Metal Scavengers in Process Chemistry
An Investigative Study

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Introduction

Compliance with GMP is a necessary condition for drug authorization however the scrutiny that it demands can pose local engineering and chemistry issues becuase process chemists are under increasing pressure to deliver products.

Catalytic reactions using metals such as Pd, Pt, Ru and Rh, are becoming more popular due to their atom economy and greener credentials. However FDA and EMEA guidance is becoming increasingly challenging to meet.

Classical methods to removal metals, such as recrystallization, distillation or extraction are energy intensive or may be irreproducible. Carbon adsorption is popular however, there is a significant risk of API loss depending on the product structure, and carbon can consume a lot of reactor space.

Metal scavenger approaches are gaining in popularity due to generic methodology and reproducible and efficient function however there is a lack of understanding on how to best implement scavengers in a process.

We present key findings and also compare carbon to metal scavengers, looking at both removal of palladium and subsequent recovery of product.

Overview

Metal scavengers were first investigated for contamination by independently confirmed ICP metal analysis methods. Additionally, these scavengers were extracted in a range of common solvents in order to show extractable and leachable levels. A metal scavenging reaction comparing API product yield, purity and also metal removal using metal scavengers was compared to corresponding carbon methods.

Experimental

Reagents: Ethyl Acetate (EA) and Palladium Metal Ligands $Pd(Cl)_2(PPh_3)_2$ were purchased from Sigma Chemical Co. (Dorset, UK). Model API analogue 2-methy-5-phenylbenzoxazole was obtained through TCI (Toyo Chemical Company, Japan).

Experiment 1

Lowest metal content from Biotage metal scavengers

Prior to use, metal scavengers were analysed directly as supplied by ICP for a range of metals and found to contain very low levels (<10ppm for the 10 key metals screened).

↓Metal Scavenger↓	Metal → As	Cd	Co	Hg	Ni	V	Cr	Cu	Li	Mo	Sb	Sn
Si-Thiol	0 (13)*	1.1	0	0 (4)*	0	1 (13)*	2	1.5	0	4	0	0
Si-TMT	0	1.3	0	3	0	2	4	2.4	0	1	0	0
MP-TMT	0	0.5	0	0	2	0	2	2.2	0	2	0	9
SCX-2	0	0.6	0	3	0	0	2	1.2	0	2	0	0
Si-Trisamine	0	0.7	0	0	0	1	2	1.2	0	0	0	0

Datapoint from similar competitive metal scavenger.

Figure 1. *Inherent Metal Content of Various Scavengers.*

Biotage metal scavengers are treated and purified during manufacture have the lowest inherent metals content of any metal scavenger, thereby eliminating risk of contamination when used in scale up processes. In contrast, some other commercially available scavengers were tested under identical conditions and found to contain 1-100 times higher levels of toxic metals such as Arsenic, Mercury or Vanadium.

Experiment 2

Low extractable from Biotage Metal Scavengers

Each metal scavenger was exhaustively extracted in EtOAc, MeOH, THF and DCM, then analysed by GC. BIotage metal scavengers exhibited no leachable residues when used in conjunction with a wide range of organic solvents and compared to other commercially available metal scavenger, were found to be much cleaner under conditions of extraction.

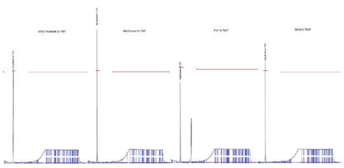

Figure 2. *Si-TMT solvent extract cleanliness.*

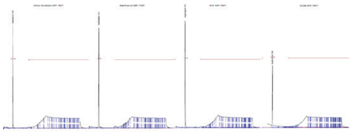

Figure 3. *MP-TMT solvent extract cleanliness.*

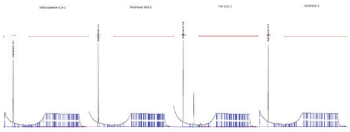

Figure 4. *SCX-2 solvent extract cleanliness.*

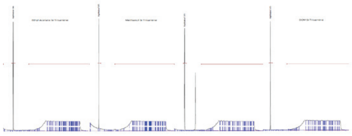

Figure 5. *Si-Trisamine solvent extract cleanliness.*

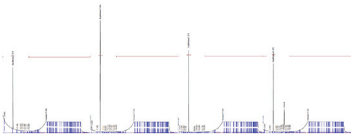

Figure 6. *Si-Thiol solvent extract cleanliness.*

Figure 2 to 6. Chromatograms demonstrate a high degree of extract cleanliness, THF traces indicate a solvent based impurity that is present in the blank (so can be eliminated).

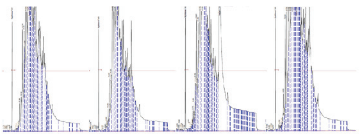

Figure 7. *Competitor P - Thiol based metal scavenger solvent extract cleanliness.*

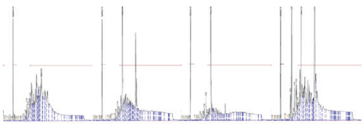

Figure 8. *Competitor S – Si Thiol solvent extract cleanliness.*

Figure 7 & 8. Demonstrate the degree of extractable residues obtained from a comparative extraction of other commercially available metal scavengers in the same solvents

Experiment 3

Pd removal with high API yield from example scavenging reaction

A model API solution (10% wt/vol) was treated with 10 wt% metal scavenger and the results compared.

