

# Rhodium and Palladium Metal Scavenging with Carboxen® Synthetic Carbon Adsorbents

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## Introduction

The ICH-Q3D-R2 guidelines on permissible elemental impurity levels in drug products require a metal scavenging clean-up step for many active pharmaceutical ingredients (APIs). Organometallic catalysts based on palladium and rhodium are commonly used as process catalysts for the synthesis of APIs. These metals fall under Class-2B of the ICH-Q3D-R2 guidelines, with an oral consumption limit of 10 ppm.<sup>1</sup>

The current best practice is to utilize functionalized silica or resin particles for metal scavenging. Although activated carbons are excellent metal scavengers, they tend to result in a lower yield of API and are thus not as common. To overcome the limitations associated with traditional carbon adsorbents, Carboxen® Synthetic Carbons were developed. Through proprietary manipulation of polymeric precursors, the Carboxen® particles were finely tuned to enable high metal scavenging while maximizing API yield.

## Materials

The study focused on two commonly used organometallic catalysts, one rhodium-based catalyst and one palladium-based catalyst. They are listed below.

1. Tetrakis(triphenylphosphine)palladium(0);  
 $\text{Pd}(\text{PPh}_3)_4$ , Pd-1
2. Chloro(1,5-cyclooctadiene)rhodium(I) dimer;  
 $[\text{Rh}(\text{COD})\text{Cl}]_2$ , Rh-2

In addition, two representative APIs were selected and are listed below.

1. PF-06651600, a potent and selective JAK3 inhibitor.
2. Valsartan

Solvents used were methanol ( $\geq 99.9\%$ ) and N,N-dimethylformamide ( $\geq 99.9\%$ , 0.2  $\mu\text{m}$  filtered).

For comparison, Carboxen® Synthetic Carbons were tested alongside a leading metal scavenger commonly used in the industry. This reference scavenger consists of silica particles functionalized with thiol-moieties and is referred to as Silica-Thiol. The particle size of the reference silica-based material falls between 40 and 63  $\mu\text{m}$ . In contrast, the Carboxen® particles are larger at 400-840  $\mu\text{m}$ . This larger size enables the material to efficiently and expediently settle out from the solution compared to the Silica-Thiol, as depicted in **Figure 1**. Despite their larger size, the tapered pore structure in Carboxen® particles, does not limit their capacity or kinetics as compared to the Silica-Thiol particles. The Silica-Thiol utilizes a material with a 6 nm pore diameter, while Carboxen® particles have a macropore mouth (pores greater than 50 nm), that enables fast diffusion into the meso (2-50 nm) and micro (less than 2 nm) working pores.



**Figure 1.** Carboxen® 564 (left) and Silica-Thiol (right) in methanol after a [Rh(COD)Cl]<sub>2</sub> scavenging experiment. The discoloration observed with the Silica-Thiol treated solution is the result of the particles suspended in the solution. Carboxen® 564 quickly settles, as can be seen by the black layer under the stir bar.

Carboxen® adsorbents exhibit high purity and pass all the extractable and leachable tests as outlined in USP 43 - NF 38.<sup>2</sup> As they are produced from a synthetic source, Carboxen® Synthetic Carbons are inherently free of heavy metals and other inorganic content found in naturally derived carbon adsorbents.<sup>3</sup> These Carboxen® synthetic carbons are spherical particles that have excellent hardness attributes. They can withstand repeated handling without cracking or generating fine particles. They have been developed to withstand up to 16,000 psi in demanding applications.<sup>3</sup> Two grades of Carboxen® were tested in this study, Carboxen® 564 and Carboxen® 1005.

## Methods

Metal reduction and API yield experiments were conducted by combining the catalyst or API with the metal scavenger in either MeOH or DMF, while shaking on an orbital shaker. The duration of contact was set at 4 and 24 hours. Before the experiment, the metal scavengers were allowed to hydrate in the designated solvent for one hour with agitation. This hydration step is crucial to remove trapped air from the highly hydrophobic Carboxen® materials. The metal scavenging experiments started with an initial concentration of 1250 ppm catalyst (0.5 grams metal scavenger and 25 mg catalyst in 20 g of solvent). Less metal scavenger and solvent were used for the API experiments to increase the API/scavenger ratio to better represent an actual use case. The quantities by weight for the API experiments were: 25 mg API and 100 mg metal scavenger in 0.5 g solvent.

