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Sorption of Carfentanil and Remifentanil Salts on Porous Materials

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RESEARCH AND TECHNOLOGY DIRECTORATE

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Interest in characterization of opioids has increased over the last few years as the U.S. tries to combat the opioid crisis. However, a lot of the work has focused around opioids inside the human body. This study focused on opioid interactions with surfaces outside of the body to potentially prevent opioids from ever entering the body. Sorption studies were performed for carfentanil citrate and remifentanil oxalate salts on SiO_2 and metal organic framework (MOF) surfaces in solution. The binding of these opioids was significantly affected by the type of solvent and pore aperture size of the material. For carfentanil in methanol, all surfaces except NU-1000 showed little to no binding of the opioid with the surface; however, when water was added to the solution, opioid binding increased dramatically for the MOFs with large pore sizes as well as for UiO-66-NH_2, which has possible reactive amine groups and missing linker defects. Remifentanil had minimal binding to the surfaces except at 100% water for large pore size MOFs. The remifentanil salt was readily hydrolyzed in solution, but when the MOFs were added, the remifentanil stabilized, likely due to the lower pH of the solution.

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PREFACE

The work described in this report was authorized and funded under the U.S. Army via the Surface Science Initiative Program (PE 0601102A Project VR9). The work was started in October 2017 and completed in August 2018. At the time this work was performed, the U.S. Army Combat Capabilities Development Command Chemical Biological Center (DEVCOM CBC; Aberdeen Proving Ground, MD) was known as the U.S. Army Edgewood Chemical Biological Center.

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SORPTION OF CARFENTANIL AND REMIFENTANIL SALTS ON POROUS MATERIALS

1. INTRODUCTION

The recent increase in opioid related drug overdoses, coupled with the potential for opioid use in chemical attacks, has generated an immense interest in the fentanyl class of molecules worldwide. In 2017, synthetic opioids were the main driver of 47,600 overdose deaths in the United States, which is 67.8 percent of all drug overdose deaths.[1] Maryland, West Virginia, California, Florida, and many other states showed significant (as high as 9.6 percent) increases in drug overdose death rates from 2016 to 2017.[2]

The first drugs of this class, fentanyl (N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenyl propanamide) and carfentanil, were developed in the 1960s by Janssen and colleagues[3,4,5] and are 100 and 10,000 times[6] more potent than morphine, respectively. Additional research led to the development of anesthetic drugs such as remifentanil and sufentanil, with short onset times[7] and high lipid solubility, increasing their pharmaceutical efficiency and potency. The structures of these opioids are shown in Figure 1. While the medicinal aspect of fentanyl analogs has been well characterized, new research efforts are underway to better understand how these molecules behave outside of the human body as well. Of particular interest is a fundamental understanding of the binding mechanisms of these molecules to surfaces.

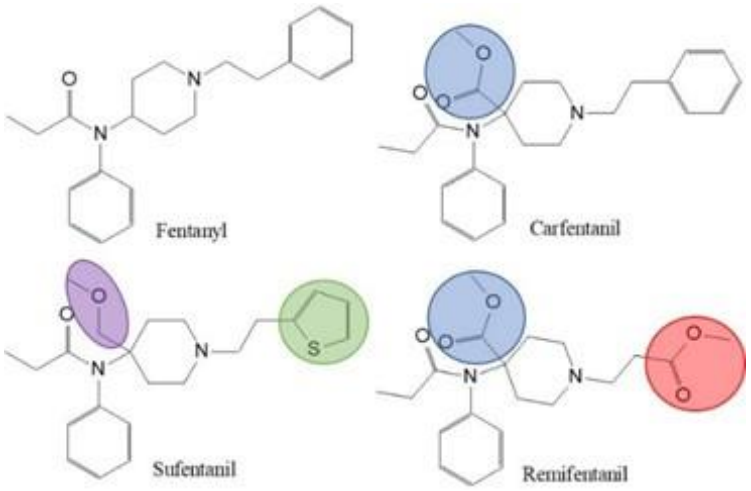

Figure 1. Opioids of interest. The colored circles represent the different functional groups that could change the binding to surfaces.

Previous opioid studies have focused primarily on opioid binding to pain receptors in the human body. This class of opioids is known to bind to the μ-receptor, but can also bind and act through δ- and κ-opiate receptors.[8] Weltrowska et al.[9] researched the binding of carfentanil to the μ-receptor via the Asp147 residue and compared it to the binding of carba-carfentanil (carfentanil molecule in which the nitrogen atom on the piperidine ring was replaced

with a carbon atom). They found that the binding affinity of the trans-isomer of carba-carfentanil to the Asp147 residue was reduced in comparison to carfentanil, but still significant; however, the cis-isomer was essentially inactive. They also found that though the binding orientation was changed with the trans-isomer, the potency (agonist activity) remained, which indicates that the Asp147 residue was not the necessary site for receptor activation. Clearly, a more fundamental understanding of how the different functional groups (i.e. moieties) on the opioid structures bind to and interact with surface sites is required.

