

## Development of a High-Throughput LC/MS/MS Assay for 13 Commonly Prescribed Pain Management Drugs from Urine with Cleanup Using Solid Phase Extraction (SPE)

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*Utilizing the ultra-high efficiency provided by core-shell technology columns, thirteen pain management opioids were resolved in 1.5 minutes with one second wide peaks at base on a Kinetex<sup>™</sup> C18 2.6  $\mu$ m 50 x 2.1 mm column. Sensitivity, reproducibility and productivity are dramatically improved after efficient sample cleanup and concentration using Strata<sup>™</sup>-X-C SPE. The combined SPE LC/MS/MS analysis provides significant reductions in analysis time, labor requirements, and cost per sample while increasing sensitivity, accuracy and precision.*

### Introduction

As the average age of healthcare patients increases, pain management medicine requires greater need for less expensive, quicker, more accurate, and reproducible methods for analyzing the presence and concentration of the pain management medication in vivo. Chronic pain affects approximately 86 million people in the United States.<sup>1</sup> Pain management centers have been established all over the country to help treat these chronic conditions. During treatment, routine testing is critical to prevent abuse.

Urine is used as it is a copiously available bodily fluid that can be collected easily and used for analysis. The nature of urine is highly dependent on the patient and their diet, hydration level, and health condition. The variances in the endogenous nature of the urine matrix can impact the chromatographic separation and quantitation. In addition, these matrix effects can cause signal enhancement, making the quantitative results for the analytes appear higher in concentration. Signal suppression is also a potential matrix effect, resulting in quantitative results for the analytes to appear lower in concentration. Endogenous urine contaminants can also cause coelution or chromatographic interference. Solid phase extraction (SPE) provides an effective means for removing potential matrix interferants prior to LC/MS/MS analysis.

Typically SPE and GC/MS have been used to perform the analysis of opioids in urine. Most GC/MS methods for the analysis of opioids can require 7 minutes or much longer from injection to injection. The method demonstrated in this technical note increases sensitivity, making analysis of lower analytical concentrations possible, as well as tremendously reducing overall analysis time.

The rapid analysis of 13 commonly prescribed pain management compounds from urine is achieved using a strong cation exchange SPE cleanup and concentration step followed by fast (<2 minutes) UHPLC analysis using a new core-shell column technology coupled to MS/MS.

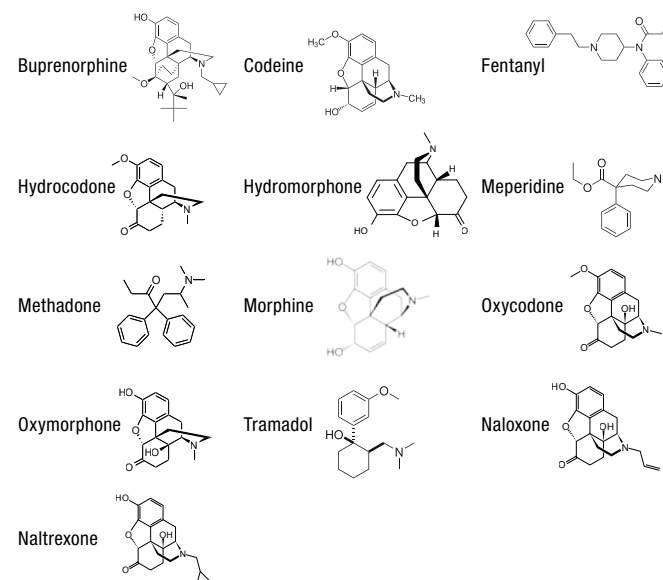
### Methods

A full bioanalytical validation protocol was attempted for a new SPE + LC/MS/MS procedure for pain management drugs. Five different lots of urine samples were spiked at therapeutically relevant concentrations with 13 commonly prescribed drugs, including hydrocodone, nalterxone, tramadol, and fentanyl. The lower limit of quantitation (LLOQ) was targeted for 10x below the therapeutic prescription limit with less than 20 % RSD at LLOQ. 10x above cutoff was set for the upper limit of quantitation (ULOQ).

