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Adsorbent Screening for Metal Impurity Removal in Pharmaceutical Process Research

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Abstract:

A microtube screening approach affords simple and convenient assessment of the selective adsorption of metal impurities by a variety of different process adsorbents. This approach is helpful in identifying rapid solutions to metal impurity problems in pharmaceutical process research. Several examples illustrating the utility of the approach are presented.

Introduction

Impurity removal is a critically important task in pharmaceutical process research, where final products must meet stringent purity requirements. Crystallization and extraction are the preferred industrial-scale techniques for rejecting impurities, but these approaches are not always suitable. Chromatography offers a versatile solution to many impurity problems but can be relatively difficult and expensive to implement on an industrial scale.

The use of process adsorbents for the selective removal of unwanted impurities from pharmaceutical process streams is a well-known approach that is gaining renewed favor as new materials and experimental approaches become available. We have recently reported on an approach for microplate evaluation of process adsorbents that enables rapid selection of the most appropriate adsorbent and conditions for carrying out a given purification task.[1] This approach grew out of earlier research on the high-throughput evaluation of chiral stationary phase libraries[2] and has recently been extended to the evaluation of reactive resins for impurity removal.[3]

Removal of trace metal impurities has become increasingly in recent years, paralleling the growing use of organometallic reagents and catalysts in pharmaceutical synthesis. Homogeneous catalytic hydrogenation is becoming a preferred method for preparing enantiopure intermediates on a large scale owing to the high enantioselectivity and turnover number that can often be realized by this approach. While heterogeneous metal catalysts can often be removed by simple filtration, the use of homogeneous catalysts frequently requires removal of residual rhodium, ruthenium, or other metals from the product, a problem that can be considerably more challenging. In addition, many syntheses now rely on metal-catalyzed coupling reactions to prepare advanced intermediates or final products, with palladium chemistry dominating this arena.[4] Owing to the convergent nature of this popular strategy, the metal-catalyzed reaction is often situated late in the process, limiting the number of downstream opportunities for impurity removal.[5] In addition, metal speciation (i.e., the existence of the metal as two or more different species) can further complicate removal of metal impurities. A variety of approaches to the removal of palladium in process development have recently been summarized.[6] Over the past few years we have used a variation on our previously reported microplate resin screening protocol for identifying adsorbent treatments to remedy metal impurity problems and report here on some recent results.

Results and Discussion

Initially, our adsorbent screening protocol, depicted in Figure 1, employed a microplate resin kit in a 96-well glass tube microplate format.[1] Each microplate kit consists of a library of 95 different adsorbents along with a control tube containing no adsorbent. Screening involves adding a solution of the sample of interest to each tube, typically via multipipettor, followed by plate agitation, and centrifugation. Subsequent analysis of an aliquot of the supernatant solution from each microtube affords a measure of the concentration

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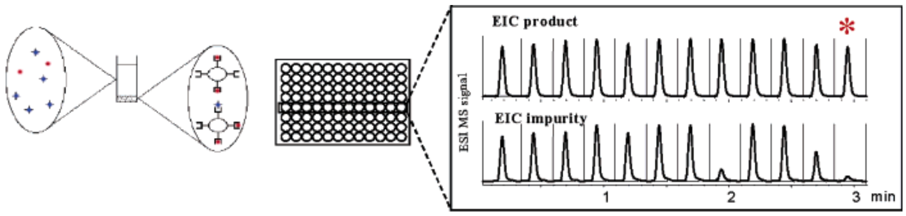

$$\alpha_{\text{apparent}} = \frac{\dfrac{1 - x_{\text{imp}}}{x_{\text{imp}}}}{\dfrac{1 - x_{\text{prod}}}{x_{\text{prod}}}}$$

Figure 1. **Microplate resin screening enables rapid identification of the most suitable adsorbent for impurity removal. Characterizing adsorbents by the selectivity factor, α, enables effective comparison of adsorbents.**

of product and impurity, which can be used to estimate the selectivity (α) of the preferential adsorption of product vs impurity under the screening conditions using the equation shown in Figure 1.[2d]

Characterizing adsorption by the selectivity factor, α, is very useful for determining which adsorbents or conditions are best suited for impurity removal. The screening results are otherwise sometimes difficult to judge. For example, evaluation of one adsorbent might show 99% product and 30% impurity remaining in the supernatant following equilibration, while another adsorbent might show 95% product and 20% impurity. Deciding between these two adsorbents is simplified considerably by calculations showing the selectivity to be 231 in the first instance and 76 in the latter. Although this approach is generally useful, caution must be exercised when the extent of adsorption of either species is very high or very low. For example, while 99% product and 30% impurity in the supernatant correspond to an α of 231, a relatively minor change to 98% product and 30% impurity results in a significant decrease in α to 114. Error of a similar magnitude in the middle regions is much less disruptive; for example, 99% product and 31% impurity corresponds to an α of 220.