Lastly, additional factors such as solvents can also affect binding on surfaces. Here we studied two different solvents, water and methanol, to compare the polar OH groups to the non-polar CH_3 groups interacting with the opioid and the surface. These solvents were selected since water is ubiquitous in the atmosphere, and alcohols easily dissolve opioid salts and are widely used in cleaning and decontamination procedures in the military and at home. The importance of understanding the impact these factors have on binding and reactivity on surfaces cannot be overemphasized and will improve future understanding of this class of molecules in many different research fields, such as synthesis, decontamination, toxicology, aerosols and obscurants, and medicine.

Here we studied the sorption of two opioids (carfentanil and remifentanil) in solution on the surfaces of UiO-66, UiO-66-NH_2, UiO-67, NU-1000, HKUST-1 and PCN-250 metal organic frameworks (MOFs) as well as SiO_2, and large-pore SiO_2 (MCM-41). The structures of these materials are shown in Figure 2. Carfentanil and remifentanil are two of the most potent and least studied opioids, and they have the same functional groups present in their structure as fentanyl. Therefore, we decided understanding the binding of these two opioids would be the most beneficial to the Warfighter and first responders.

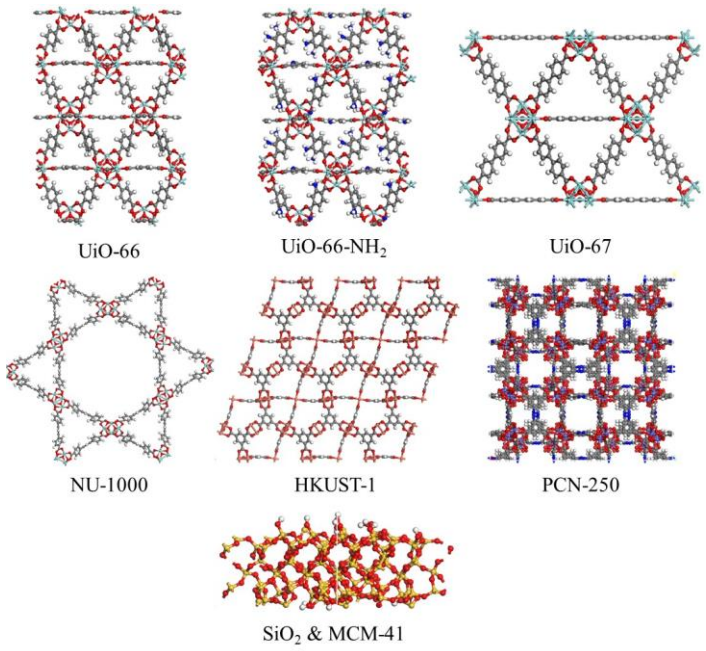

Figure 2. Calculated structures of UiO-66, UiO-66-NH_2, UiO-67, NU-1000, HKUST-1, PCN-250, SiO_2, and MCM-41. The Zr, Cu, Fe, C, O, N, and H atoms are cyan, orange, light blue, gray, red, blue and white.

2. EXPERIMENTAL PROCEDURES

To evaluate sorption of carfentanil and remifentanil to solid substrates of interest, we constructed single point equilibrium sorption experiments. The solid substrates of interest were suspended in methanol solutions of carfentanil and remifentanil, and the suspensions were allowed to equilibrate with stirring overnight at ambient temperature. Following the equilibration period, the suspensions were centrifuged, and a portion of the supernatant was analyzed to determine the change in opioid concentration and the corresponding amount of opioid sorbed on the surface. Control samples with no solid substrates were run the same way to account for any opioid sorption to the glass vial or degradation through opioid hydrolysis.

Solid substrates[10,11,12], with the exception of silica (SiO_2), were synthesized by NuMat technologies (Skokie, IL). Carfentanil citrate and remifentanil oxalate salts were synthesized in house by the Agent Chemistry Branch using the synthesis procedure developed by Waals et al.[13]

2.1 Sample Preparation

Unless otherwise indicated, sorption studies were conducted using the parameters listed in Table 1 and illustrated in Figure 3.

Table 1. Parameters for Sorption Study

Sorbates	Carfentanil citrate, remifentanil oxalate in solution
Solvent Composition (% Methanol)	0, 25, 50,75, 100
Sorbate Concentration:	2 μg/mL (salt corrected)
Substrates	SiO_2, UiO-66, UiO-66-NH_2, UiO-67, NU-1000, HKUST-1, PCN-250, MCM-41
Solid Concentration	10 mg/mL
Equilibration Period	18-24 h

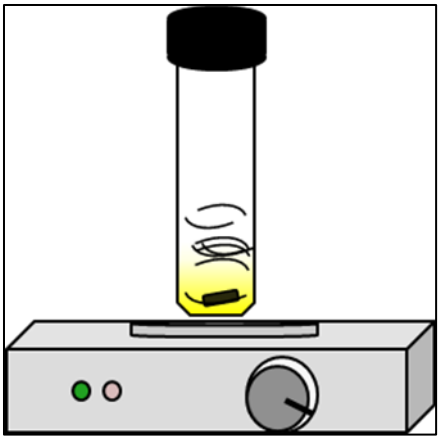

Figure 3. Illustration of apparatus used for sorption study.