Urine samples were first hydrolyzed to convert the glucuronide metabolites to native form using  $\beta$ -glucuronidase. This was done by first weighing 1 g of  $\beta$ -glucuronidase and diluting with 20 mL of DI water. A 100  $\mu$ L aliquot of this solution was added to 1 mL of urine and vortexed to mix (6200 units in 1 mL of urine). Samples were incubated for 2 hours at 60 °C, then centrifuged for 10-15 minutes at 9,500-13,000 rpm to form a pellet of protein and solids. The clarified supernatant (~1 mL) was then removed and diluted with 1 mL of 100 mM ammonium acetate buffer (pH 5.95).

Cleanup was done using a 30 mg/3 mL polymer-based high ion-exchange capacity media to remove endogenous matrix components. Analysis was done using an Agilent<sup>®</sup> 1200SL HPLC coupled to an Applied Biosystems<sup>®</sup> 4000 QTRAP<sup>®</sup> (with Turbo V<sup>™</sup> ion source) using a new core-shell HPLC column technology. Conditions for both are listed in their respective figures & tables.

**Table 1.**  
Drugs Monitored\*

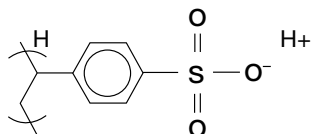


\* All standards were purchased from Cerilliant<sup>®</sup> Corporation.

# TN-1070

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**Table 2:**  
SPE Protocol



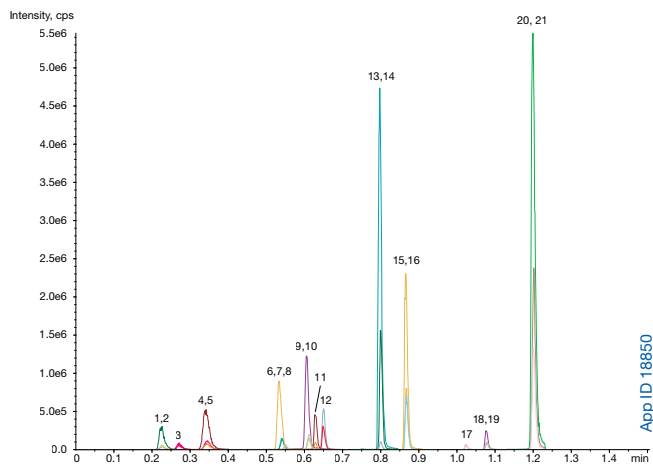
- Cartridge:** Strata-X-C 30 mg/3 mL
- Part No.:** 8B-S029-TBJ
- Condition:** 1 mL methanol
- Equilibrate:** 1 mL 100 mM ammonium acetate buffer (pH 5.95)
- Load:** Pretreated sample diluted with 1 mL 100 mM ammonium acetate buffer (pH 5.95)
- Wash:** 2 x 1 mL 100 mM ammonium acetate buffer (pH 5.95)
- Wash:** 2 x 1 mL methanol
- Dry:** Full vacuum for 2-5 minutes to remove residual water and methanol as much as possible
- Elute:** 2 x 0.5 mL 60:24:16 ethyl acetate / IPA / NH<sub>4</sub>OH

Evaporate to dryness using warm nitrogen gas and heating block at 45 °C, then reconstitute in 1 mL of mobile phase for LC/MS/MS analysis.

### Results and Discussion

The analysis of all 13 pain management drugs was completed in less than 1.5 minutes with a total gradient cycle time from injection to injection of less than 2.2 minutes (**Figure 1**). The use of the new Kinetex core-shell HPLC column technology provided extremely sharp chromatographic bands with average peak width at base of 1-2 seconds. This extremely narrow peak width challenged the scan rate of the 4000 QTRAP MS requiring the use of scheduled MRM transition windows to ensure enough scans per peak for accurate quantitation. The narrow peak width also translated to a significant increase in MS sensitivity, requiring the dilution of some samples by 20 times to bring concentrations within the dynamic range of the system.