HPLC or HPLC-MS with flow injection analysis is typically used to measure the concentration of product and organic impurities in the supernatant solutions. We previously described the use of the colorimetric indicator, Eriochrome Black T, to monitor selective adsorption of Zn(II),[1] and while this approach was interesting and useful, it was by no means general. We rely on the use of inductively coupled plasma-mass spectroscopy (ICP-MS) for metals analysis.[7] ICP-MS analysis is accurate to the part per billion (ppb) to part per trillion (ppt) range and applicable to virtually all metal contaminants of interest in pharmaceutical process research.

It should be noted that in addition to selectivity, capacity is a critically important criterion for adsorbent selection. Clearly, an adsorbent with excellent selectivity but poor capacity would be of limited practical utility. Because selectivity can decrease dramatically upon sample overload, we had previously advocated initial adsorbent screening at high dilution to identify those materials with greatest selectivity, with follow-up studies at a higher concentration to determine loading capacity. Owing to the difficulty of measuring metals at low concentrations in highly dilute samples, we have adopted a more direct approach in which the actual process streams themselves are evaluated using a resin load between 25 and 100 wt % (mass adsorbent/mass product).

Figure 2. **Stockpiled microcentrifuge tubes containing 50 mg of a variety of different adsorbents facilitate adsorbent screening studies.**

After using the microplate kits containing 95 different adsorbents for developing solutions to a number of separation problems, we came to the realization that most "hits" were coming from only a few of the adsorbents and that certain groups of adsorbents tended to be useful for solving certain classes of impurity problems. Not surprisingly, we also noted that process chemists were reluctant to incorporate treatments utilizing materials with limited bulk availability or with unacceptably high prices into their processes. We accordingly shifted to a simpler screening strategy in which a fewer number of adsorbents are initially evaluated, focusing on readily available inexpensive materials with some track record of success for metal removal problems.

We typically evaluate 12−30 different adsorbents, which are each stockpiled in microcentrifuge tubes containing 50 mg of premeasured adsorbent (Figure 2). We have found that the Powdernium[8] solid dispensing robot is a valuable

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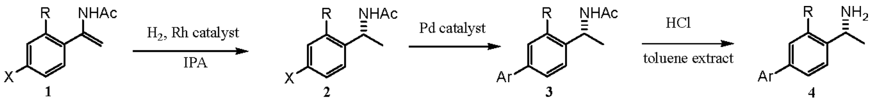
(7) Thomas, R. *Practical Guide to ICP-MS*; Marcel Dekker: New York, 2003.

(8) www.autodose.ch.

Scheme 1



tool for this operation. The microcentrifuge tubes are placed in a rack, and a 1 mL solution of the appropriate sample of process stream is added to each. The rack is agitated for 15−30 min, at which point the samples are centrifuged and a sample of the supernatant from each is withdrawn for analysis. As with the microplate screening approach, analysis of the concentration of the substrate and impurity in the supernatant compared to a blank solution containing no added adsorbent allows the selectivity of each adsorbent to be estimated.

Several recent examples from our laboratories illustrate the utility of this screening approach. Evaluation of an impurity problem generally suggests a preferred point at which remediation should take place, with treatment of

