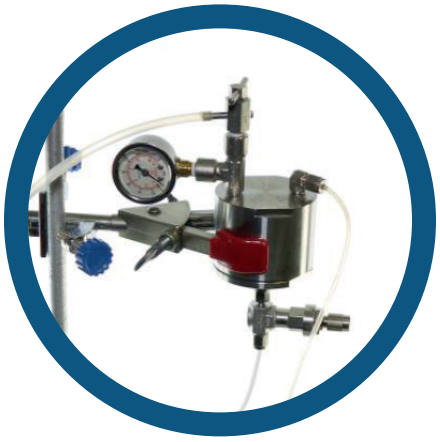
APPLICATION NOTE
#EP002-0

SiliCycle

SiliaMetS® E-PAK®



Suzuki Catalyst Scavenging Study with Activated Carbon and SiliaMetS

In recent years, the removal of post-reaction residues has become a major issue in the pharmaceutical industry. For several years, SiliCycle has offered SiliaMetS metal scavengers allowing customers to achieve this goal. SiliCycle now offers a new proprietary technology called E-PAK to purify API from residual metals. Tests were conducted to measure the efficiency of the E-PAK technology with SiliaMetS and activated carbon to remove $Pd(Ph_3)_4$ from a Suzuki coupling reaction. Screening tests in bulk were performed in a multi-reaction apparatus to select the best sorbents. In this Application Note, we demonstrate the direct and straightforward transfer from bulk to E-PAK for the removal of palladium.

LEARN MORE about our scavengers and E-PAK in our brochure "*Solutions for Metal & Organic Scavenging*".

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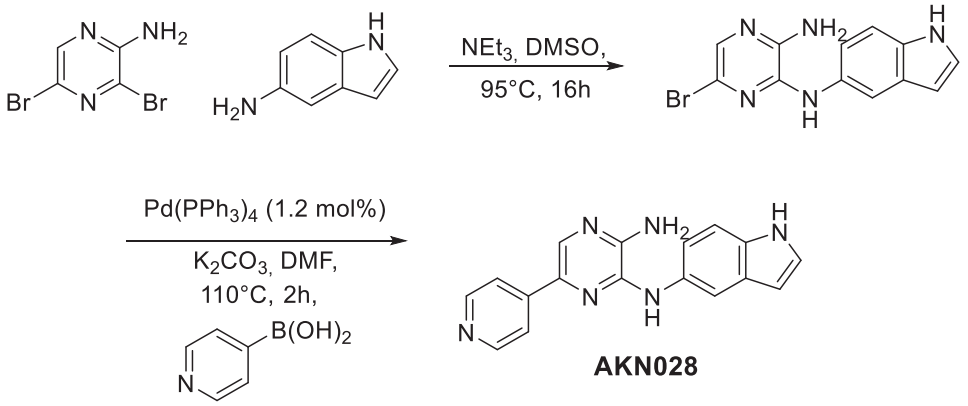
Suzuki Catalyst Scavenging Study with Activated Carbon and Silia*MetS*

The following scavenging studies were performed based on the model reaction used in the synthesis of the kinase inhibitor AKN028. The last step of this reaction is the Suzuki coupling of a 4-pyridinylboronic acid to the main scafold using $Pd(PPh_3)_4$ yielding AKN028. Scavenging studies were done on the resulting Pd contaminated product.



The synthesis is adapted from Wennerberg *et al.* (*Org. Process. Res. Dev.* **2018**, *22*, 1360-1364).
Palladium concentration in the crude product was measured at 4,960 mg/kg.

STEP 1: ACTIVATED CARBON SCREENING

Procedure

A preliminary screening of various activated carbons were tested using 50 % and 100 % w/w to the API. The samples were pre-weighed in polypropylene tubes suited for a multi-reaction apparatus. Portions of the crude API in a DMF solution were added to each tube without any previous purification. They were orbitally shaken for the desired time and temperature. Then, portions of each solution were collected and filtered (*0.45 µm*), providing samples to be analyzed by ICP-OES for Pd content.