Due to the inherent difficulty of weighing microgram quantities of solids and the limited solubility of opioid salts in water, we first prepared high concentration stock solutions of carfentanil and remifentanil (71 and 68 mg/mL, respectively) in methanol. Subsequently, intermediate and working solutions were prepared by serial dilution into each of the desired solvent combinations: 0% (100% water), 25% (25/75% methanol/water), 50% (50/50% methanol/water), 75% (75/25% methanol/water), and 100% (0% water). The resulting concentration of opioid in each working solution at each solvent condition was 2 µg/mL. It should be noted that as a result of the serial dilution of the original stock, the 0% methanol condition actually contains 0.003% methanol.

The sorption samples were prepared such that the loading of the solid substrates to the opioid-solvent combinations resulted in a concentration of 10 mg of substrate per mL of the 2 µg/mL opioid solution. The reactors containing the substrate-opioid-solvent combinations were then stirred at 500 rpm at ambient conditions for 18 to 24 h.

At the end of the equilibration period, a portion of the contents of the reaction vessel was centrifuged to drive any suspended solids to the bottom, ensuring that the supernatant was free of solid substrate. The supernatant was diluted in methanol for analysis. Quantification of the concentration of opioid in the supernatant was performed by ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS-MS). Control samples were prepared without solid substrates for each opioid and solvent combination and were carried through the entire sample treatment process.

It should be noted that initial attempts were made to use syringe filters to separate the solids from the supernatant following equilibration. However, carfentanil was found to sorb to several of the filter materials used when water was in the solution (see Appendix A). The centrifuge step was added to the procedure as a replacement for the filtration step.

2.2 Sample Analysis

Carfentanil was quantified using an Applied Biosystems API5500 QTrap Triple-Quadrupole mass spectrometer (MS), equipped with the TurboV Ion Source (Applied

Biosystems; Foster, CA). Sample introduction and chromatography were performed with an Agilent 1290 Infinity series UHPLC system, which included the Agilent Infinity binary pump, degasser, thermal column compartment (TCC), high performance automatic liquid sampler (ALS), and the ALS thermostat (Agilent Technologies; Santa Clara, CA). Sample effluent was directed from the UHPLC system directly to the TurboV ion source of the API5500MS. The instrument operation and data analysis were performed with the Applied Biosystems Analyst software package (v. 1.5.1.). Detailed analytical instrument parameters are listed in Table **2**.

Table 2. Analytical Instrument Parameters

UHPLC Parameters		
Mobile Phase A: 0.1% Formic acid in deionized water		
Mobile Phase B: 0.1% Formic acid in acetonitrile		
Gradient:		
Time (min)	%A	%B
0.00	70.0	30.0
0.50	70.0	30.0
1.25	20.0	80.0
1.50	20.0	80.0
1.60	70.0	30.0
2.25	70.0	30.0
Flow Rate: 0.5 mL/min		
Analytical Column: Waters Acquity HSS T3, 1.8 µm, 2.1 x 50 mm		
Typical Column Pressure: 330 bar		
Analytical Column Temperature: 40 ºC		
Injection Volume: 1 µL		
Autosampler Temperature: 5 ºC		
Post-injection Needle Wash: 10 s of mobile phase B		
Mass Spectrometer (MS) Parameters		
Scan Type: Multiple reaction monitoring (MRM)		
Polarity: Positive mode		
Curtain Gas: 30		
CAD Gas: Medium		
Source Temperature: 500 ºC		
GS1: 45		
GS2: 55		
Declustering Potential: 100		
Exit Potential: 10		
Collision Energy: 25 (for all analytes)		
MRM for Carfentanil: 395.2 > 335.2 MRM for Remifentanil: 377.2 > 228.1		

3. RESULTS AND DISCUSSION

3.1 Uptake Studies with Carfentanil Citrate

Differences in substrate properties may substantially affect opioid binding on surfaces, and so, we initially chose seven surfaces with varying porosities and surface groups to study the uptake of fentanyl compounds. The initial materials included nonporous SiO_2 as well as six MOFs: UiO-66, UiO-66-NH_2, UiO-67, NU-1000, HKUST-1 and PCN-250.