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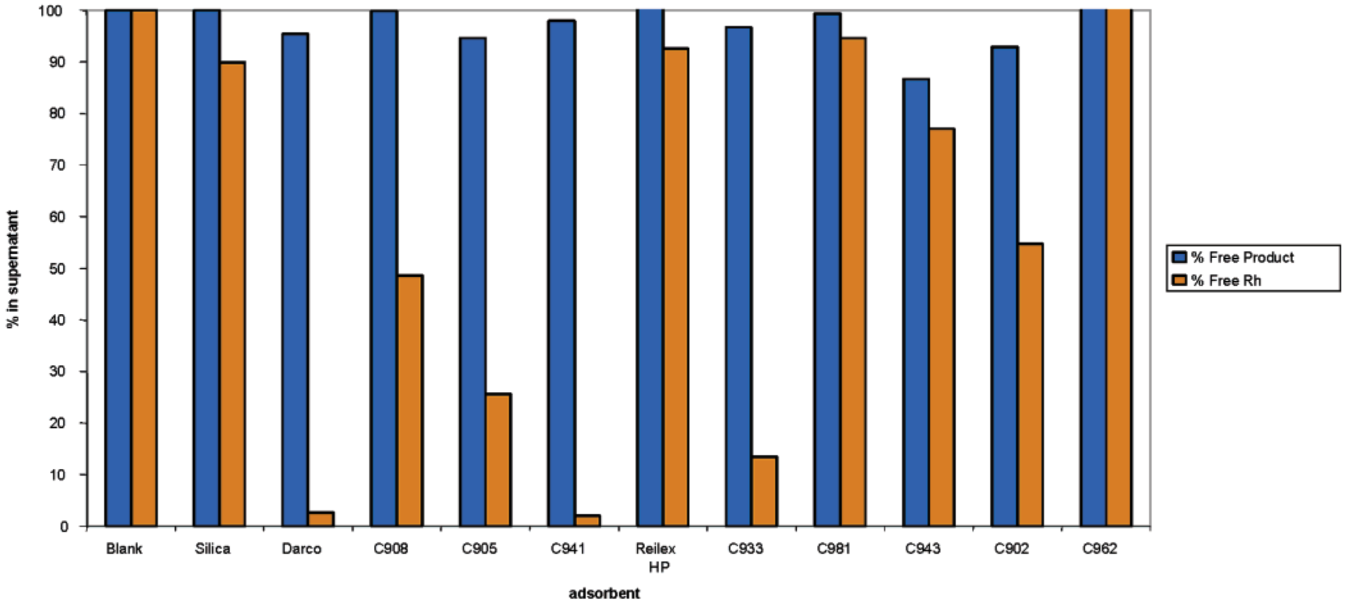


Figure 3. **Results of screening for selective removal of rhodium from amide, 2, indicate Ecosorb C941 as an effective adsorbent. Screening conducted at 50 wt % adsorbent using the IPA posthydrogenation process stream containing 2.**

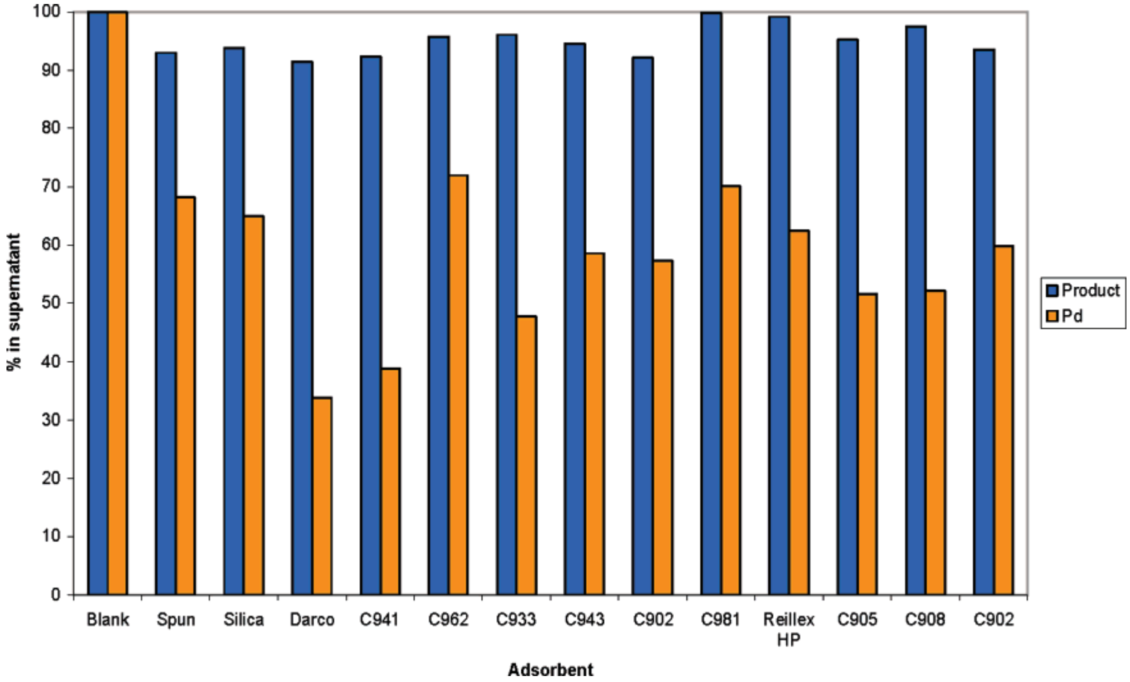


Figure 4. **Results of screening for selective removal of palladium from biaryl acetamide, 3, shows poor selectivity for most adsorbents. Screening conducted at 50 wt % adsorbent using the methanol/toluene process stream coming from workup of the coupling reaction.**