Table 1: Activated carbon scavenging (%) using 50 and 100 % w/w of activated carbon/API at 22°C in DMF

Activated carbon scavenging (%) using 50 and 100 % w/w of activated carbon/API at 22°C in DMF				
Carbon	1h		4h	
	50 % w/w	100 % w/w	50 % w/w	100 % w/w
C-941	64	79	71	82
C-944	16	23	23	42
C-947	49	66	51	66
C-948	50	65	50	67

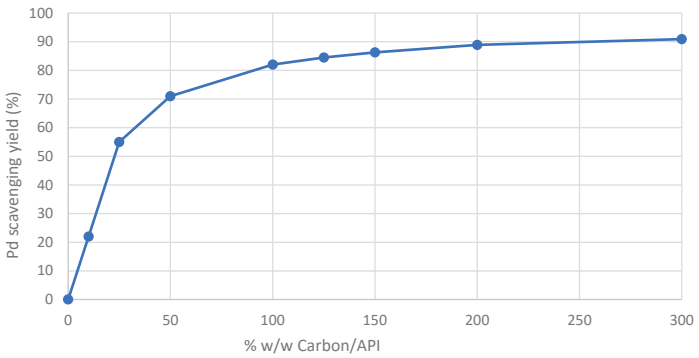
The results from the experiment (*Table 1*) demonstrates that C-941 was the most efficient carbon with up to 82 % of Pd scavenged after 4 hours. It was also observed that prolonged time and increased temperature had little influence on scavenging yields. Hence, one-hour contact time at room temperature was the selected set of conditions for this step.

In order to tune the optimal amount of C-941 to be used, various amounts of this activated carbon were tested at room temperature for one hour (*Table 2*).

Table 2: C-941 scavenging (%) using various % w/w of activated carbon/API at 22°C in DMF for 1h

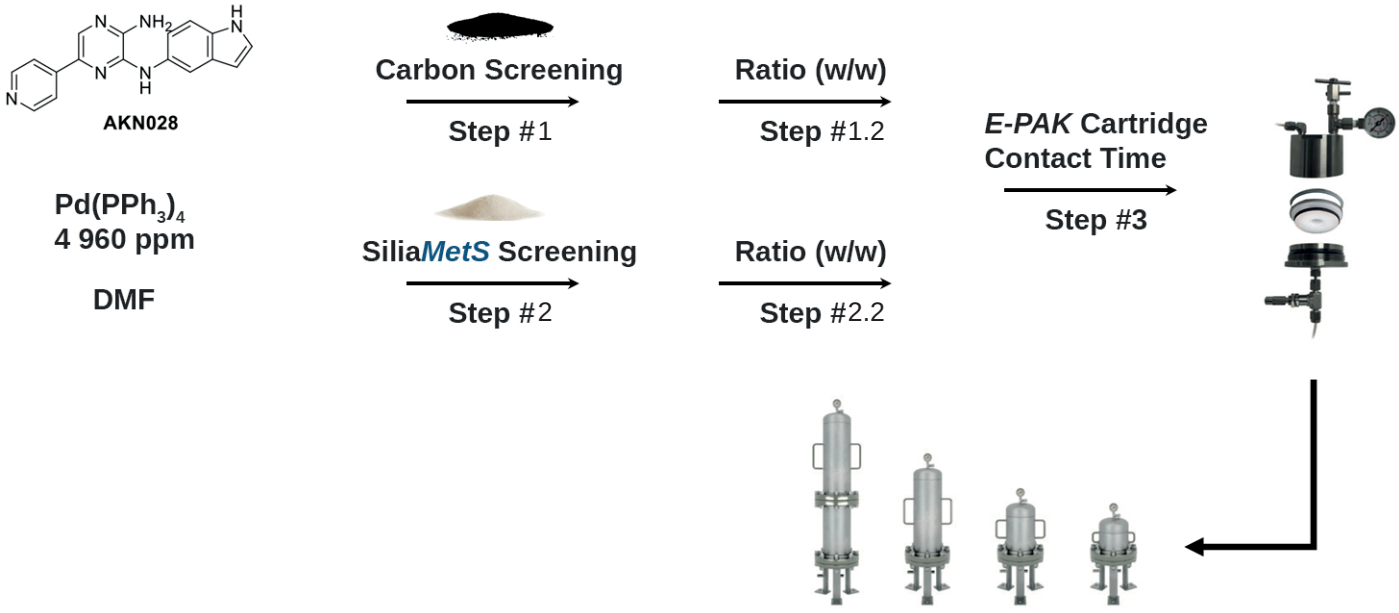
C-941 scavenging (%) using various % w/w of activated carbon/API at 22°C in DMF for 1h	
% w/w	Scavenging (%)
10	22
25	55
50	71
100	79
125	85
150	86
200	89
300	91