Silica contains polar OH surface sites that have the ability to hydrogen bond with the oxygen and nitrogen groups of the opioids. MOFs contain inorganic oxide nodes called secondary building units (SBUs) connected by organic linkers that form three-dimensional crystal lattices. Additionally, MOFs contain both polar and nonpolar groups that may allow for multiple binding sites for the opioid molecules. The polar groups for this set of MOFs include hydroxyl groups (OH bonds) on the SBU and amine groups (NH bonds) on the organic linkers, which both can hydrogen bond to the opioid. Pi-bonding in aromatic rings can also allow for binding in the organic linkers of the MOFs. The Zr-based UiO series MOFs are advantageous for their stability in water, high surface areas (~500-2000 m^2/g), and controllable aperture sizes. For additional comparison, a Cu-based MOF (HKUST-1) and an Fe-based MOF (PCN-250) were also studied to determine whether different metal sites affect the binding of opioids on surfaces. The pore apertures and volume sizes for UiO-67, HKUST-1, PCN-250, and NU-1000 are all large enough to encompass the opioid salts.

We began by conducting a single point uptake screening of each of the seven substrates. The concentrations of carfentanil found in the supernatant of the screening samples are provided in Table 3, and the sample vials with substrates in 100% methanol are shown in Figure 4.

Table 3. Carfentanil Concentration in Supernatant of Screening Samples

Substrate (n=1)	**Carfentanil Concentration (ng/mL)**		
	100% Methanol	**50/50% Methanol/Water**	**100% Water**
Control 1 (no substrate)	2145	1308	2085
SiO_2	2006	2161	555
UiO-66	2112	1826	1356
UiO-66-NH_2	1702	1590	1002
UiO-67	1967	1948	352
HKUST-1	1972	1571	1590
PCN-250	2021	1373	10
NU-1000	606	26	3

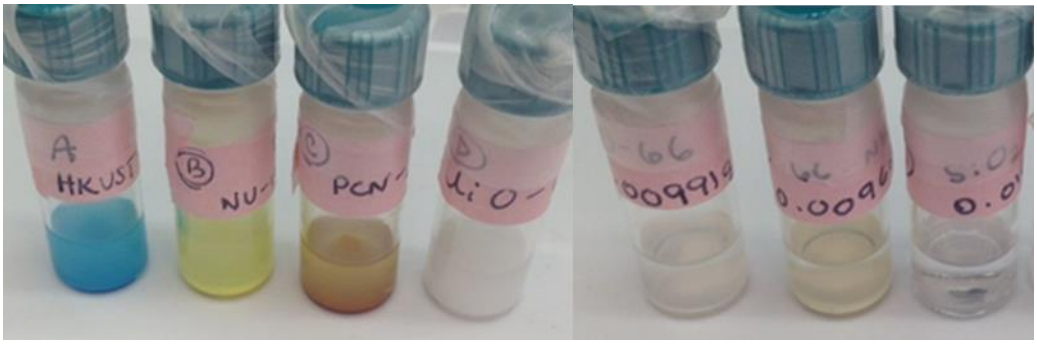

Figure 4. Carfentanil uptake study vessels in 100% methanol. Substrates (left to right): HKUST-1, NU-1000, PCN-250, UiO-67, UiO-66, UiO-66-NH_2, SiO_2.

After screening, the substrates were downselected to SiO_2 and the four Zr-based MOFs (UiO-66, UiO-66-NH_2, UiO-67 and NU-1000) for further evaluation. Carfentanil concentrations found in the supernatant for the Fe- and Cu-based MOFs were similar to concentrations found for the Zr-based MOFs; thus, differing metal sites do not greatly affect opioid binding. A fifth substrate, porous SiO_2 (MCM-41), was also added so we could compare binding on nonporous and porous SiO_2 surfaces.

More detailed sorption studies were conducted with each substrate in five solvent conditions. All sample combinations, including the non-substrate controls, were prepared in triplicate. The average concentration of carfentanil found in the supernatant is reported in Table 4 and depicted in Figure 5.

Table 4. Carfentanil Concentration in Supernatant

Substrate	***Average (n=3) Carfentanil Concentration (ng/mL)**				
	100% Methanol	**75/25% Methanol/ Water**	**50/50% Methanol/ Water**	**25/75% Methanol/ Water**	**100% Water**
Control (no substrate)	1901	1665	1600	1416	882
SiO_2	1937	1733	1659	1427	820
UiO-66	1875	1730	1609	1317	1018
UiO-66-NH_2	1450	1576	965	118	47
UiO-67	1914	1753	1531	1305	50
NU-1000	1064	1276	154	0	1

*The standard deviations are depicted in Figure 4 as error bars.