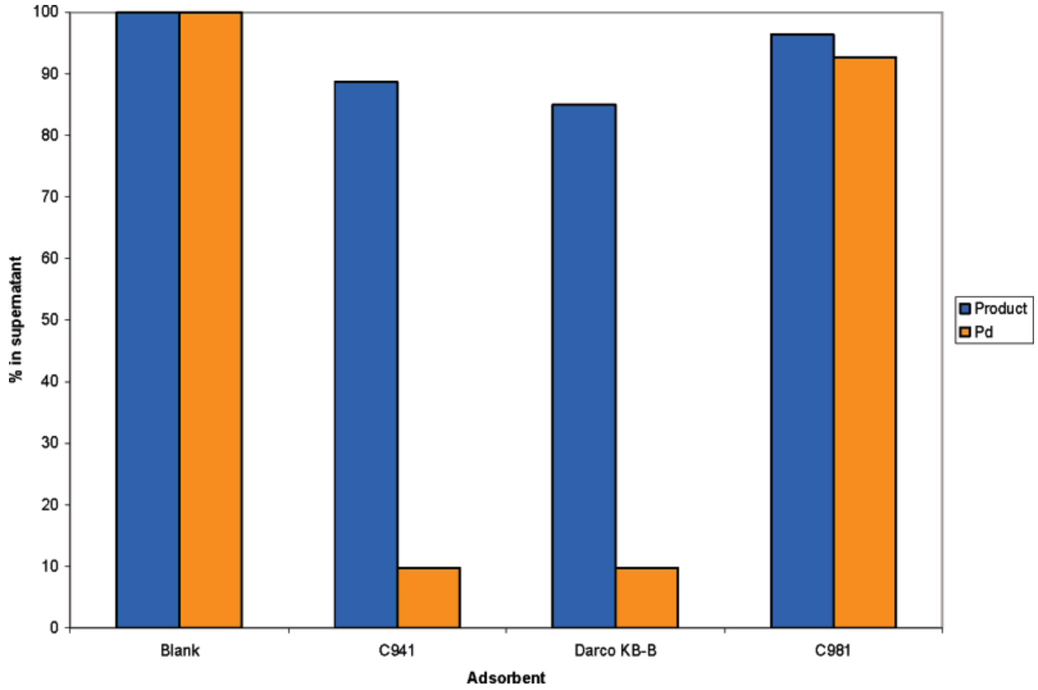


Figure 5. **Results of screening for selective removal of palladium from biarylamine, 4, show good efficacy for both Ecosorb C941 and Darco KB-B. Screening conducted at 50 wt % adsorbent using the toluene process stream coming from extractive workup following hydrolysis of acetamide, 3.**

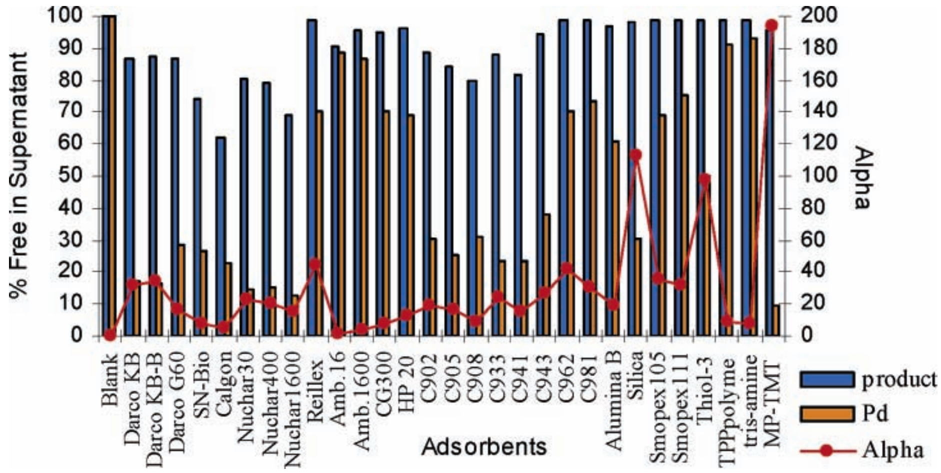
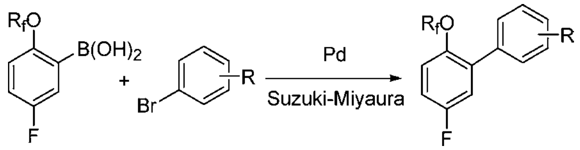
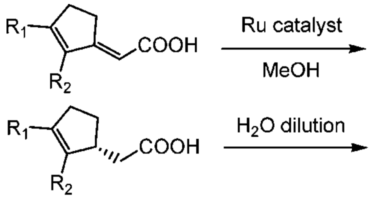