The remaining catalyst concentration in the solution after the scavenging was measured using a Mettler Toledo UV5 equipped with LabX software and standard quartz cuvettes. External calibration standards were used to generate calibration curves, employing the same solvent and wavelengths falling in the range of 341 – 350 nm for monitoring purposes.

At the corresponding time point, an aliquot of the reaction containing API was diluted to 70:30 water:methanol (v/v). The API concentration was determined by HPLC-UV using a Thermo Ultimate 300RS LC system. Chromatographic separation was performed using an Ascentis® Express C18 HPLC column (2.7 µm; 5 cm x 2.1 mm) with a 2 µL injection (**Table 1**). Additionally, a stock of concentrated API used to spike the reaction was also diluted and employed as calibrators in the 70:30 water:methanol (v/v) mixture.

**Table 1. Conditions for the API analysis by HPLC-UV.**

<b>Column:</b>	Ascentis® Express C18 column 5 cm x 2.1 mm I.D, 2.7 µm (53822-U)		
<b>Mobile phase:</b>	[A] 10 mM ammonium acetate (pH 5.0 with acetic acid); [B] Acetonitrile		
	<b>Time (min)</b>	<b>% A</b>	<b>% B</b>
	0	95	5
	0.5	95	5
<b>Gradient:</b>	5.0	0	100
	5.5	0	100
	5.6	95	5
	8.6	95	5
<b>Flow Rate:</b>	0.4 mL/min		
<b>Column Temp:</b>	30 °C		
<b>Detector:</b>	UV, 254 nm		
<b>Inj. Vol:</b>	2 µL		
<b>Sample:</b>	Prepared by 1:5 dilution into 70:30, water:methanol		

## Results and Discussion

### Pd Catalyst Removal

The optimal conditions for scavenging of **Pd-1** using Carboxen® 564 were first identified and then applied to the Silica-Thiol scavenger for comparison. The outcomes of these experiments are provided in **Table 2**. The effectiveness of Carboxen® 564 at sequestering **Pd-1** was greater in methanol than dimethylformamide. A continuing decrease in the concentration of **Pd-1** was evident as the incubation time increased from 4 to 24 hours at room temperature (approximately 23 °C). However, it is important to note that the remaining concentration levels of **Pd-1** exceeded the allowed limits as mandated by the ICH-Q3D-R2 guidelines. Further optimization of the sequestration was identified by increasing the temperature slightly to 40 °C. Under these conditions, Carboxen® 564 out-performed the leading industry practice of Silica-Thiol scavenging.

**Table 2. Scavenging of Pd(PPh<sub>3</sub>)<sub>4</sub>, Pd-1**

Scavenger	Solvent	Temperature [°C]	Catalyst Concentration after 4 hrs. [ppm]	Catalyst Concentration after 24 hrs. [ppm]
Carboxen® 564	DMF	RT ~ 23	640	129
Carboxen® 564	MeOH	RT ~ 23	233	45
Carboxen® 564	MeOH	40	19	12
Silica-Thiol	MeOH	40	Not Measured	41

### Rh Catalyst Removal

An investigation to optimize the conditions for scavenging of **Rh-2** with Carboxen® 564 were explored and are outlined in **Table 3**. As was shown with **Pd-1**, the scavenging was better in methanol as compared with dimethylformamide. However, the removal of **Rh-2** was less effective, with approximately half of the initial concentration remaining. Contrary to the results seen with **Pd-1**, raising the temperature to 40 °C, did not lead to the same observation. Rather than optimizing the conditions further, the Carboxen® material was modified in a way to increase the surface area of the graphene-like hydrophobic surface. This modified particle is referred to as Carboxen® 1005.