**Figure 1.**  
LC/MS/MS Analysis of Pain Panel Drugs



**Column:** Kinetex 2.6 μm C18 100 Å  
**Dimensions:** 50 x 2.1 mm  
**Part No.:** 00B-4462-AN

**Mobile Phase:** A: 0.1% Formic acid in Water  
B: 0.1% Formic acid in Acetonitrile

Gradient	Time (min)	A (%)	B (%)
	0.00	95	5
	1.30	40	60
	1.31	5	95
	1.51	5	95
	1.52	95	5
	2.20	95	5

**Flow Rate:** 1.2 mL/min  
**Detection:** MS (ambient)  
**Temperature:** 25 °C (column)

Sample:	1. Morphine	2. Morphine-d3	3. Oxycodone	4. Hydromorphone	5. Hydromorphone-d6	6. Codeine	7. Codeine-d6	8. Naloxone*	9. Oxycodone	10. Oxycodone-d6	11. Naltrexone	12. Hydrocodone	13. cis-Tramadol	14. cis-C13-Tramadol-d3	15. Meperidine	16. Meperidine-d4	17. Fentanyl	18. Buprenorphine	19. Buprenorphine-d4	20. Methadone	21. Methadone-d3
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\* Analysis required 20x dilution of reconstituted sample extract.

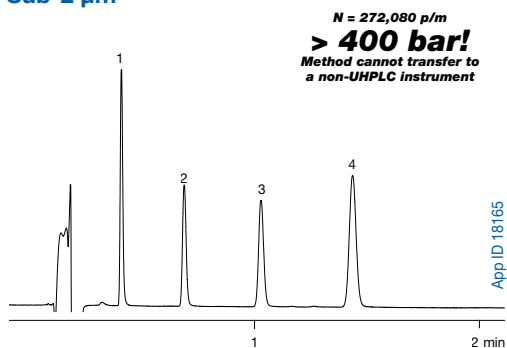
# TN-1070

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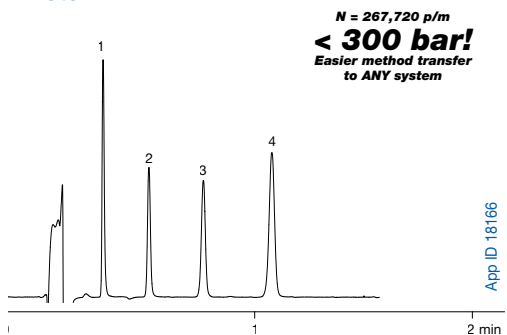
The efficiency obtained by the Kinetex columns is the result of a revolutionary new particle technology that provides sub-2  $\mu\text{m}$  like efficiencies at backpressures that can be used on any conventional HPLC system (**Figure 2**). **Figure 3** shows the particle geometry of these new columns that are generated by growing a 0.35  $\mu\text{m}$  porous layer onto a 1.9 non-porous core. The resulting 2.6  $\mu\text{m}$  particles can be used to obtain extremely high column efficiencies on any HPLC system.

