraction as stated in the Experimental Section. Figure 2A shows that cisplatin displays a strong absorption (charge-transfer band) at 208 nm, with molar extinction coefficient (ε_M) of 3145 M^{-1} cm^{-1}. In addition, it exhibits a much weaker band at 300 nm, with ε_M calculated as 117 M^{-1} cm^{-1} (from the d−d transitions of the square planar Pt^{2+} ion.[32]) Absorption was measured for cisplatin concentrations from 20 μM to 1.2 mM. To minimize possible errors of instrumental origin such as slight shifts in wavelength over time, we report, instead of absorbance at a single wavelength, the absorbance over a band, i.e. the sum of intensities for a range of wavelengths.

In Figure 2B are shown integrated intensities for cisplatin for 205−210 nm (open squares), 210−220 nm (filled squares), 220−235 nm (open triangles) and 300−330 nm (filled triangles), as functions of drug concentration. We avoided wavelengths below 200 nm, since the spectrophotometer has its measurement limit at 190 nm and the intensities obtained in the neighboring region are not reliable. Linear regression of band intensity vs concentration for cisplatin gave the following results ([cisplatin] is in μM): For the 205−210 nm band, S (integrated intensity) = $(254.0 \pm 13.0) \times 10^{-4}$ [cisplatin] $\pm$ (0.725 ± 1.602) ($r^2 = 0.906$); for the 210−220 nm band, $S = (185.9 \pm 13.2) \times 10^{-4}$ [cisplatin] + (0.958 ± 0.965) ($r^2 = 0.952$); and, for the 220−235 nm band S = $(105.5 \pm 4.5) \times 10^{-4}$ [cisplatin] + (-0.053 ± 0.325) ($r^2 = 0.982$). The intercept is statistically zero in each case. For the 300−330 nm band, $S = (20.5 \pm 0.7) \times 10^{-4}$ [cisplatin] + (-0.266 ± 0.054) (r^2 = 0.987), the slightly negative intercept probably being due to the low reliability of the small intensities obtained for low concentrations. An intercept which is statistically zero means that band intensity is proportional to drug concentration, indicating that the absorbance all originates with the same compound and that any band intensity can be used as a measure of drug concentration.

In Figure 2C, the spectrum of transplatin at 1.0 mM shows two differences from that of the *cis*-isomer. First, there is an absorption peak at 203 nm (ε_M = 2013 M^{-1} cm^{-1}), which is weaker than the one for cisplatin at 208 nm. This implies a weaker charge-transfer transition for the *trans*-compound. Second, instead of one band near 300 nm in the case of cisplatin, there appear two bands with peaks at 269 and 313 nm (ε_M = 34 and 23 M^{-1} cm^{-1}, respectively), probably due to the distorted d−d transitions within a *trans* square planar structure. Band intensities for [transplatin] from 60 μM to 1.6 mM are shown in Figure 2D. As with cisplatin, the sums of the intensities for 205−210 nm (open squares), 210−220 nm (filled squares), 220−235 nm (open triangles), and 300−330 nm (filled triangles) were measured, and linear regression was carried out on band intensity vs drug concentration. The following results were obtained ([transplatin] is in μM): for the 205−210 nm band S (integrated intensity) = $(87.6 \pm 1.1) \times 10^{-4}$ [transplatin] + (0.110 ± 0.091) ($r^2 = 0.999$); for the 210−220 nm band, $S = (94.3 \pm 0.8) \times 10^{-4}$ [transplatin] + (0.049 ± 0.068) ($r^2 = 0.999$); for the 220−235 nm band, $S = (48.9 \pm 0.4) \times 10^{-4}$ [transplatin] + (0.042 ± 0.032) ($r^2 = 0.999$); for the 300−330 nm band, $S = (5.7 \pm 0.2) \times 10^{-4}$ [transplatin] + (-0.006 ± 0.018) ($r^2 = 0.988$). The intercept is statistically zero in each case; therefore, intensities of all bands are proportional to [transplatin], proving that all bands are due to platinum-containing species.