The surface area of Carboxen® 564 is around 450 m<sup>2</sup>/g whereas Carboxen® 1005 has a surface area of around 750 m<sup>2</sup>/g. For reference, the Silica-Thiol has a surface area roughly in the range of 500 m<sup>2</sup>/g. Carboxen® 1005 was effective at removing **Rh-2** across different solvents or time-point under room temperature conditions (approximately 23 °C). The Silica-Thiol showed similar scavenging results as compared to Carboxen® 1005.

Although Carboxen® 564 demonstrated limited effectiveness for **Rh-2** removal in this study, it is currently used in industrial applications for this purpose. Therefore, it is advisable to start the scavenging process with Carboxen® 564 due to its cost-effectiveness when compared to Carboxen® 1005 and its competitor Silica-Thiol.

**Table-3. Scavenging of [Rh(COD)Cl]<sub>2</sub>, Rh-2**

Scavenger	Solvent	Temperature [°C]	Catalyst Concentration after 4 hrs. [ppm]	Catalyst Concentration after 24 hrs. [ppm]
Carboxen® 564	DMF	RT	1128	1034
Carboxen® 564	MeOH	RT	735	631
Carboxen® 564	MeOH	40	826	732
Carboxen® 1005	DMF	RT	29	15
Carboxen® 1005	MeOH	RT	25	28
Silica-Thiol	DMF	RT	27	21
Silica-Thiol	MeOH	RT	30	28

### API Yield

An effective metal scavenger should also demonstrate a low binding affinity for the API product. Following contact with Carboxen® 564 for up to 24 hours, high yields of both APIs were obtained. The PF-06651600 compound exhibited a remarkable recovery of >99% while Valsartan's recovery was 96%.

Both APIs were evaluated using methanol at room temperature in 4 equivalent ratio (w/w) of excess Carboxen® to API. Carboxen® 1005 has yet to be tested for API yield. However, it is expected that the more hydrophobic Carboxen® 1005 will have lower affinity for these and additional polar APIs.

## Conclusions

The newly developed Carboxen® Synthetic Carbons have demonstrated an effective capacity to scavenge **Pd-1** and **Rh-2**. Carboxen® 564 worked well to decrease **Pd-1** from an initial concentration of 1250 ppm down to 12 ppm and outperformed an industry preferred thiol functionalized silica material.

The newest member of the Carboxen® family, Carboxen® 1005, was developed for Rh-2 removal and worked well to decrease its concentration from 1250 to 15 ppm. These hydrophobic Carboxen® Synthetic Carbons also show low affinity for common polar APIs resulting in high product yield. Finally, because of the larger size of these particles, they offer quick and easy filtration as compared to the silica-thiol competitor.

## Featured Products

Metal Scavenger	Cat. No.
Carboxen® Adsorbent, matrix Carboxen® 564	CX2564
Carboxen® Adsorbent, matrix Carboxen® 1005	CX21005
HPLC Column	
Ascentis® Express C18, 2.7 µm HPLC Column	53822-U
L x I.D. 5 cm x 2.1 mm	
Solvent	
Sigma-Aldrich Methanol	34860
OmniSolve® N,N-Dimethylformamide	DX1726
APIs	
PF-06651600	PZ0316
Valsartan	PHR1315
Catalyst	
Tetrakis(triphenylphosphine)palladium(0), 99%	216666
Chloro(1,5-cyclooctadiene)rhodium(I) dimer, 98%	227951

## Reference

1. International Council for Harmonization. ICH Topic Q3D (R2) on elemental impurities. Eur. Med. Agency - Sci. Med. Heal. 31, 1–86 (2022).
2. USP 43-NF38 Activated Charcoal. [https://online.uspnf.com/uspnf/document/1\\_GUID-1357BC23-BC29-48BF-84B2-A162A10410BF\\_3\\_en-US](https://online.uspnf.com/uspnf/document/1_GUID-1357BC23-BC29-48BF-84B2-A162A10410BF_3_en-US) (2018).
3. Abrahamson, J. Synthetic Carbon Adsorbents for Industrial Water Purification, MilliporeSigma, 2021. <https://www.sigmaaldrich.com/deepweb/assets/sigmaaldrich/marketing/global/documents/361/165/carboxen-water-purification-wp8009en-ms.pdf>

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