**Figure 2.**  
Efficiency Comparison of Kinetex vs. Sub-2  $\mu\text{m}$  Column

### Sub-2 $\mu\text{m}$



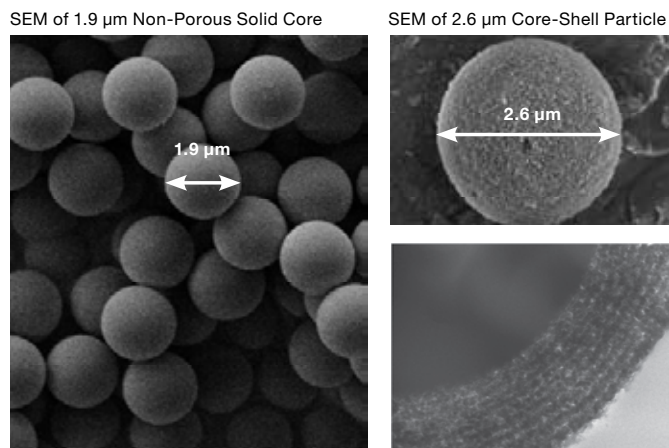
### Kinetex



**Conditions for both columns:**

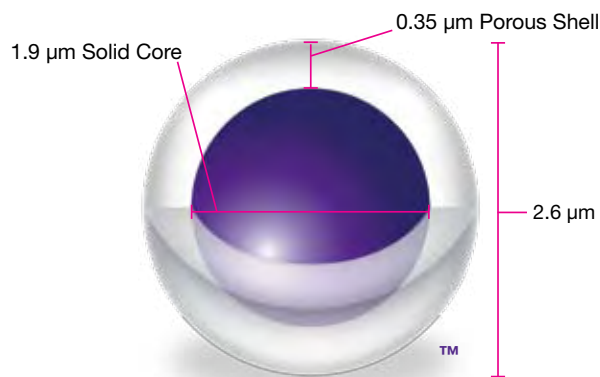
- Column:** Kinetex 2.6  $\mu\text{m}$  C18  
Traditional 1.7  $\mu\text{m}$  C18
- Dimensions:** 50 x 2.1 mm
- Mobile Phase:** Acetonitrile / Water (50:50)
- Flow Rate:** 0.6 mL/min
- Temperature:** 25  $^{\circ}\text{C}$
- Detection:** UV @ 254 nm
- Instrument:** Waters<sup>®</sup> ACQUITY<sup>®</sup> UPLC<sup>®</sup>
- Sample:** 0.5  $\mu\text{L}$  test mixture
  1. Acetophenone
  2. Benzene
  3. Toluene
  4. Naphthalene

**Figure 3.**  
SEM Images of Solid Core vs. Core-Shell Particles



### Kinetex 2.6 $\mu\text{m}$ Core-Shell Particle

- Reduced diffusion path maximizes efficiency
- Ultra-high performance on any system with Kinetex 2.6  $\mu\text{m}$  columns

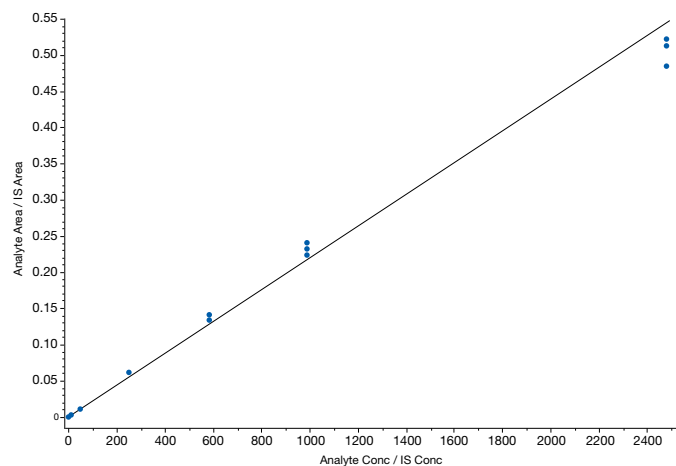


# TN-1070

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**Table 3** summarizes the results obtained using this analytical method. The chromatographic flow rate of 1.2 mL/min allowed for the fast separation of the 13 compounds and the internal standards, with retention times ranging from 0.22 minutes for morphine to 1.2 minutes for methadone. Some internal standards were used as reference for analytes for which a deuterated compound was not readily available. The analytical method resulted in an LLOQ of 2.5 ng/mL with accuracy of 83-98 % for all compounds, with the exception of fentanyl, which had a LLOQ of 0.05 ng/mL due to its low therapeutic concentration. At LLOQ and 3x LLOQ, most RSDs were well below 15 %, indicating a wide linear working range for all compounds. Method performance at cutoff was better than at the LLOQ or ULOQ, indicating that there may have been problems with dilutions during sample preparation; future work will be done to confirm this. The cutoff concentrations are defined as 300 ppb for all compounds except for fentanyl. Due to the relatively high pharmacological efficacy of fentanyl, ~50 times greater than morphine, the linear analytical range of fentanyl is reported at 50x lower concentration than the other pain panel opioids. At cutoff concentrations all compounds were analyzed with 84 %-102 % accuracy and 5 % or less RSD values. Lot-to-lot precision and accuracy was examined by using five different urine donors to examine potential matrix effects across multiple urine matrices at the cutoff concentration values; the RSD values were all less than 7 % with high accuracy regardless of the urine donor. **Figure 4** shows an example of analytical linearity range from 2.5-2500 ppb for morphine, with  $1/x^2$  weighting;  $r = 0.9912$ .