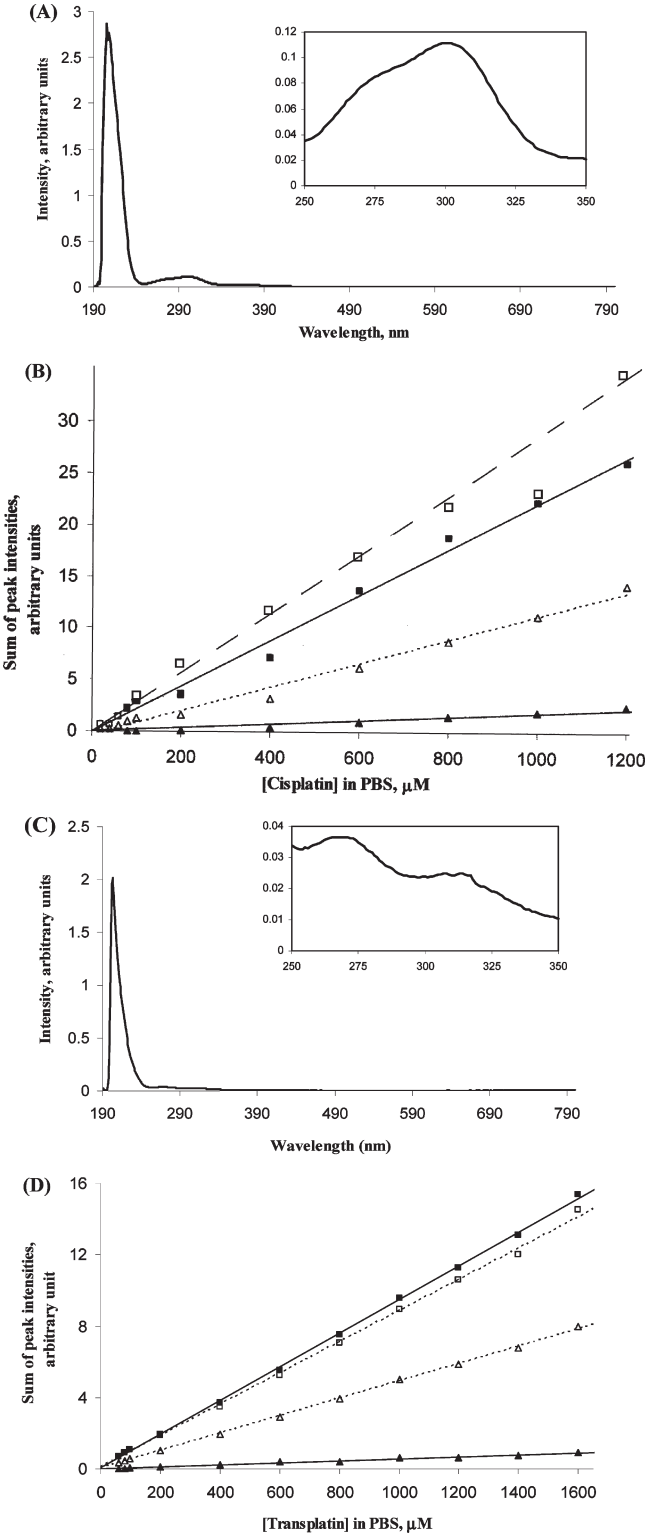

Figure 2. UV−vis spectrum of 1.0 mM cisplatin (A) or transplatin (C) freshly dissolved in PBS. Integrated intensities from cisplatin (B) and transplatin (D) for 205−210 nm (open squares), 210−220 nm (filled squares), 220−235 nm (open triangles) and 300−330 nm (filled triangles), as functions of [platinum drugs] in μM. Linear regressions of these integrated intensities versus drug concentration were employed, giving fitted lines for 205−210 nm (dashed line), 210−220 nm (solid line), 220−235 nm (dotted line), and 300−330 nm (solid line).

Thus, all band intensities can be used to measure transplatin concentrations.

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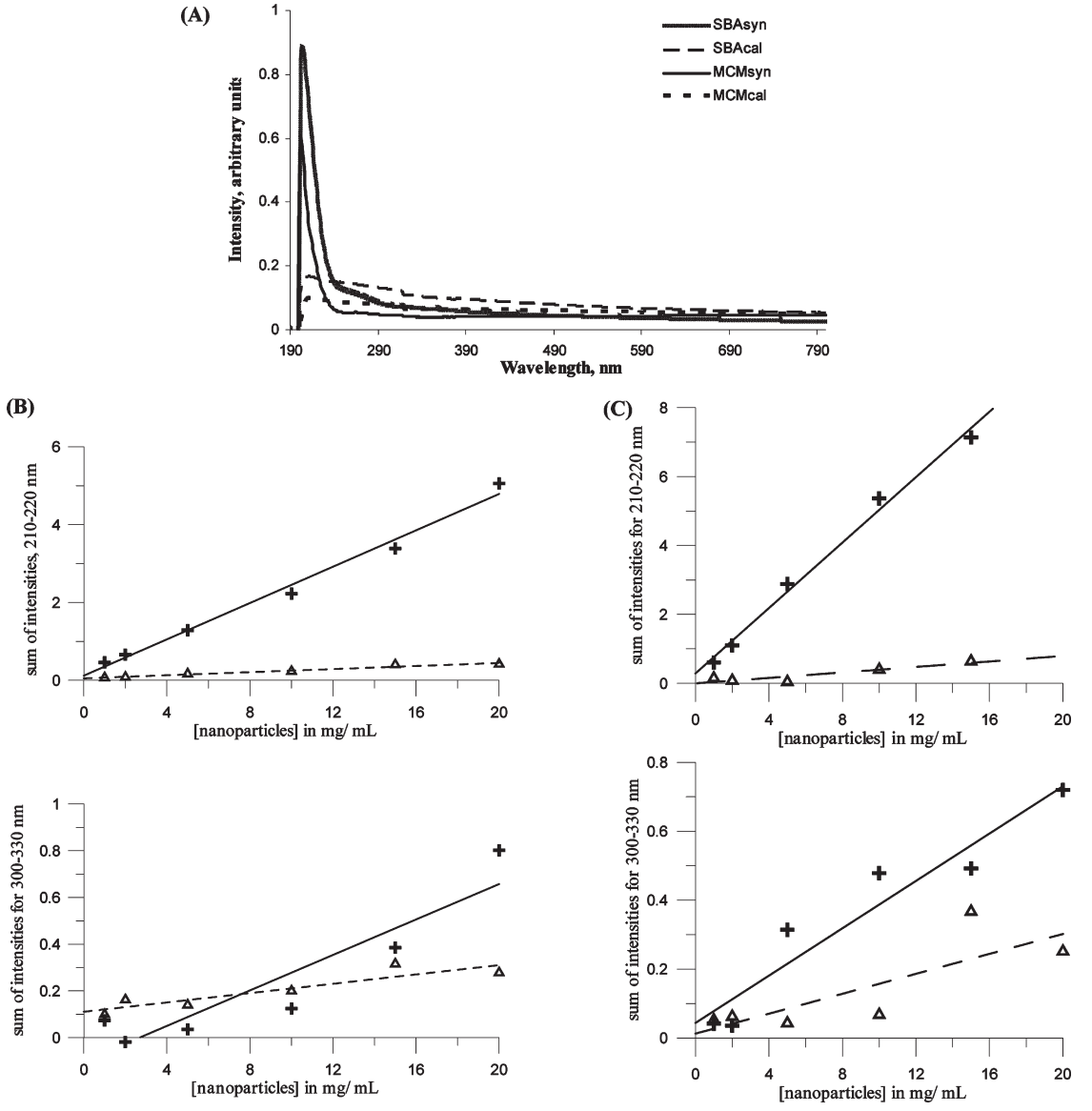

Figure 3. (A) Pseudoabsorption spectra of nanoparticles. The 10 mg/mL SBAsyn (solid gray line), SBAcal (dotted gray line), MCMsyn (solid line), and MCMcal (dotted line) samples were first dissolved in PBS, respectively. The suspensions were sonicated and centrifuged at 5,585 g for 10 min. The supernatant was then collected for spectroscopic measurements. The resulting "absorptions" are due to the scattering from the nanoparticle residues in the solutions. The scattering intensities of MCM (B) and SBA (C) nanoparticle residues were thus plotted versus original addition of nanoparticles (1, 2, 5, 10, 15, and 20 mg/mL, respectively). Band intensities for 210−220 nm (upper panel) or 300−330 nm (lower panel) are fitted into linear functions of the amount of nanoparticles that were originally added in PBS. "+" symbols and solid line for particles as-synthesized; "△" symbols and dashed line for particles calcined.