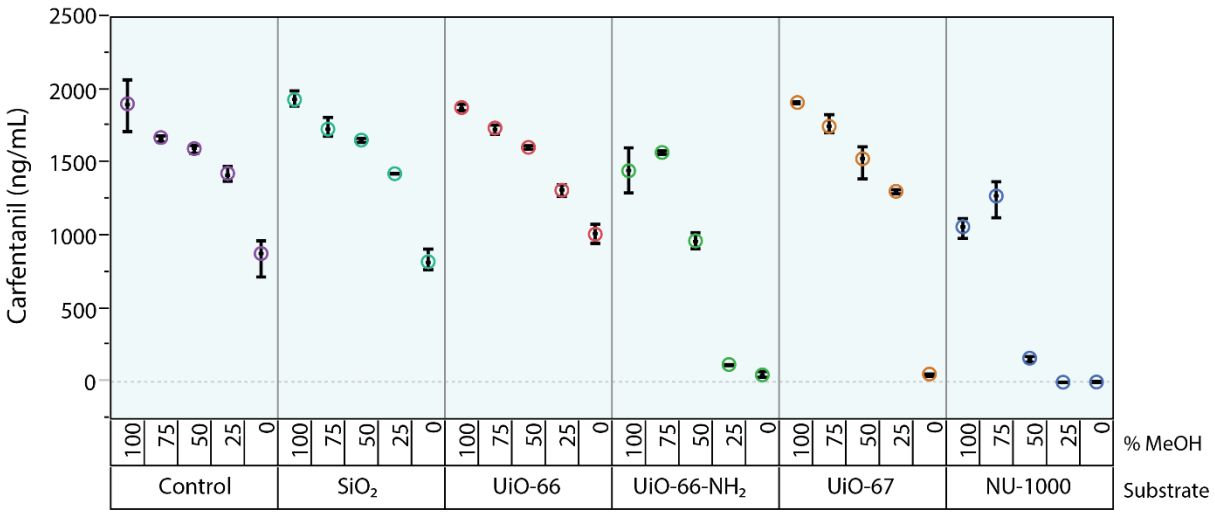

Figure 5. Graphical representation of the carfentanil concentration in the supernatant after uptake on the surface. The surfaces used are ordered in increasing pore aperture from left to right.[14] The standard deviations based on the average of three repeated experiments are depicted as error bars for each solution mixture.

The control experiment with only opioid and no substrate present showed a gradual decrease in opioid concentration as more water was added to the mixture. This loss of opioid concentration in the control is likely due to either the opioid interacting with the walls of the vial and/or some opioid precipitating out of solution. Carfentanil citrate results showed no binding (complete recovery with respect to the control) of the opioid on the non-porous SiO_2 and the UiO-66. In the case of SiO_2, there were likely fewer binding sites interacting with the opioid than when the opioid was in a pore of the MOF; whereas with UiO-66, the pore apertures (~6 Å) were too small for carfentanil to penetrate into the pores. In the case of UiO-67, with an increased pore size of ~12 Å, carfentanil uptake was observed, but only when the water content was high. Finally, for NU-1000, with a pore diameter of ~30 Å, uptake occurred in both methanol and water, with more uptake in water.

Since the polar OH sites of UiO-66 showed minimal carfentanil uptake, the organic linker was changed to include an amine ($-NH_2$) group. The UiO-66-NH_2 substrate has a similar aperture size (~6 Å) to UiO-66 , which should not allow for the opioid to diffuse into the pores; however, the synthesis to make UiO-66-NH_2 can create more defects (missing linkers) in the MOF structure. The intent was to see if the C=O modes in the opioid might interact more strongly with the amine linker than the OH groups on the MOF surface. Indeed, the uptake increased with the addition of the amine group in the UiO-66-NH_2 MOF. Water further increased the uptake of the opioid on the surface in comparison with methanol. Another possible reason for the increased uptake could be the amine groups that orient outside the pore on the MOF particle surface interacting with the opioid. However, additional studies will be required to elucidate the role of the NH_2 linkers and potential structural defects in the UiO-66-NH_2 MOF in opioid uptake results.

It is believed that the differences in carfentanil uptake observed with water content stem primarily from a solvent effect as opposed to a conformational change in the carfentanil molecule. Since there was no appreciable difference in uptake between the non-porous silica and the UiO-66 MOF, but there was a significant difference in uptake between UiO-66 and UiO-67, an additional screening experiment was conducted to probe the effect of specific surface sites on uptake.

An additional sorption study was conducted with mesostructured porous silica (MCM-41), with pore aperture sizes on the order of 21 to 27 Å, which are similar to NU-1000 pore aperture sizes. Carfentanil uptake by MCM-41 was investigated under three solvent conditions: 100% methanol, 100% water, and a 50/50% methanol/water mix. Some uptake of the carfentanil by the porous silica was observed in 100% methanol; however, near complete uptake by the silica occurred when in the presence of the water. Since the porous SiO_2 only contains polar OH sites, these results indicate that the hydrogen bonding sites are the dominant binding sites for carfentanil, and the pi-bonding aromatic bonds on the organic linkers do not show significant uptake. The average concentration of carfentanil found in the supernatant is reported in Table 5 and depicted in Figure 6.

Table 5. Carfentanil Concentration in Supernatant from MCM-41 Uptake Study

Substrate	***Average (n=3) Carfentanil Concentration (ng/mL)**		
	100% Methanol	**50/50% Methanol/ Water**	**100% Water**
Control (no substrate)	3847	3347	2470
MCM-41	2777	225	28

*The standard deviations are depicted in Figure 6 as error bars.