Figure 6. **Selective removal of palladium from the process stream coming from workup of Suzuki–Miyaura biaryl coupling reaction. Adsorbent screening conducted at 50 wt % loading.**

Scheme 2



Scheme 3



existing process streams being strongly favored over treatments requiring a solvent switch. In a recent example, we were presented with a situation where removal of two different metals from two different steps in a process sequence was required (Scheme 1). Enantioselective reduction of ene amide, **1**, afforded amide, **2**, with high yield and enantioselectivity but with significant rhodium contamination that was not easily rejected by crystallization. Rhodium contamination in **2** had an adverse effect on the subsequent palladium coupling to afford biaryl species, **3**, precluding the possibility of a single late stage treatment to remove both metals. Finally, isolated **3** or the corresponding amine, **4**,

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(9) www.gravertech.com.
(10) www.norit-americas.com.
(11) www.reillyind.com.

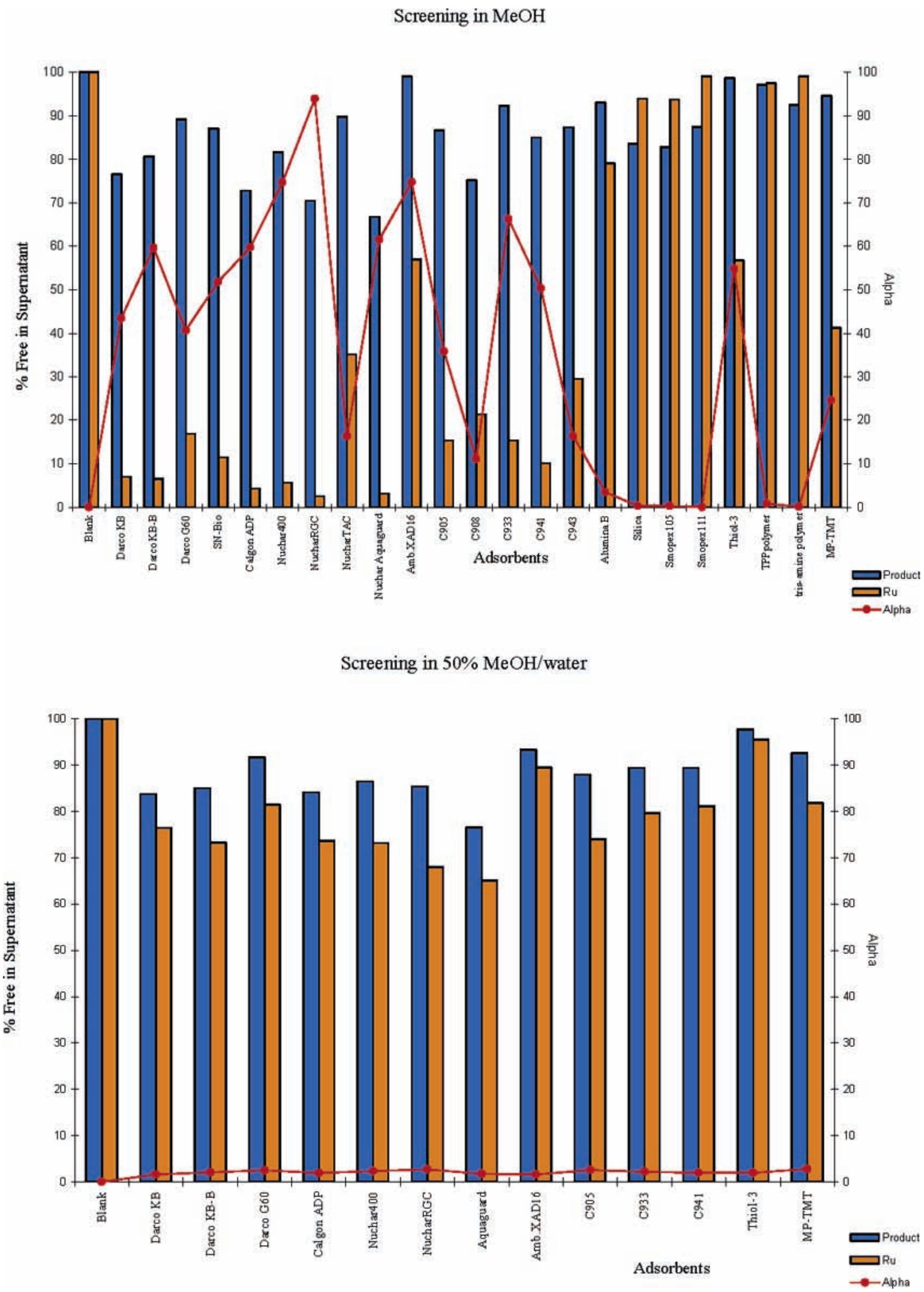
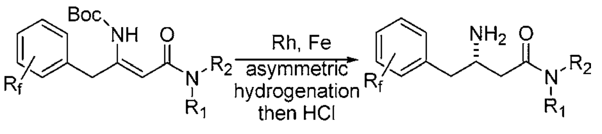