Figure 1: Scavenging efficiency (%) of C-941 according the % w/w Carbon/API



A ratio of 125 % w/w was selected for the remaining of the study, as any increase in scavenging efficiency was negligable as compared to the amount of carbon needed (seen as the plateau in *Figure 1*).

In summary, the results of the screening tests of the different activated carbon showed that C-941 yielded the best results with up to 91 % scavenging.



STEP 2: SILIA*METS* SCREENING

Procedure

Preliminary to the screening, a solution of AKN028 in DMF was treated with 125 % w/w of C-941 for one hour at room temperature and filtered on a pad of Celite 545. The cake was rinsed with DMF. The filtrate was passed through a 5 mm membrane, providing a solution to be used for the Silia*MetS* screening.

To screen the scavengers, 20 % w/w to API of different Silia*MetS* were pre-weighed in polypropylene tubes, suited for a multi-reaction apparatus. Portions of the prepared solution were added in each tube. They were orbitally shaken for the desired time and temperature. Then, portions of each solution were collected and filtered (*0.45 µm*), providing samples to be analyzed by ICP-OES for Pd content. The results provided in Table 3 show that Diamine and Imidazole were the most performant scavengers for this application. Hence, a secondary screening was performed with them in order to optimize the conditions. As the results were more promising with Silia*MetS* than with activated carbon regarding this application, a secondary screening was only done for the Silia*MetS*.

Table 3: Palladium scavenging (%) using 20 % w/w of Silia*MetS*/API at 22°C in DMF for 20h

Palladium scavenging (%) using 20 % w/w of Silia*MetS*/API at 22°C in DMF for 20h	
Scavenger	Scavenging (%)
DMT	25
Diamine	68
DEAM	2
Imidazole	93
TAAcONa	25

Secondary Screening

Following the preliminary screening tests in which Diamine and Imidazole had the best scavenging efficiency, a secondary screening was performed to see how efficiency was affected by temperature, screening time and % w/w of Silia*MetS* used.

Table 4: Palladium scavenging (%) using various % w/w of Silia*MetS*/API at **22**°C in DMF

Palladium scavenging (%) using various % w/w of Silia*MetS*/API at 22°C in DMF												
Scavenger	10 % w/w			20 % w/w			30 % w/w			40 % w/w		
	1h	4h	20h	1h	4h	20h	1h	4h	20h	1h	4h	20h
Diamine	25	37	57	40	62	68	64	87	96	84	92	97
Imidazole	59	80	93	93	94	95	94	95	95	95	96	96

Table 5: Palladium scavenging (%) using various % w/w of Silia*MetS*/API at **50**°C in DMF

Palladium scavenging (%) using various % w/w of Silia*MetS*/API at 50°C in DMF												
Scavenger	10 % w/w			20 % w/w			30 % w/w			40 % w/w		
	1h	4h	20h	1h	4h	20h	1h	4h	20h	1h	4h	20h
Diamine	34	48	83	78	92	96	92	96	97	95	96	97
Imidazole	73	93	93	94	95	95	95	95	96	96	96	96

Silia*MetS* Final Results

- SiliaMetS Imidazole proved to be more efficient at room temperature than SiliaMetS Diamine (Table 4).
- At least four hours of contact are necessary to reach high scavenging efficiency for SiliaMetS Imidazole.
- Higher temperature has an effect on scavenging with SiliaMetS Diamine (Table 5).
- SiliaMetS Imidazole was selected for the E-PAK experiment, due to it's higher kinetics, and its performance at room temperature (Table 4).