**Figure 4.** Example of extracted standard linearity for morphine from 2.5 ppb to 2500 ppb. Regression performed using weighting of  $1/x^2$ , this distributes the error across all points without the higher concentration values skewing disproportionately the values at lower concentration;  $r=0.9912$



**Table 3.**  
LC/MS/MS Results from Bioanalytical Validation Protocol

Analyte	ISTD	RT (min)	Q1	Q3 quant	Q3 confirm	ISTD Q1	ISTD Q3	Linear range (ng/mL)	Accuracy @ LLOQ (n=4)	Precision @ LLOQ (n=4)	Accuracy @ 3xLLOQ (n=7)	Precision @ 3xLLOQ (n=7)	Accuracy @ cutoff (n=5)	Precision @ cutoff (n=5)	Accuracy lot to lot @ cutoff (n=5)	Precision lot to lot @ cutoff (n=5)	%ME
morphine	d3-morphine	0.22	286.1	128.2	152.2	288.8	152.1	2.5-2500	81.20 %	26.40 %	61.3 %	30.0 %	93.5 %	3.30 %	94.4 %	2.6 %	83.6
oxymorphone	d6-hydromorphone	0.26	302.2	198.2	227.2	292.0	198.2	2.5-1000	101.4 %	10.1 %	89.0 %	4.0 %	83.9 %	2.9 %	85.5 %	3.3 %	92.1
hydromorphone	d6-hydromorphone	0.33	286.1	185.1	157.2	292.0	198.2	2.5-1000	105.3 %	9.4 %	90.0 %	6.3 %	91.5 %	3.1 %	91.1 %	2.7 %	97.8
codeine	d6-codeine	0.53	300.2	115.1	152.1	306.2	152.1	2.5-1000	97.6 %	14.5 %	88.8 %	5.4 %	92.6 %	4.8 %	93.0 %	6.4 %	80.1
naloxone	d6-oxycodone	0.54	328.4	212.3	268.2	322.2	247.1	2.5-2500	86.2 %	14.0 %	85.5 %	7.5 %	96.8 %	3.9 %	97.9 %	4.9 %	88.5
oxycodone	d6-oxycodone	0.6	316.0	241.1	256.3	322.2	247.1	2.5-1000	97.4 %	10.2 %	94.5 %	10.2 %	94.0 %	3.2 %	94.0 %	4.1 %	93.0
naltrexone	d6-oxycodone	0.62	342.4	270.2	324	322.2	247.1	2.5-1000	83.7 %	6.8 %	98.3 %	6.7 %	91.1 %	4.7 %	89.0 %	5.6 %	86.1
hydrocodone*	d6-oxycodone	0.64	300.2	199.2	128	322.2	247.1	2.5-1000	110.1 %	20.6 %	83.4 %	11.1 %	87.1 %	5.2 %	84.4 %	5.0 %	N/A
cis-tramadol*	cis-C13-d3-tramadol	0.79	264.4	58.2	42.2	268.2	58.1	2.5-1000	95.6 %	19.9 %	97.7 %	6.2 %	101.6 %	2.9 %	93.7 %	3.2 %	N/A
meperidine*	d4-meperidine	0.86	248.1	220.2	174.2	252.2	224.2	2.5-1000	81.4 %	11.2 %	77.0 %	7.5 %	93.2 %	4.8 %	87.6 %	4.8 %	N/A
fentanyl	d4-buprenorphine	1.0	337.3	105.1	188.2	472.3	400.4	0.05-20	117.46 %	12.5 %	83.24 %	4.6 %	85.1 %	3.3 %	76.8 %	5.8 %	63.7
buprenorphine	d4-buprenorphine	1.1	468.3	396.2	414.4	472.3	400.4	2.5-1000	105.78 %	13.2 %	91.64 %	7.5 %	95.6 %	3.0 %	95.6 %	3.7 %	81.7
methadone*	d3-methadone	1.2	310.2	265.2	105.1	313.0	268.2	10-1000	N/A	N/A	N/A	N/A	100.2 %	2.1 %	91.8 %	5.8 %	N/A