Since nanoparticle suspensions appear to absorb radiation, we investigated the apparent absorption spectra of nanoparticle suspensions. Nanoparticles (MCMsyn and MCMcal, SBAsyn, and SBAcal) were added to PBS (10 mg/mL for each sample), sonicated until well suspended and then centrifuged. The spectra of the supernatants are shown in Figure 3A. The "absorptions" are due to the scattering from the nanoparticle residues (possibly including the residual surfactants) in solution. For solutions with SBAsyn residues (solid gray line), the spectrum shows peak "absorption" at 203 nm, near the region of strong absorption for cisplatin and transplatin. The scattering intensities near 300 nm are much smaller, but still high compared to those of platinum drugs. For solutions with SBAcal residues (dotted gray line), the major absorption around 200 nm vanishes, but the scattering intensities in the other regions are generally increased. Scattering is lower for MCM nanoparticles than for their SBA counterparts, possibly because, for the same mass, there are fewer MCM-type particles than SBA-type particles. A maximum "absorbance" occurred at 202 nm for the solutions with MCMsyn residues (solid line), but there is no evident peak in the spectrum of solutions with MCMcal residues (dotted line).

We added different amounts of nanoparticles (1, 2, 5, 10, 15, and 20 mg/mL) to PBS solutions, centrifuged out the precipitates, and measured the scattering intensities of the nanoparticle residues. As for the spectra of platinum solutions, the intensities from 210 to 220 nm or from 300 to 330 nm were combined. Results are shown in Figures 3B (MCM) and 3C (SBA). In some cases, the intensities are appreciable compared to the absorbance of cisplatin or transplatin in the same wavelength regions. In Table 1, we show the results of the linear fits for four spectral bands for all four particles. For each of the 16 cases are listed the slopes and y-intercepts with their statistical errors, plus the R^2 value. It can be

Table 1. Linear Fits to Band Intensities from Scattering of SBA and MCM

nanoparticle	band (nm)	slope	intercept	R^2
SBAsyn	205−210	0.337 ± 0.031	0.352 ± 0.262	0.975
	210−220	0.475 ± 0.026	0.285 ± 0.218	0.991
	220−235	0.250 ± 0.027	0.317 ± 0.309	0.954
	300−330	0.034 ± 0.005	0.044 ± 0.057	0.919
SBAcal	205−210	0.012 ± 0.006	0.043 ± 0.049	0.599
	210−220	0.040 ± 0.010	−0.003 ± 0.082	0.849
	220−235	0.029 ± 0.017	0.013 ± 0.186	0.438
	300−330	0.015 ± 0.005	0.013 ± 0.060	0.650
MCMsyn	205−210	0.189 ± 0.006	0.095 ± 0.066	0.996
	210−220	0.233 ± 0.013	0.120 ± 0.147	0.988
	220−235	0.139 ± 0.016	−0.040 ± 0.176	0.952
	300−330	0.038 ± 0.008	−0.102 ± 0.089	0.850
MCMcal	205−210	0.007 ± 0.001	0.008 ± 0.015	0.859
	210−220	0.020 ± 0.002	0.051 ± 0.022	0.962
	220−235	0.026 ± 0.003	0.059 ± 0.032	0.953
	300−330	0.034 ± 0.003	0.148 ± 0.029	0.977

seen that the *y*-intercept differs significantly from zero only for the 300−330 nm band of MCMcal (this apparent exception may be due to the experimental errors in the small intensities). An intercept close to zero, with large R^2, shows intensity of scattering by residual particles is proportional to the concentration of nanoparticles before centrifugation, which implies that multiple scattering is unimportant. The proportionality justifies using the fits of Table 1 to estimate the scattering due to nanoparticle fragments and templating material. This scattering intensity can then be subtracted from measured absorption band intensities for drug + nanoparticle conditions. In every case (including the 300−330 nm band of MCMcal, which has very small intensity), the error in the estimated scattering intensity is small enough so that the subtraction does not introduce large errors.

It is possible that the apparent absorption in the spectra of as-synthesized SBA and MCM nanomaterials results from strong absorption by surfactant residues. Experiments were thus performed to verify the influence of these templating chemicals on optical absorbance. We dissolved 5.0 mg/mL Pluronic P123 or CTAB (the surfactants for SBA or MCM synthesis) in PBS at 40 or 80 °C respectively, reproducing the temperature at which SBA or MCM had been synthesized. Solutions were well mixed and collected for centrifugation at 23,000 X g, and no precipitate was observed. Figure S2 in the Supporting Information shows the spectra of P123 (dotted line) and CTAB (solid line) in PBS, demonstrating that both P123 and CTAB absorb near 200 nm. The P123 spectrum has a peak at 201 nm, and the CTAB solution has one at 209 nm, although neither solution exhibits noticeable absorption in the region 250−350 nm. Therefore, the template does contribute to the apparent absorption near 200 nm in the spectra of MCMsyn and SBAsyn in PBS.

The potential chemical reaction between platinum drugs and P123 or CTAB templating agents was next investigated by HPLC. Cisplatin and transplatin (1 mM in PBS) were incubated with or without 10 mg/mL CTAB or P123 for 16 h (these concentrations are much higher than those used in our syntheses). The resultant solutions were diluted 50 times in PBS and run on HPLC, with detection at 210 and 300 nm, respectively. Under all conditions, the HPLC peaks possessed the same retention time and area under the curve (results not shown), suggesting no chemical reaction or interference between platinum drugs and templating chemicals.