STEP 3: E-PAK CARTRIDGE SCAVENGING EXPERIMENT

The crude product was first pretreated with 125 % w/w of C-941 to reduce the Pd concentration from 4,960 mg/kg to 415 mg/kg. Then, the resulting solution was treated using the E-PAK technology with Silia*MetS* Imidazole. For this procedure, a 5 x 1 cm E-PAK Silia*MetS* Imidazole (*containing 8 g of grafted silica*) was inserted in the appropriate housing. Portions of 150 mL of DMF was used to pre-condition the unit. Next, 875 mL of a solution containing 27 g of AKN028 in DMF (*pretreated with 125 % w/w of C-941; 4,960 mg/kg of Pd reduced to 415 mg/kg for a 92 % scavenging yield*) was recirculated through the cartridge at room temperature (*60 mL/min flow*). Samples of 0.5 mL were collected after 1, 4, 6, 24 and 48 hours, and analyzed by ICP-OES for Pd content. It showed a scavenging ability of up to 95 % after 24 hours getting a final palladium concentration of 19 mg/kg from 415 mg/kg (*Table 6*). Increasing contact time did not result in an increase of scavenging efficiency (*or a reduction in Pd content*) after a certain point.

Table 6: Palladium scavenging (%) on E-PAK technology using Silia*MetS* Imidazole (loading of 1.0 mmol/g) at 22°C in DMF

Palladium scavenging (%) using various % w/w of Silia*MetS*/API at 50°C in DMF					
Pd initial concentration mg/kg	1h	4h	6h	24h	48h
415	87	91	92	95	95

Notes: Volume of solution treated on E-PAK cartridges: 875 mL Flow rate: 60 mL/min

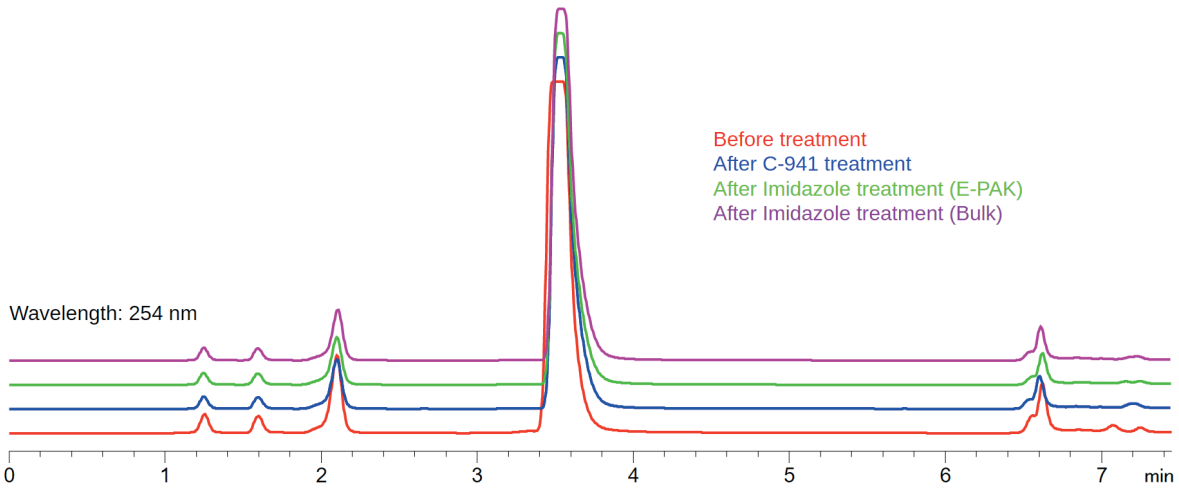
EVALUATION OF RECOVERY AND LEACHING

In order to confirm that there was no leaching during the E-PAK and the bulk treatments, LC-UV (*254 nm*) were run comparing crude AKN028 to the treated samples, and no significant product loss was observed. Furthermore, no side products were detected (*Figure 2*).

Portions of 10 mg of dried products were dissolved in 10 mL of methanol and injected.