\* Analysis required 20x dilution of reconstituted sample extract.

# TN-1070

## APPLICATIONS

The highly selective nature of LC/MS/MS reduces the number of co-elutions that interfere with analyte quantitation, but these components do accumulate in the system, requiring more frequent maintenance. The use of Strata-X-C SPE material significantly reduced matrix interference for all compounds. The effect of the SPE was most dramatic for fentanyl due to the low cutoff concentration for this analyte. By using a 30 mg bed mass we were able to significantly reduce the solvent volume required for conditioning, wash, and elution steps. This reduced solvent volume translated into significant cost and time savings for the subsequent blowdown steps. The removal of matrix is also important for long term instrument stability.

The Strata-X-C SPE protocol has been optimized for the 13 analytes and the internal standards. The pKa values of the cationic analytes are all close to 8. The buffer chosen, ammonium acetate, is adjusted to pH 5.95 in order to protonate and charge the cationic analytes at 2 pH units below their pKa values. This ensures the sulfonic acid ligand on Strata-X-C will retain the analytes. Endogenous contaminants with lower pKa values will not be retained which allows for the 100 % methanol wash to more effectively remove contaminants such as urobilin which may appear yellow. The elution solution is 60:24:16 ethyl acetate/ IPA/ NH<sub>4</sub>OH, which is employed to solubilize or disrupt the retention of fewer endogenous contaminants during elution. Optimized wash and elution solutions yield clearer and cleaner eluents and more reproducible and accurate chromatography (**Figure 5**). The sorbent mass was also optimized to 30 mg of media in a 3 mL tube. The high ion-exchange capacity of the media allows for processing small sample volumes even at low concentrations. Due to the tremendously high sensitivity of the method, only 1 mL of urine was required for loading on Strata X-C SPE. Using less sorbent reduces cost and solvent consumption, and allows for small volume elution aliquots thereby saving time during evaporation for high sample throughput and increased productivity.

**Figure 5.**  
Optimization of Wash & Elution Conditions for SPE



# TN-1070

## APPLICATIONS

Ultra-high efficiency and fast chromatographic separations result in very narrow peak widths, enhancing resolution and sensitivity. However, these very narrow peaks also present detection challenges as peak widths approach 1-2 seconds in width. This is especially true for this method when three MRM transitions must be monitored concurrently for each of the thirteen compounds and the eight internal standards. To optimize data acquisition on the API 4000 QTRAP, scheduled  $\pm 3$  second MRM windows were used to get as close to 20 data points per second as possible (15-18 Hz experimentally) to avoid under-sampling. Under-sampling of the chromatographic peaks results in loss of sensitivity, precision, accuracy, and resolution. To avoid losing chromatographic efficiency and resolution, 8-10 points are required to define each peak, but if peaks are closely eluting more points are needed. The MRM settings used here are highly recommended as the separation provided using the ultra-high efficiency Kinetex column produces very narrow, low volume peaks.

Additionally, when using Kinetex core-shell technology columns, LC/MS/MS instrumentation should be set up so narrow analyte bands are not compromised via extra-column band broadening. The setup used includes bypassing the MS grounding union, eliminating diverter valves in-line, and utilizing the near zero dead volume KrudKatcher™ Ultra in-line column filter (Phenomenex, Torrance, CA) to protect the column. Also it is recommended to use the narrowest ID and shortest lengths of connecting tubing possible. Dispersion can also be avoided by using fast flow rates, injecting the sample in weaker solvent conditions than the mobile phase, and running a ballistic gradient when possible.