In order to measure the adsorption of cisplatin or transplatin by SBA and MCM-type nanomaterials, solutions of cisplatin or transplatin (1 mM in PBS) were prepared 16 h before adding 1, 2, 5, 10, 15, or 20 mg/mL nanoparticles (hydrolysis of platinum drugs is complete in 16 h).[33] Nanoparticles were removed by centrifugation after 30 min incubation, and the supernatants were scanned by spectrophotometer. Intensities for each of three bands (205−210, 220−235, and 300−330 nm) were obtained for each amount of nanoparticles. The corresponding intensities for the nanoparticle residues were subtracted, to give the absorption of the platinum drug remaining in solution.

Band intensities after subtraction of nanoparticle residue pseudoabsorption were plotted against original nanoparticle additions. The results for MCM materials are shown in Figure 4A. The four panels are for as-synthesized MCM particles with cisplatin (upper left), calcined MCM particles with cisplatin (upper right), as-synthesized MCM particles with transplatin (lower left), and calcined MCM particles with transplatin (lower right). Expecting drug uptake to be proportional to the amount of nanoparticles, linear fits are shown for each band. In Table S3 (Supporting Information) we give, for each of the 12 cases, the slopes and the *y*-intercepts from the linear fits. These are used to calculate the fraction of drug that would be removed by 5 mg/mL of nanoparticles using

$$\text{fraction } 5 = -[\text{slope} \times 5]/[\text{intercept}] \quad (1)$$

The calculation is given in Table S3 (Supporting Information) with the statistical error, which comes mostly from the statistical uncertainty in the slope. It should be the same, within statistical error, for all three bands. This is clearly the case for MCMsyn particles with cisplatin, and less definitively for the other three cases, where statistical errors are larger. The results (average + sample standard deviation) are given in Table 2, columns 2 and 3. Since MCMsyn contains 47.6% CTAB by mass, the results should be divided by 0.524, giving columns 4 and 5. Fraction 5 for MCMsyn + cisplatin is greater than for MCMcal + cisplatin. For adsorption of transplatin, the difference between syn and cal is even slightly greater. It is also clear that both synthesized and calcined MCM particles adsorb slightly more transplatin than cisplatin.

The same experiments and calculations were performed to obtain adsorption profiles of cisplatin and transplatin by SBA nanomaterials. Band intensities for three bands (205−210, 220−235, and 300−330 nm) were obtained, and intensities for the nanoparticle residues were subtracted to give the net absorption due to platinum drug. These were plotted against original addition of nanoparticles, with linear fits, as shown in Figure 4B. The slopes and the *y*-intercepts, with statistical errors, are listed in Table S4 (Supporting Information). Calculated values of fraction 5, which were consistent between bands within the stated errors, are shown in Table 2. After correcting the results for SBAsyn by dividing by 0.671 (the as-synthesized particles contain 32.9% P123 by mass), we find that SBAsyn particles adsorb more of the platinum drugs than the calcined particles. Furthermore, both synthesized and calcined SBA particles adsorb more transplatin than cisplatin. The adsorption of cisplatin and transplatin by SBAcal nanoparticles is somewhat less than their adsorptions by MCMcal nanomaterials. This is consistent with the higher surface area of MCMcal compared to SBAcal for the same mass (Table S1) (Supporting Information). It is also interesting that the two isomers show different adsorptions by the same nanomaterial.

The next study involved varying the amount of platinum compounds, to see the effect on their adsorptions by a fixed amount of nanoparticles. Solutions with various concentrations of cisplatin

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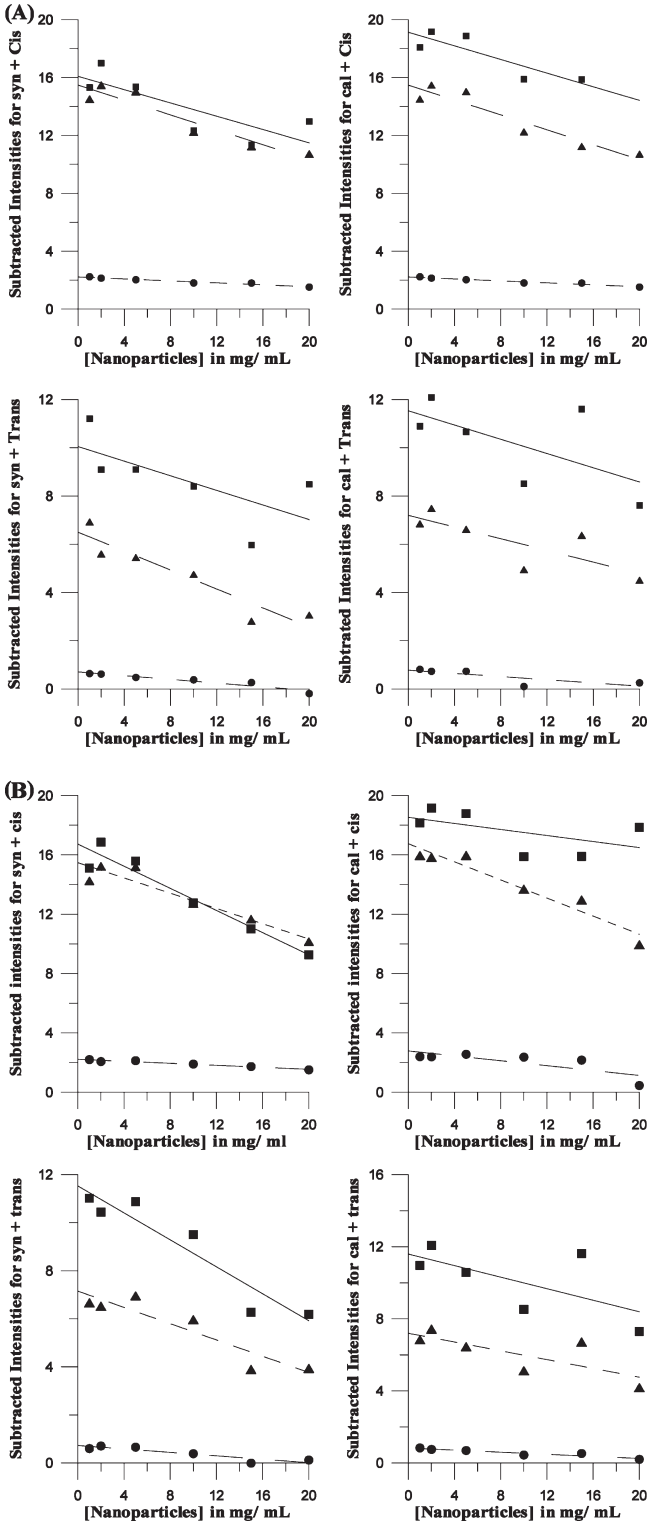