Column: Silia*Chrom*® Plus C18, 4.6 x 150 mm, 5 µm, 100 Å
MPA: H_2O/MeOH (95/5) 0.1 % F.A.
MPB: H_2O/MeOH (5/95) 0.1 % F. A
Gradient: 70 % MPA 30 % MPB hold for 4 min, then 30 % MPA 70 % MPB for 1 min, then hold at 30 % MPA 70 % MPB for 3 min.
IonSpray Voltage, ESI voltage: 5.5 kV (ESI+)
Flow rate: 1 mL/min
Run time: 8 min

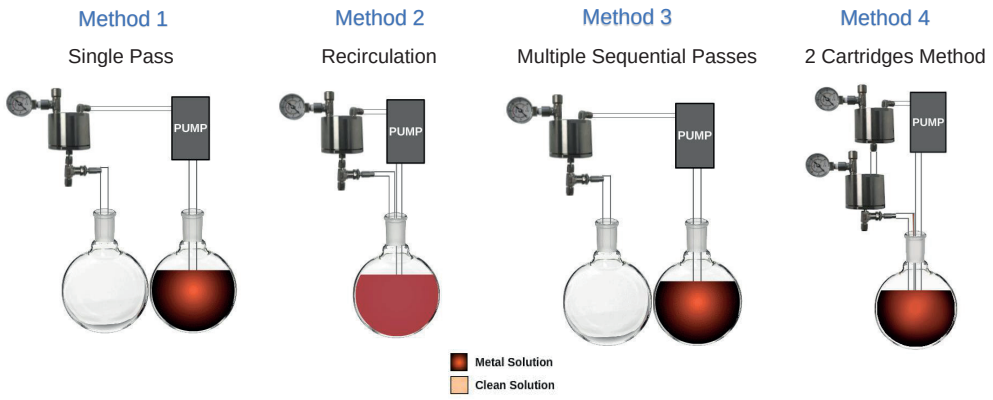
Figure 2: LC-UV of AKN028 before and after treatment



CONCLUSION

- Treatment with C-941 allowed to decrease Pd levels by 85-90 % (*4,960 mg/kg to 415 mg/kg*).
- Silia*MetS* Imidazole proved to be the most efficient scavenger to remove up to 95 % of the remaining Pd. A ratio of 30 % w/w Silia*MetS* Imidazole/API at room temperature for more than 4 hours was necessary to reach those yields, in bulk.
- Similar conditions were transferred onto an E-PAK Silia*MetS* Imidazole, providing similar results.
- No leachables were detected after treatment with C-941 neither with the E-PAK Silia*MetS* Imidazole experiment.
- No major product loss was observed.

Various methods of using lab scale Silia*MetS* E-PAK cartridges



Lab scale Silia*MetS* E-PAK cartridge

Lab scale Activated carbon E-PAK cartridge

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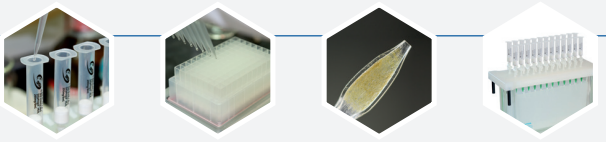
Silia*Bond*® – Organic Scavengers
***E-PAK*®** – Fixed Bed Flow-Through Purification Cartridges

CHROMATOGRAPHY & PURIFICATION

Silia*Flash*® – Irregular Silica Gels
Silia*Sphere*™ PC – Spherical Silica Gels
Silia*Bond*® – Chromatographic Phases
Silia*Sep*™ – Flash Cartridges
Silia*Plate*™ – TLC Plates

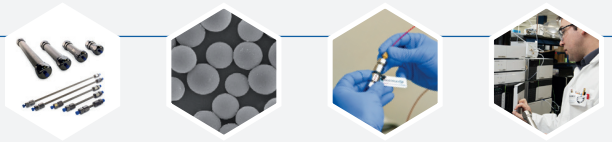
SAMPLE PREPARATION

Silia*Prep*™ – Silica-based SPE Cartridges & Well Plates
Silia*PrepX*™ – Polymeric SPE Cartridges & Well Plates
Silia*Prep*™ – Micro-SPE Tips



ANALYTICAL & PREPARATIVE CHROMATOGRAPHY

Silia*Sphere*™ – Spherical Silica Gels
Silia*Chrom*® – HPLC Columns



ORGANIC SYNTHESIS

Silia*Bond*® – Reagents & Oxidants

R&D SERVICES

Metal & Organic Scavenging Screening
Organic Synthesis
Extraction & Purification
Custom Column Packing
Material Science

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