### Conclusions

A bioanalytical validation procedure was performed for 13 commonly prescribed pain management drugs from urine. The use of Strata-X-C polymeric SPE material allowed for removal of matrix interferences and allowed for sample concentration.

The 30 mg / 3 mL format reduces the amount of solvent used for processing and the time required for blowdown steps. The Kinetex HPLC column technology provided ultra-fast run times and significantly improved method sensitivity for many drugs requiring 20x dilutions of samples. The complete solution represents a pre-validated method ready for implementation in any lab interested in analyzing pain management samples.

### References

1. American Chronic Pain Association website.

# TN-1070

## APPLICATIONS

### HPLC

#### Kinetex Ordering Information

##### 1.7 µm Minibore Columns (mm)

Phases	50 x 2.1	100 x 2.1	150 x 2.1
C18	00B-4475-AN	00D-4475-AN	00F-4475-AN
PFP	00B-4476-AN	00D-4476-AN	00F-4476-AN
HILIC	00B-4474-AN	—	—

##### 2.6 µm Minibore Columns (mm)

Phases	50 x 2.1	100 x 2.1	150 x 2.1
C18	00B-4462-AN	00D-4462-AN	00F-4462-AN
PFP	00B-4477-AN	00D-4477-AN	00F-4477-AN
HILIC	00B-4461-AN	00D-4461-AN	00F-4461-AN

##### 2.6 µm MidBore™ Columns (mm)

Phases	50 x 3.0	100 x 3.0	150 x 3.0
C18	00B-4462-YO	00D-4462-YO	00F-4462-YO
PFP	00B-4477-YO	00D-4477-YO	00F-4477-YO
HILIC	—	—	00F-4461-YO

##### 2.6 µm Analytical Columns (mm)

Phases	50 x 4.6	100 x 4.6	150 x 4.6
C18	00B-4462-E0	00D-4462-E0	00F-4462-E0
PFP	00B-4477-E0	00D-4477-E0	00F-4477-E0
HILIC	00B-4461-E0	00D-4461-E0	00F-4461-E0



#### KrudKatcher Ultra In-line Filter

The KrudKatcher Ultra filter body houses an integrated 0.5 µm 316 stainless steel filter element that efficiently removes microparticulates from the flow stream without contributing to system back-pressure or dead volume (<0.2 µL).



#### KrudKatcher Ultra In-Line Filter Ordering Information

Part No.	Description	Unit
AF0-8497	KrudKatcher Ultra In-Line Filter, 0.5 µm Porosity x 0.004 in. ID	3/pk

KrudKatcher Ultra requires 5/16 in. wrench. Installation wrench not provided.

### SPE

#### Strata-X-C Ordering Information

Format	Sorbent Mass	Part Number	Unit
<b>Tube</b>			
	30 mg	8B-S029-TAK	1 mL (100/box)
	30 mg	8B-S029-TBJ	3 mL (50/box)
	60 mg	8B-S029-UBJ	3 mL (50/box)
	100 mg	8B-S029-EBJ	3 mL (50/box)
	100 mg	8B-S029-ECH	6 mL (30/box)
	200 mg	8B-S029-FBJ	3 mL (50/box)
	200 mg	8B-S029-FCH	6 mL (30/box)
	500 mg	8B-S029-HBJ	3 mL (50/box)
	500 mg	8B-S029-HCH	6 mL (30/box)
<b>Giga™ Tube</b>			
	500 mg	8B-S029-HDG	12 mL (20/box)
	1 g	8B-S029-JDG	12 mL (20/box)
	1 g	8B-S029-JEG	20 mL (20/box)
	2 g	8B-S029-KEG	20 mL (20/box)
<b>96-Well Plate</b>			
	10 mg	8E-S029-AGB	2 Plates/Box
	30 mg	8E-S029-TGB	2 Plates/Box
	60 mg	8E-S029-UGB	2 Plates/Box



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