Figure 4. Band intensities of absorption spectra of platinum drugs remaining in solutions after centrifuging out MCM (A) and SBA (B) nanoparticles. Various amounts of the nanoparticles (1, 2, 5, 10, 15, or 20 mg/mL) were added into 1 mM cisplatin (Cis) or transplatin (Trans) PBS solutions that had been aged for 16 h. After 30 min incubation, nanoparticles were removed by centrifugation. Band intensities for 205−210 nm (■), 220−235 nm (▲), and 300−330 nm (●) are plotted as functions of original additions of nanoparticles.

and transplatin were prepared 16 h before mixing with 5 mg/mL different nanoparticles. After addition, nanoparticles were quickly removed by centrifugation and the supernatants were measured spectroscopically (preparation time $\sim^1/_2$ h). If the amount of drug that nanoparticles can adsorb were limited, the concentration of adsorbed drug would be given by the Langmuir isotherm (eq 2):

$$c_{\text{ads}} = \frac{k(c - c_{\text{ads}})}{1 + K(c - c_{\text{ads}})} \tag{2}$$

where c is the initial drug concentration in solution. According to this, c_{ads} is proportional to $(c-c_{ads})$, the platinum drug concentration remaining in solution, for small c and approaches k/K for large c, so that k/K is the maximum concentration that can be adsorbed. We measure $(c-c_{ads})$ spectroscopically, where, from the Langmuir isotherm,

$$(c - c_{\text{ads}}) = \frac{Kc - 1 - k + \sqrt{(Kc - 1 - k)^2 + 4Kc}}{2K} \tag{3}$$

so that a plot of drug concentration remaining in solution vs initial drug concentration is concave upward.

Plots of measured band intensities (proportional to drug concentration) vs initial drug concentration were fitted to linear and quadratic forms. Results for all four conditions for MCM particles, three bands for each, are shown in Table 3, including R^2 for both fits. Fitting to quadratics did not improve R^2, or led to concave downward functions. This means that curvature is not important, so there is no evidence of saturation. The corresponding results for SBA particles are in Table 4. Fitting these absorption intensities to quadratics did not improve R^2, or led to concave downward functions, showing that there is no evidence of saturation for SBA either.

To investigate time-dependent drug adsorption of the platinum drugs by the nanoparticles, nanoparticles were added to 1 mM cisplatin or transplatin PBS solutions, 5 mg/mL SBA (Figure 5) or MCM (Figure 6) at time zero, with stirring continued throughout the experiments. These drug solutions were freshly made, so that hydrolysis of the platinum drugs was not complete at time zero. At each time point, 2.0 mL of the mixture was taken for centrifugation and the supernatant was scanned in the spectrophotometer. After background subtraction (see Experimental Section), band intensities were calculated. Drug-free PBS solutions with addition of 5 mg/mL nanoparticles were treated similarly: band intensities, due to scattering from nanoparticle residues, were calculated after background subtraction. These were in turn subtracted from the band intensities from drug-nanoparticle solutions to give absorbance of the remaining drug in solution.

The band intensities for drug alone (triangles) and for drug + nanoparticles (filled and half-filled squares) are plotted against time in Figures 5 and 6 (time = time of sampling +0.5 h, representing the preparation time before samples could be measured on the spectrometer). For drug alone, we show the best fit to the function $A - Be^{-kt}$, which represents the effect of hydrolysis. For cisplatin, the hydrolysis rate constant k is known to be 0.186 h^{-1},[33] so only two parameters are varied in the fit. For transplatin, k is not known, so three parameters are varied. We find $k = 0.586$ h^{-1} from the 205−210 nm band and $k = 0.551$ h^{-1} from the 300−330 nm band, showing that transplatin hydrolyzes three times as fast as cisplatin.

Figure 5 shows the change in the platinum-drug concentration, due to the loading by SBA nanoparticles, with time. It is obvious that, at the first time point ($^1/_2$ h), the intensities are always much lower for solutions exposed to nanoparticles than for solutions of drug alone, showing rapid adsorption of drug by the nanoparticles. The latter intensities show a sharp increase over the first few

hours, due to the hydrolysis of the drugs, which is not shown by the intensities for drug + nanoparticles. This shows further adsorption of platinum drug by SBA nanoparticles. In Figure 5, we show least-squares linear fits to measured band intensities vs time for SBAsyn (filled squares and solid lines) and SBAcal (half-filled squares and dotted lines) nanoparticles. The slopes with the statistical errors are listed in Table S5. In each of the four cases, the slope is significantly larger for SBAsyn particles than for SBAcal particles. Since the intensity is increased by hydrolysis and decreased by removal of drug by the nanoparticles, this implies that, after the first half hour, calcined SBA particles take up more drug than do synthesized SBA particles. However, the y-intercepts are the same for synthesized and calcined particles in three of four cases (the other, 205−210 nm for SBAsyn + cisplatin, has too much scatter to be useful). After the mass correction between syn and cal particles, the adsorption of drug in the first half hour is seen to be greater for the syn particles. Subsequently, the calcined particles slowly encapsulate additional drug into their inner pores (which are blocked in the synthesized particles).