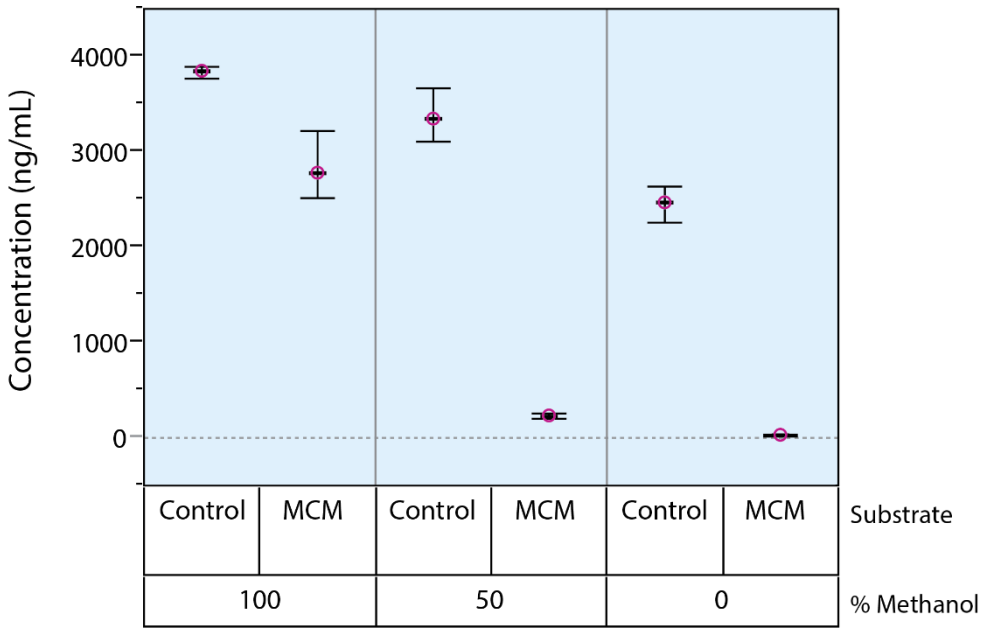

Figure 6. Graphical representation of the carfentanil concentration (mean, range, n=3) in the supernatant from the MCM-41 porous silica.

3.2 Uptake Studies with Remifentanil Oxalate

Uptake studies of remifentanil oxalate were conducted using the same five substrates in the same manner as the detailed carfentanil uptake studies. Oxalate salt was used instead of citrate due to availability and relevance to the military. The uptake for each substrate was measured in triplicate, and the average supernatant concentration is reported in Table 6 and illustrated in Figure 7.

Table 6. Remifentanil Concentration in Supernatant

Substrate	***Average (n=3) Remifentanil Concentration (ng/mL)**				
	100% Methanol	**75/25% Methanol/ Water**	**50/50% Methanol/ Water**	**25/75% Methanol/ Water**	**100% Water**
Control (no substrate)	1737	1768	1576	1112	466
SiO_2	1714	1670	1469	966	328
UiO-66	1544	1495	1809	1983	1558
UiO-66-NH_2	1365	1602	2112	2010	1360
UiO-67	1808	1852	2253	2192	419
NU-1000	1707	1699	1328	6.2	9.9

*The standard deviations are depicted in Figure 7 as error bars.

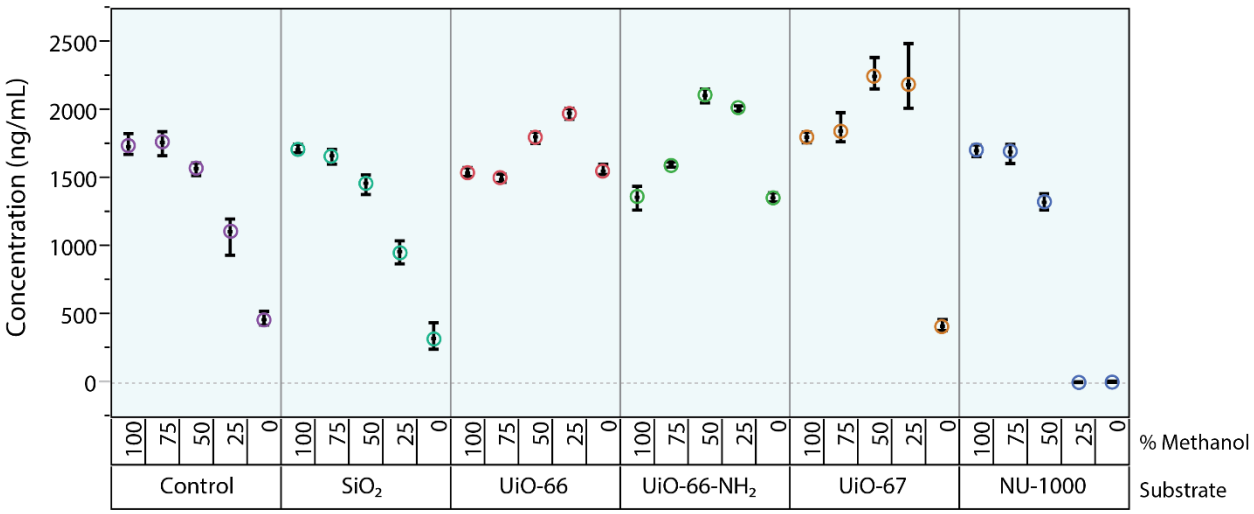

Figure 7. Graphical representation of the remifentanil concentration (mean, range, n=3) in the supernatant. The surfaces used are ordered by increasing pore aperture from left to right.[14]