Figure 7. **Effect of solvent on selective removal of ruthenium from process streams resulting from catalytic hydrogenation of ene acid. Adsorbent screening conducted at 50 wt % loading. Immediate post hydrogenation stream in methanol (top) and upon aqueous dilution (bottom).**

generated by acetamide hydrolysis afforded material with high levels of palladium contamination, again not easily rejected by crystallization.

Investigation of removal of Rh from the posthydrogenation IPA reaction stream containing **2** using a variety of adsorbents at 50 wt % loading (i.e., 50 mg of adsorbent + 100 mg of product) showed several adsorbents with good selectivity, as illustrated in Figure 3. In this instance, the best adsorbent was found to be Ecosorb C-941, a carbon-

Scheme 4



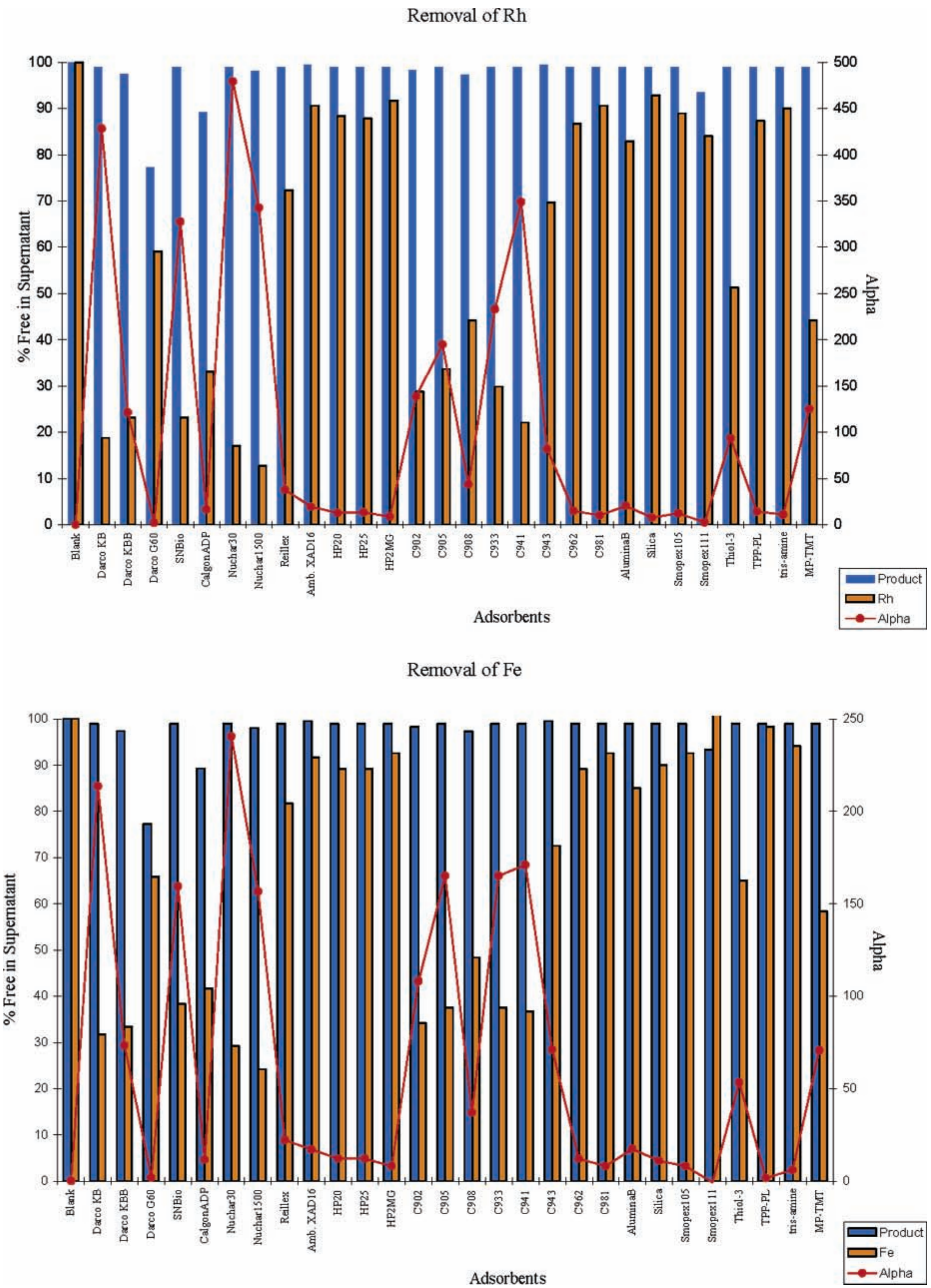


Figure 8. **Concomitant removal of rhodium (top) and iron (bottom) from a posthydrogenation process stream. Adsorbent screening conducted at 50 wt % loading.**

based product from Graver Technologies,[9] although the results for Darco[10] also look quite good. In contrast, silica and Reillex HP (a polyvinylpyridine material from Reilly, Inc.[11]) are practically useless under these conditions.

Removal of palladium in the subsequent step proved a bit more problematic. Examination of the ~5% methanol/toluene process stream containing biarylacetamide, **3**, coming from the worked up palladium coupling reaction showed rather unremarkable results for palladium removal, with Darco affording the best selectivity (Figure 4). As is often the case with palladium reactions, the postworkup process stream was heterogeneous owing to the presence of colloidal palladium, and even simple centrifugation, indicated by the “spun” designation, helped to reduce palladium levels somewhat.

Examination of the toluene solution of amine, **4**, resulting from extractive workup following hydrolysis of acetamide, **3**, showed much better selective removal of palladium (Figure 5). In this instance Ecosorb C-941 and Darco KB-B were found to be comparably effective.