The corresponding experiments on MCM nanoparticles differ in one respect from those on SBA particles. The cisplatin solutions used for the MCM−particle experiments were made by diluting commercial cisplatin solutions, so that hydrolysis has already occurred, and there is no rapid rise in band intensity. Therefore, the band intensities for cisplatin alone are fitted to lines, as shown in Figure 6, parts A and C. The transplatin solutions, like all the solutions used with SBA, were made freshly from the powdered drug, so the transplatin band intensities are fitted to the function $A - Be^{-kt}$ as above. All the other data sets, band intensity vs time for either drug in the presence of either type of nanoparticle, are fitted to lines. The y-intercepts of these fits are almost the same. By comparing the intensity at $t = 0.5$ h for drug alone with that for drug exposed to nanoparticles, one can estimate the fraction of drug that was rapidly removed by the nanoparticles. For cisplatin with MCMsyn particles, we get 0.28 ± 0.02 from the 205−210 nm band and 0.25 ± 0.07 from the 300−330 nm band. For cisplatin with MCMcal particles, we get 0.18 ± 0.05 and 0.19 ± 0.04 from the two bands. For transplatin, there is too much scattering in the

Table 2. Fraction 5 (Fraction of Drug That Would Be Absorbed by 5 mg/mL of Nanoparticles) with Standard Deviation, before and after Correction for Weight Fraction of Silica[a]

	before correction		after correction	
system	average fraction	standard deviation	average fraction	standard deviation
MCMsyn + cisplatin	0.077	0.006	0.147	0.011
MCMcal + cisplatin	0.104	0.061	0.104	0.061
MCMsyn + transplatin	0.167	0.082	0.319	0.156
MCMcal + transplatin	0.120	0.066	0.120	0.066
SBAsyn + cisplatin	0.091	0.019	0.136	0.028
SBAcal + cisplatin	0.089	0.061	0.089	0.061
SBAsyn + transplatin	0.162	0.073	0.241	0.109
SBAcal + transplatin	0.110	0.057	0.110	0.057

[a] The table indicates that transplatin is absorbed about twice as much as cisplatin for MCMsyn and SBAsyn, which indicates a very significant difference. For the MCMcal and SBAcal, there is an increase adsorption of transplatin in both materials, while MCMcal adsorbs more platinum compounds than SBAcal.

Table 3. Drug Adsorbed by 5 mg/mL MCM Nanoparticles, Measured Spectroscopically, Where Saturation Would Give a Quadratic Function of Drug Concentration

drug	particle	band (nm)	slope	y-intercept	R^2, linear	R^2, quadratic
cisplatin	synthesized	205−210	3.266	12.595	0.624	0.861 (D)[a]
		220−235	13.539	1.545	0.999	0.999
		300−330	2.224	−0.052	0.998	0.999
	calcined	205−210	4.580	11.790	0.665	0.739 (D)[a]
		220−235	14.083	0.410	0.999	0.999
		300−330	2.354	0.013	0.998	0.998
transplatin	synthesized	205−210	5.845	0.592	0.989	0.995 (D)
		220−235	3.274	0.356	0.974	0.956
		300−330	0.154	0.218	0.298	0.173
	calcined	205−210	6.351	0.133	0.950	0.950
		220−235	3.752	0.120	0.956	0.956
		300−330	0.432	0.118	0.946	0.947

[a] (D) in R^2 from quadratic means concave downward and so unacceptable for Langmuir.

Table 4. Drug Adsorbed by 5 mg/mL SBA Nanoparticles (Measured Spectroscopically); Saturation Would Give a Quadratic Function of Drug Concentration

drug	particle	band (nm)	slope	y-intercept	R^2, linear	R^2, quadratic
cisplatin	synthesized	205−210	1.940	12.876	0.660	0.717 (D)[a]
		220−235	6.577	5.040	0.957	0.986 (D)[a]
		300−330	2.375	−0.139	0.952	0.980
	calcined	205−210	9.114	6.872	0.860	0.877
		220−235	9.519	0.951	0.984	0.990 (D)[a]
		300−330	1.971	−0.284	0.893	0.919
transplatin	synthesized	205−210	4.699	2.011	0.986	0.990 (D)[a]
		220−235	3.106	−0.189	0.977	0.986 (D)[a]
		300−330	0.468	−0.349	0.506	0.520
	calcined	205−210	5.368	−0.449	0.884	0.939
		220−235	2.858	−1.176	0.839	0.891
		300−330	−0.121	0.173	0.059	0.089

[a] (D) in R^2 from quadratic means concave downward and so unacceptable for Langmuir.