Evaluation of the control samples (no substrate) revealed that the remifentanil concentration decreased as the water content of the solvent mixture increased even more than the carfentanil citrate salt control concentration did. Further review of the liquid chromatography-mass spectrometry (LC-MS) data depicted in Figure 8 indicated that remifentanil (molecular weight (MW)=377) hydrolyzed to the acid product (MW=363) in the aqueous-solvent mixtures. As expected, the results for the SiO_2 samples were comparable to the controls in all solvent mixtures, including the generation of the remifentanil acid by-product, indicating that remifentanil does not bind to nonporous SiO_2.

Uptake studies with the Zr-based UiO series MOFs yielded different results. With the exception of UiO-67 and NU-1000 in 100% water, minimal binding or hydrolysis of remifentanil was observed in the samples. The addition of the MOF surfaces likely decreased the pH of the total solution mixture, inhibiting the hydrolysis of the remifentanil in those samples. In the case of the UiO-67 in 100% water, the remifentanil loss was comparable to the control sample. However, the absence of the remifentanil acid peak in the LC-MS results suggests that remifentanil and/or the acid sorbed into the larger pores of the UiO-67. Finally, in the case of the NU-1000 sample, there was a significant reduction of remifentanil in comparison to the control samples when the water content of the solution was 75% or more. While NU-1000 is also a Zr-based MOF, it has a greater affinity for opioid binding than the UiO MOFs. The absence of remifentanil acid in the chromatogram suggests that the loss of remifentanil was due to uptake of either the opioid and/or its acid product by NU-1000. These results are illustrated in the overlaid LC-MS chromatograms in Figure 8**Error! Reference source not found.**.