Solutions to both of these metal impurity problems were obtained in just a few days. An Ecosorb C-941 treatment for removal of rhodium from the posthydrogenation IPA stream of **2** and a Darco KB-B treatment for removal of palladium from the toluene extraction stream of **4** were incorporated into the process for implementation in the first kilogram scale demonstration of the process, affording a final product with acceptable levels of both metals.

In another example, the product of a Suzuki−Miyaura coupling to form a biaryl system was isolated from the reaction mixture by crystallization to afford a solid with an unacceptable level of palladium (Scheme 2).

Attempts at rejection of palladium downstream in the process were unsuccessful, and cleanup immediately following the coupling step was required. Adsorbent screening as described above led to identification of several hits, with MP-TMT[12] exhibiting the highest selectivity in this instance (Figure 6). In contrast with the previous examples where carbon-based adsorbents were selected, MP-TMT is a polystyrene-based resin available from Argonaut, Inc., which has been specifically developed for metal impurity remediation. While somewhat costly, this material often affords highly selective metal adsorption. Estimation of selectivity (α), as previously described, provides useful insights for cost analysis. In this instance, inexpensive silica is seen to exhibit quite satisfactory selectivity, albeit with lower capacity than the more expensive MP-TMT. Accordingly, palladium remediation was effected in this instance using treatment with 200 wt % silica. (2 kg of silica for every kg of product)

As outlined previously, treatment of existing process streams is preferred, when possible. In some instances, several potential points for adsorbent treatment are available. For example, a recent ruthenium-catalyzed asymmetric hydrogenation of an ene acid afforded product with unacceptably high levels of ruthenium that was not easily rejected by crystallization. Treatments in methanol or in a 1:1 methanol/water mixture were possible (Scheme 3).