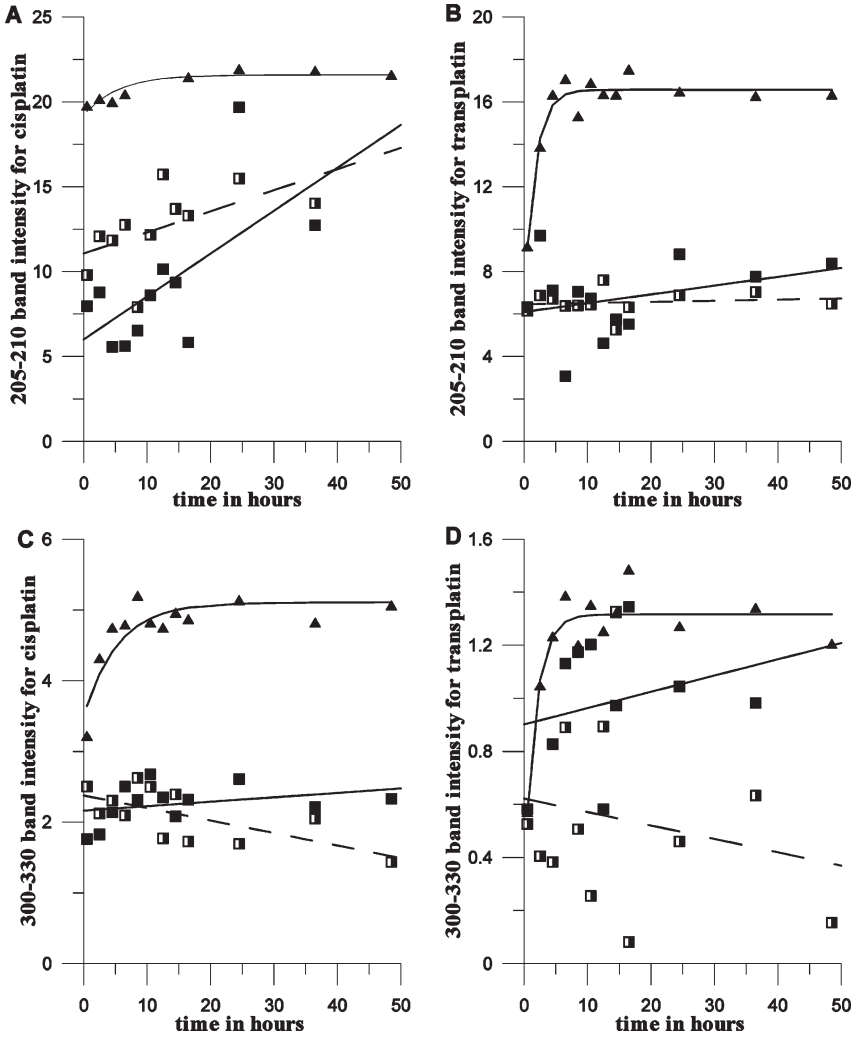

Figure 5. Integrated intensities of adsorption spectra resulting from platinum drugs remaining in solutions after centrifuging out SBA nanoparticles. Platinum drugs were freshly dissolved in PBS solution, without (▲) and with 5 mg/mL SBAsyn (■) or SBAcal (□). The sum of intensities for 205−210 nm (upper panel) and 300−330 nm (lower panel) were least-squares fitted to functions of time. For drug alone (upper solid line), the best fit to the function $A - Be^{-kt}$ represents the effect of hydrolysis; for drug loaded by either SBAsyn (lower solid line) or SBAcal (dashed line), linear regressions were adopted. Time zero corresponds to the addition of nanoparticles into freshly made drug solution.

300−330 nm band intensities to get any meaningful information; from the other band, we find the fraction removed to be 0.25 ± 0.02 for MCMsyn particles and 0.33 ± 0.01 for MCMcal particles. Thus, the fraction of cisplatin adsorbed in 0.5 h is greater for MCMsyn particles than for MCMcal particles; for transplatin, the situation may be reversed. However, after correction for the different masses of syn and cal particles, we find more adsorption of both drugs per particle for syn.

To study the adsorption of drugs at longer time, we consider the slopes of the lines in Figure 6. Table S6 in the Supporting Information gives the slopes of these lines, with the statistical errors. For the MCM particles, it does not seem that calcination (forming the mesoporous channels) leads to a slower adsorption of drug. (The only case in which the slope is appreciably more negative for MCMcal than for MCMsyn is the last, but the scatter makes the results doubtful.) Generally, the slopes are all very small, indicating very little slow adsorption of platinum drugs into MCM nanoparticles.

Finally, the release of the cisplatin and transplatin drugs from drug-loaded SBA and MCM nanoparticles was studied. Nanoparticles (5 mg/mL) were first soaked in 1 mM PBS drug solutions for 48 h. Afterward, they were removed from the solution by centrifugation, and resuspended in fresh PBS at concentrations of 5 mg/mL. At various times (i.e., 2, 4, 6, 8, 12, 24, and 48 h), samples were taken from the suspension and centrifuged to remove the particles. The supernatant from each sample was measured by spectrophotometer. Intensities of three bands (205−210, 220−235, and 300−330 nm) were measured with the results given in Table S7 (Supporting Information).

In each case, we have fit the band intensity as a function of time to a line; Table S7 (Supporting Information) gives the y-intercept and the slope with the statistical errors. The y-intercept (band intensity extrapolated back to $t = 0$) gives the concentration of platinum drugs in the solution after a rapid release of drug, if any, has occurred. The slope, if greater than zero, shows the slow release of drug, presumably from the internal mesopores of the nanoparticles. In fact, the slope is equal to zero within the statistical error (which is sometimes quite large) in all but a few cases. These exceptions, underlined in Table S7, correspond to transplatin + calcined SBA. Note that only the calcined particles can adsorb drug into interior pores, from which slow release is likely to occur.