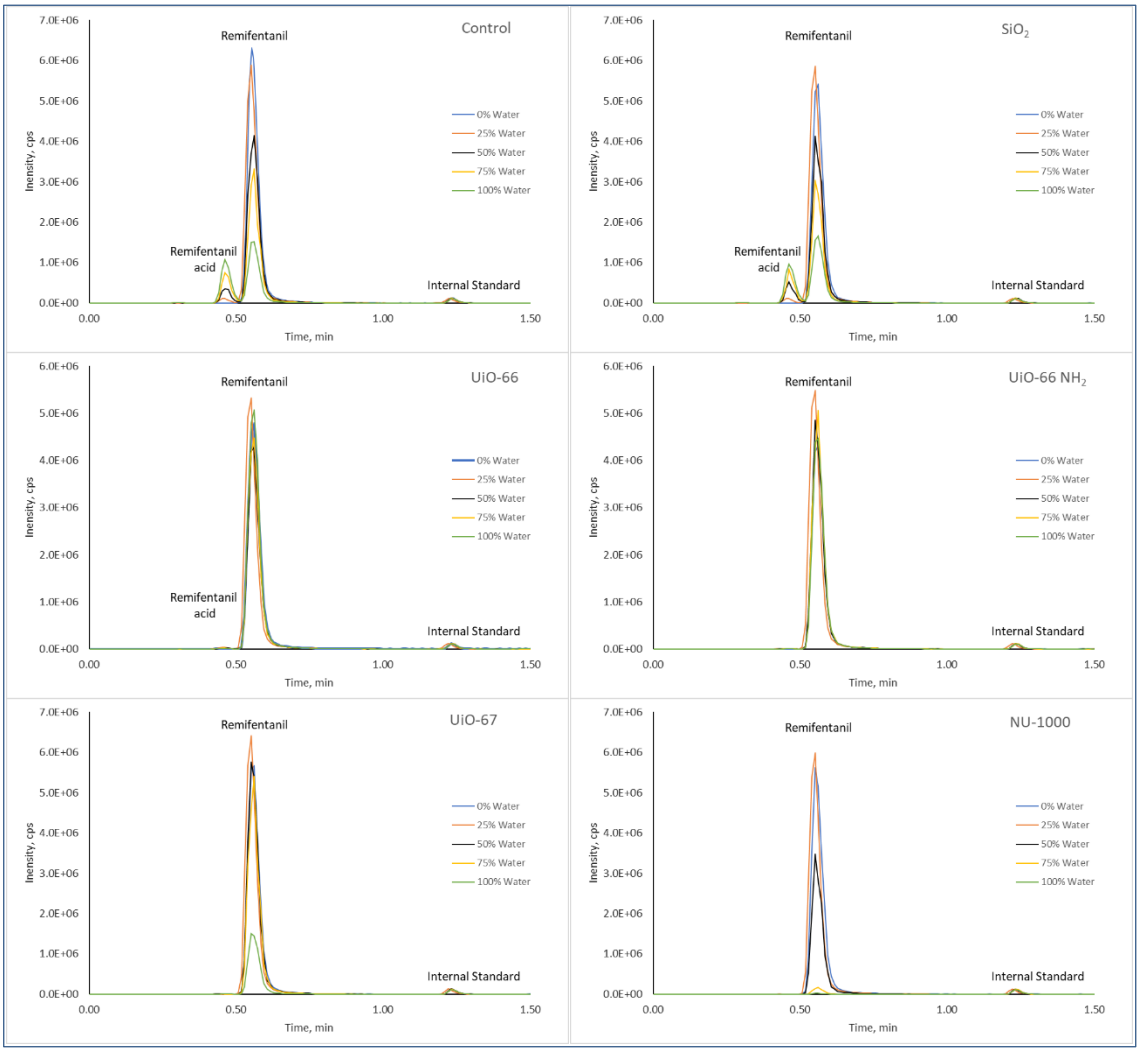

Figure 8. Overlays of the LC-MS total ion chromatograms (TICs) resulting from the uptake studies of remifentanil with the six substrate conditions: control (upper left), SiO_2 (upper right), UiO-66 (middle left), UiO-66-NH_2 (middle right), UiO-67 (bottom left) and NU-1000 (bottom right).

4. SUMMARY

Uptake studies were performed for carfentanil citrate and remifentanil oxalate salts on SiO_2 and MOF surfaces in solution. The binding of these opioids was significantly affected by the solvent and pore aperture size of the substrate. For carfentanil in methanol, all surfaces except NU-1000 showed minimal opioid uptake on the surface; however, when water was added to the methanol solution, opioid binding increased dramatically for the MOFs with large aperture sizes (UiO-67 and NU-1000) as well as for UiO-66-NH_2, which has possible reactive amine groups and missing linker defects. Remifentanil had little to no binding to the surfaces except at 100% water for UiO-67 and NU-1000. The remifentanil salt was readily hydrolyzed in solution, but when the MOFs were added, remifentanil stabilized, likely because

the solution pH was lowered. These results indicate that porous SiO_2 and MOFs in a water-based solution are good adsorbers of opioids, whereas alcohol might be a good extractor of opioids from surfaces. These results can be used to enhance the fields of decontamination and hazard mitigation.

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ACRONYMS AND ABBREVIATIONS

ALS	automatic liquid sampler
DEVCOM CBC	U.S. Army Combat Capabilities Development Command Chemical Biological Center
ECBC	U.S. Army Edgewood Chemical Biological Center
LC-MS	liquid chromatography-mass spectrometry
MOF	metal organic framework
MRM	multiple reaction monitoring
MS	mass spectrometer
MW	molecular weight
NMR	nuclear magnetic resonance
PTFE	poly(tetrafluoroethylene)
PVDF	poly(vinylidene difluoride)
SiO_2	silica
SBU	secondary building unit
TCC	thermal column compartment
TIC	total ion chromatogram
UHPLC	ultra-high performance liquid chromatography
UHPLC-MS-MS	ultra-high performance liquid chromatography tandem mass spectrometry

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APPENDIX A
FILTER STUDY

During the method development stage of this study, several syringe filter membranes were screened for compatibility with the opioids. Solutions of a known concentration of carfentanil in methanol, water, and a 1:1 ratio of methanol to water were passed through the filters, then evaluated for any loss of carfentanil following filtration. Carfentanil was found to adhere to several of the filtration membranes, precluding their use as a separation mechanism for the study. As a result, centrifugation was employed in lieu of filtration. The results of the diffusion efficiency of the carfentanil through the filter membranes are provided in Table A-1. The results reveal that other porous surfaces show similar opioid uptake trends to MOF and SiO_2 surfaces. These experiments were performed once for each filter; therefore, the standard deviation associated with each value cannot be guaranteed <10%.

Table A-1. Diffusion Efficiency of Carfentanil Using Various Syringe Filters

Filter	**Carfentanil Recovery (%)**		
	In Methanol	**In Water**	**In 1:1 Ratio of Methanol/Water**
Control-No Filter	93.1	94.4	87.4
Nylon	94.5	69.9	84.8
PVDF	99.0	9.7	53.5
PTFE	96.5	79.4	91.2
Glass PreF	100.0	45.1	88.4
Anotop	96.9	N/A*	87.0
PVDF Syringeless	104.8	66.6	88.0

N/A = not applicable
PTFE = poly(tetrafluoroethylene)
PVDF = poly(vinylidene difluoride)
*Anotop filter was incompatible with 100% aqueous solution.

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