Both opportunities for adsorbent treatment were evaluated, and a dramatic influence of solvent on ruthenium removal was noted. Screening in methanol clearly showed Nuchar RGC[13] to provide very good selectivity (Figure 7, top). However, when the screen was repeated with selected adsorbents in a 1:1 mixture of methanol/water, the selectivity for all adsorbents dropped drastically (Figure 7, bottom). These results emphasize the important role that solvent plays in any solution adsorption-based separation process.

In another example, asymmetric hydrogenation of an enamine (Scheme 4) afforded chiral amine product intimately laced with both rhodium and iron.

As before, rejection downstream in the process proved problematic. A single adsorbent screening experiment allowed identification of a number of materials suitable for removal of rhodium (Figure 8, top) or iron (Figure 8, bottom) with Nuchar SA 30 being selected as the adsorbent of choice for concomitant removal of both metal contaminants.

A few practical matters concerning adsorbent selection and utilization have been discussed in our earlier work[1−3] but deserve some mention here. The experimental protocols described herein provide only an initial identification of a suitable adsorbent, and follow-up loading, optimization, and front run experiments are typically performed prior to utilization at process scale. Product loss in adsorbent treatment can be minimized if adsorbents with very high selectivity are used. In cases where selectivity is modest, product losses can be reduced by passing a solution of the crude product through an adsorbent-filled column or cartridge having just a few theoretical plates. While such approaches can be useful, we have found that it is important to first evaluate all adsorbents using the single theoretical plate method described herein so as to guide the selection of the best adsorbent. Subsequent implementation may rely on the use of multiplate filtration or chromatographic techniques if warranted. Finally, it is important to point out that the technique described herein is simply a “try it and see” screening approach and does not purport to provide rules or suggestions about what adsorbent and solvent should be used to remediate a given type of problem. Indeed, it is our contention that the wide variety of available adsorbents and the wide range of impurity scenarios encountered in pharmaceutical process research makes a screening approach the most convenient and direct path to an implementable solution.

Experimental Section

HPLC analysis was carried out using an Agilent 1100 system with diode array UV−visible detection. HPLC-MS analysis was carried out using an Agilent 1100 MSD system, operating in positive ion mode using a pH 3.5 acetonitrile/water eluent buffered to pH 3.5 with ammonium formate (0.2 mM). Centrifugation (10 000 rpm, 5 min) was carried out in snap cap polypropylene microcentrifuge tubes using a tabletop Fisher microcentrifuge.

General Procedure for Adsorbent Screening. Adsorbent screening is carried out by placing selection of polypropylene microcentrifuge tubes, each containing 50 mg of a different candidate adsorbent into a rack, along with an empty tube containing no adsorbent. A 1 mL solution of a sample process stream is added to each tube, and the rack is agitated for 15−30 min. The tubes are centrifuged (5 min, 10 000 rpm), and a sample of the supernatant from each tube is withdrawn for analysis to determine the concentration of the product and impurity.

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[12] www.argotech.com.

[13] www.meadwestvaco.com.

Metal Analysis by ICP-MS. Absorbent-treated supernatant from each microcentrifuge tube was either diluted or suspended directly in concentrated nitric acid or rotovap-evaporated first and then redissolved in concentrated nitric for ICP-MS analysis. Depending on the concentration range of the element, either the Perkin-Elmer Elan 6000 quadrupole ICP-MS spectrometer (Perkin-Elmer, Norwalk, CT) or the Thermo Finnigan Element 2 high-resolution ICP-MS spectrometer (Finnigan, Bremen, Germany) was used for the analysis.

Conclusion

These examples serve to illustrate the value of adsorbent screening for remediating metal impurity problems in pharmaceutical process research. Over the past few years we have conducted dozens of such screens and are usually successful in identifying a suitable adsorbent treatment within a few days. Further refinements in the protocol can be imagined, including miniaturization, direct coupling of screening with metal analysis, and faster turnaround metal analysis. Impurity removal via batch adsorption can be expected to gain in favor as new materials for selective impurity removal become available in bulk at affordable cost.

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