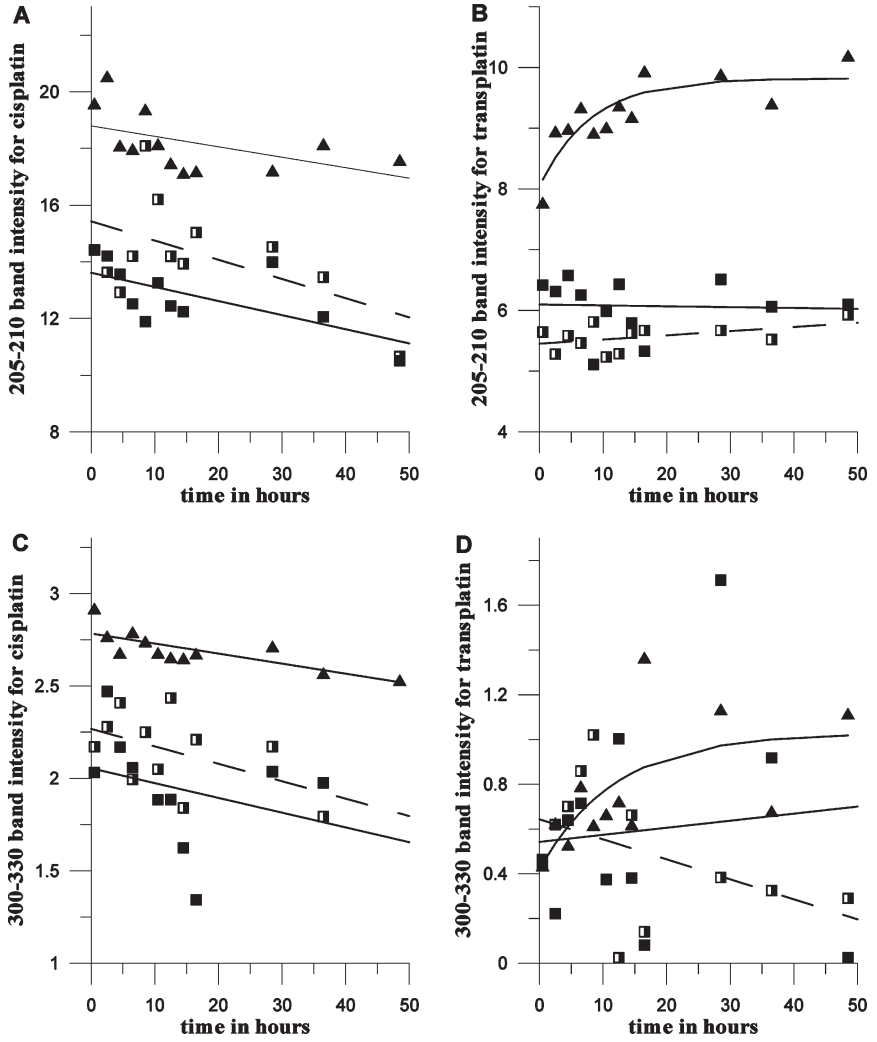

Figure 6. Band intensities for 205−210 nm (upper panel) and 300−330 nm (lower panel) from platinum drugs remaining in solution after centrifuging out MCM nanoparticles. Platinum drugs were diluted from the commercial products, without (▲) and with 5 mg/mL MCMsyn (■) or MCMcal (□). Band intensities were fitted into functions of time. For drug alone (light solid line), the function $A - Be^{-kt}$ was used, representing the effect of hydrolysis; for drug loaded by either MCMsyn (dark solid line) or MCMcal (dashed line), linear regressions were adopted. Time zero corresponds to the addition of nanoparticles into the drug solution.

To measure the extent of rapid release of drug, we subtract the scattering of the nanoparticle residues (measured as indicated above and given in Table S7 (Supporting Information)) from the *y*-intercept in Table S7 (Supporting Information). For SBAsyn particles with cisplatin or transplatin, the *y*-intercept for the first band is less than the residual intensity, but not by more than the statistical error, while the *y*-intercepts for the other two bands are greater than the residual intensities. This suggests that substantial amounts of cisplatin and transplatin are released quickly from the SBAsyn nanoparticles. For SBAcal particles, the three band intensities from residual scattering are much smaller than the corresponding *y*-intercepts for cisplatin and transplatin. There is no doubt that considerable amounts of both drugs are released quickly from the SBAcal nanoparticles. For cisplatin + MCMsyn, the *y*-intercepts in Table S7 (Supporting Information) are significantly greater than the residual intensities for the second and third bands, and about the same for the first, indicating that cisplatin is readily released by these particles. For transplatin + MCMsyn, the *y*-intercepts are smaller than the residual intensities, suggesting that the MCMsyn particles do not release the surface-bound transplatin. Finally, the band intensities from residual scattering from MCMcal particles are smaller than the *y*-intercepts; we hence conclude that the MCMcal particles readily release most of the bound cisplatin and transplatin.

Conclusions

We studied the adsorption and release of both cis- and transplatin by two types of particles (SBA and MCM), either as-synthesized (syn) or further calcined to remove the templates (cal). The UV−vis spectra of both platinum compounds were obtained and the intensities of several bands (205−210 nm, 210−220 nm, 220−235 nm, and 300−330 nm) were measured as functions of drug concentration, showing that these band intensities could serve to measure drug concentration. Centrifugation of nanoparticle solutions did not suffice to remove the residue of particles, resulting in a pseudoabsorption in band regions. Therefore, this pseudoabsorption had to be subtracted from measured band intensities for drug in supernatants in which the same nanoparticles had been suspended.

Studies of adsorption of cisplatin and transplatin by four materials (SBAsyn, SBAcal, MCMsyn, and MCMcal), showed that calcined MCM particles adsorb less cisplatin or transplatin than uncalcined MCMsyn particles, the difference being larger for

transplatin. The same is true for SBA particles. The reason for the decreased adsorption of particles after calcination may be that calcination changes the nature of the particle surface, such as by removing residual surfactant, or that there is an enhanced adsorption of the drugs into the surfactant assemblies or by replacing them in the as-synthesized materials. Immobilization of drugs or many organic molecules into surfactant assemblies is not uncommon.[34−36] In fact, additives such as mesitylene and pentane have been used to swell cylindrical micelles and enlarge their templated nanopores.[37] Consequently, in this case, the surfactant assembly in the as-synthesized SBA and MCM may have behaved as a sponge for physisorption of the drug molecules, increasing its adsorption capacity per particle compared to the calcined counterparts. Although HPLC study showed no chemical interaction between surfactant and drug molecules, it can not rule out the possible physical interaction (e.g., physisorption). Furthermore, the platinum species could replace some of the surfactant in the same way as protons or salt ions substitute them during solvent extraction in dilute aqueous acidic solution.[38] So, this may also be responsible for the slightly higher adsorption of the platinum drugs in the as-synthesized samples compared to their calcined counterparts. On the basis of particle mass, SBA nanoparticles adsorb slightly more cisplatin than MCM, and slightly less transplatin. Possible saturation of the samples by the drug molecules was checked by measuring band intensities with particle concentration fixed at 5 mg/mL and drug concentration varied up to 2 mM. If a Langmuir-like isotherm (which includes saturation) were followed, a plot of drug concentration in solution after adsorption by nanoparticles vs original drug concentrations would be curved concave upward, rather than linear. Our results show clearly that this is not the case.

Adsorption of cisplatin or transplatin in PBS solutions was measured as a function of time for 5 mg/mL SBA or MCM nanoparticles. The results indicate that drug is rapidly adsorbed by all four species of particles. Linear fits were made to plots of band intensities vs time, for $t > {}^1/_2$ h. After taking drug hydrolysis into account, we found small negative slopes for SBA particles (smaller for SBAcal than for SBAsyn), showing that, after the first ${}^1/_2$ h, there is a slow take-up of drug by these particles, probably associated with the internal pores or continuous surfactant assemblies in the SBAsyn case. For MCM particles, on the other hand, there is no statistical difference between the slopes for MCMsyn and MCMcal, indicating that either the adsorption into internal pores or continuous surfactant assembly is less important. The external surfaces of the particles as well as likely the surfactant assemblies in the case of as-synthesized samples may be responsible for the rapid adsorption (for $t < {}^1/_2$ h). By measuring Pt band intensities in PBS in which drug-loaded particles were suspended, we showed there was substantial quick release of both drugs from all particles, but very little slow release of Pt species, except for transplatin in SBAcal.

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Supporting Information Available: Text giving experimental details, tables of characteristics and elemental analyses of silica nanoparticles, drug adsorption results, and band intensities, and figures showing Nitrogen gas physisorption and BJH pore size distribution and spectra of Pluronic P123 and CTAB. This material is available free of charge via the Internet at http://pubs.acs.org.

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