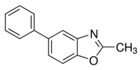

Figure 9. *Model API [2-methyl-5-phenylbenzoxazole].*

Ethyl Acetate (29mL), 2-methyl-5-phenylbenzoxazole (3g, 14mmol), dichlorobis(TPP)Pd II (500ppm) as 1mL THF) was stirred at RT for 16 hours with selected metal scavengers (300mg, 0.1mmol, 0.007 – 0.027 equiv).

The extracts were filtered and dried. Recovered benzoxazole was measured and the extract analysed by GC-FID and ICP-MS analysis to determine Palladium removal.

Metal Scavenger	Initial Pd ppm	Final Pd ppm	Initial Mass	Recovered Mass/g	% Mass API recovered
Si TMT	500	0*	3.0	3.08	100
MP-TMT	500	0*	3.0	3.09	100
Si-Thiol	500	0*	3.0	3.09	100
SCX-2	500	150*	3.0	3.04	100
Si-Trisamime	500	0*	3.0	3.04	100

Figure 10. *API Recovery and Palladium removal using selected Biotage Metal Scavengers.*

Experiment 4

Biotage Scavengers, more compact, higher yielding and remove more metal than carbon.

In the final part of the study, we compared the relative efficiency of two Biotage metal scavengers Si-Thiol, MP-TMT with activated carbon. 0.2g, 1g, 2g of each scavenger and carbon was weighed into 15mL Polypropylene reaction vessels.

2-methy-5-phenylbenzoxazole (1 g), dichlorobis(TPP)Pd(II) 500ppm (0.0471mmol Pd), 1mL in THF was dissolved in ethylacetate (9mL) and added to each reaction vessel. The reactors were agitated at RT for 16 hours, filtered, washed with EtOAc (2mL) and filtrate evaporated to dryness. Recovered API samples were then analysed.

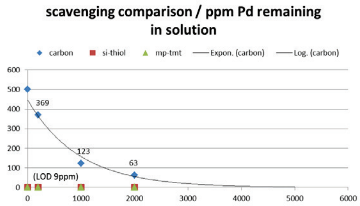

Figure 11. *Palladium scavenging efficiency of selected Biotage Metal Scavengers versus Carbon at different mass loading.*

Activated carbon removed some metal from solution but failed to remove 100%. even at a maximum load of 2g / 10mL, almost 13% Pd still remained after 16 hours. Activated carbon has a bulk density of 2.9mL/g, so the carbon treatment consumed almost 30% of reactor vial space (total solvent volume 10mL). Furthermore, an estimated 5g (14.5mL) of carbon would be necessary to reach completion, requiring more space than available in the reactor.

In contrast, metal scavengers were much more effective, removing 98.2%+ Pd, even at the lowest load of 0.2mg / 10mL. Since the bulk density of silica metal scavengers, is 1.66mL/g (0.6g/mL), only 3% of reactor space was required.

MP-TMT scavenger is between silica and carbon in terms of density but was far more effective than carbon meaning that 0.45mL of reactor space (4.5% of total) was required for 100% Pd removal.

This data suggest that it would take 48 times less Biotage metal scavenger compared to carbon, to complete the same Pd scavenging in this application. Additionally, the API recovery from the carbon would be lower.

Figure 12. *Palladium removal and product recovery of selected Biotage Metal Scavengers versus Carbon at different mass loading.*

Metal Scavenger	Mass Scavenger/mg	Equiv. of Scavenger/ Pd	Final Pd ppm	% Pd Reduction	% Mass API recovered**
Si Thiol	200	5.5 equiv.	0*	>98.2	100
	1000	27 equiv.	0*	>98.2	100
	2000	55 equiv.	0*	>98.2	100
MP-TMT	200	5.5 equiv.	0*	>98.2	100
	1000	27 equiv.	0*	>98.2	100
	2000	55 equiv.	0*	>98.2	100
Carbon	200	-	369*	26	100
Worse!	1000	-	123*	75	85
	2000	-	63*	88	46

*Limit of detection was for ICP analysis was 9ppm.
**Normalized to reduce experimental error, and also allowing for analytical LOD sensitivity.

Conclusion

Biotage metal scavengers are a more effective alternative to traditional carbon batch adsorption processes. They have the lowest metals content, and also excellent extractable profiles, therefore not likely to risk contamination, unlike competitive materials we tested. Furthermore, Biotage metal scavengers offer volumetrically, a much more compact solution than carbon, requiring 48 times less volume for the same degree of Pd removal in our studies. Finally, Biotage metal scavengers afforded 100% recovery (mass yield) of our chosen API, compared to carbon treatments, which led to API losses equivalent to upto 50%.

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