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Removal of Soluble Palladium Complexes from Reaction Mixtures by Fixed-Bed Adsorption

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Abstract:

The increasing use of metal-containing catalysts in producing pharmaceutical intermediates and active pharmaceutical ingredients, in conjunction with requirements of low metal content in a drug substance, has motivated the development of efficient separations processes for metals removal. In this paper, fixed-bed adsorption, an attractive alternative to batch adsorption, was investigated using a reaction mixture from a Heck coupling. Adsorption isotherm determinations using three candidate adsorbents revealed that QuadraPure TU had the greatest affinity and identified the optimal adsorption temperature. The bed residence time was key in obtaining good adsorption efficiency in subsequent fixed-bed experiments. Methods for palladium detection by HPLC were developed to monitor adsorption column performance in quasi real-time. A preliminary design methodology was developed in which actual breakthrough time is estimated from the experimentally determined tradeoff between bed efficiency and residence time. Even at the realized 55% bed efficiency, fixed-bed adsorption requires less than one-fourth the adsorbent needed for a single-stage batch adsorption process.

Introduction

Metal-containing catalysts, used as organometallic complexes in solution (especially for cross-coupling reactions) and as solid-supported metals for various reactions (e.g., hydrogenations) are employed extensively in the production of pharmaceutical intermediates and active pharmaceutical ingredients (API's).[1,2] The specifications for low metal content in the final product (e.g., as low as <10 ppm for palladium in an orally administered drug substance[3]) require efficient separations processes for removal of dissolved metals from reaction mixtures, and high-throughput methods have been reported to identify suitable palladium scavengers.[4–6] Among palladium removal processes, adsorption on solids is the most common, in which a solid adsorbent (e.g., activated carbon) is added, often as fine particles, to a reaction vessel, and after a contacting period the slurry is filtered to give a mixture of much lower dissolved metal content.[7]

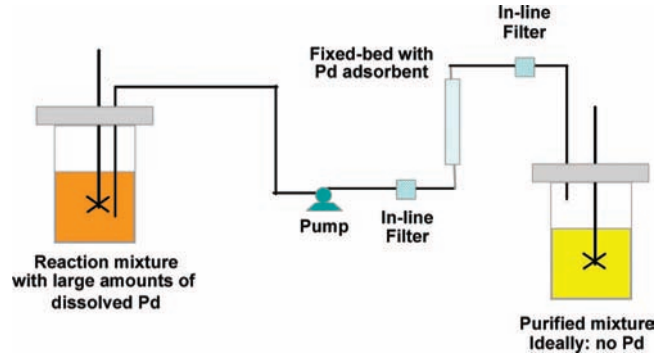

Figure 1. **Schematic diagram of fixed-bed adsorption process for palladium-containing feed. The filters shown upstream and downstream of the fixed bed serve as a precaution against solids formation, respectively, during reaction and due to particle attrition in the fixed bed.**

An attractive alternative to adding fine adsorbent particles to vessels is to place the adsorbent in a fixed bed placed outside a vessel (Figure 1) and pump the reaction mixture through the bed. As the reaction mixture contacts the solid in the fixed bed, dissolved metal species are adsorbed, giving a product at the bed exit that is very low in metals content. Such an external fixed-bed process offers several advantages over adding the adsorbent to a vessel:

- Vessel fouling, especially when the particles are fine, is eliminated, along with subsequent tedious vessel cleaning, which typically requires several solvent rinses and may require manual scrubbing.[8] Solvent consumption and disposal are thus reduced greatly, cutting material and disposal costs and decreasing waste. With vessel cleaning time being much less, vessel availability for subsequent reactions is greater, leading to greater plant productivity.
- A possibly slow slurry filtration is eliminated, being replaced with a clarifying filtration that removes much smaller amounts of solids. The time for filter preparation and subsequent cleaning is thus reduced.

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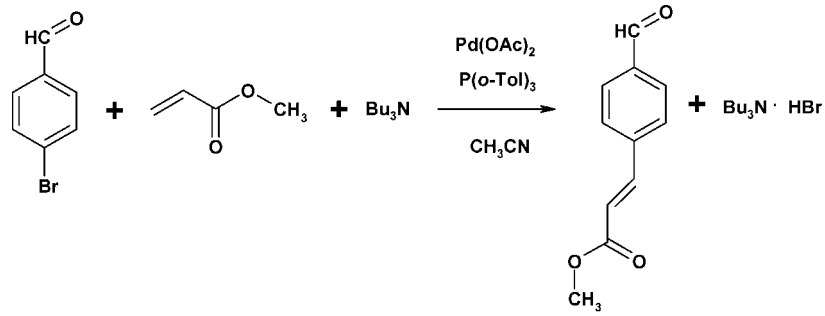

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• The amount of adsorbent required can be much less relative to a slurry adsorption due to a greater average driving force for adsorption, cutting material and disposal costs significantly.[8]
• An adsorbent in a fixed bed can be potentially regenerated in situ, allowing for possible multicycle use and thus decreasing the amount of disposed solid adsorbent.

Design procedures for fixed-bed adsorbers are well-known.[9] For example, assuming that liquid plug-flow is present and that thermodynamic equilibrium between liquid and solid phases is established rapidly, the liquid-phase adsorbate concentration is essentially zero at the bed exit but rises sharply to the feed value at the "breakthrough time", when the solid adsorbate concentration is in equilibrium with the liquid-phase feed value; in such cases, the breakthrough time can be calculated on the basis of adsorption thermodynamics, the feed metals concentration, and adsorber operating parameters:[9]

$$t_{\mathrm{brkthru}} = \frac{L}{v}\left[1 + \frac{\rho_{\mathrm{B}}}{\varepsilon}\frac{q_0^*}{\rho_{\mathrm{f}} c_0}\right] \qquad (1)$$

where t_{brkthru} = breakthrough time, h; L = length of fixed bed, cm; v = fluid interstitial velocity, cm/h; ρ_{B} = bed density, g of solid/cm^3 of bed volume; ε = bed void fraction, cm^3 of liquid/cm^3 of bed volume; ρ_{f} = liquid density, g of liquid/cm^3 of liquid; c_0 = feed metals concentration in ppm, (g metal/g of liquid) $\times$ 10^6; and q_0^* = solids metals concentration in equilibrium with feed liquid in ppm, (g metal/g of solid) $\times$ 10^6.

Design procedures have also been established for more complex situations (e.g., presence of axial dispersion, finite liquid−solid mass transfer resistance).[9]

Although cartridge filters for fixed-bed operation are commercially available,[10,11] little has been published regarding design procedures for fixed-bed adsorber operation applied to removal of dissolved metal species from reaction mixtures, primarily because the adsorption has not been characterized quantitatively (i.e., in terms of adsorption isotherms). Typically, examples are given describing metals removal for a particular set of conditions (e.g., feed metals content, column volumes processed per hour).[12] While such descriptions can be instructive, it becomes difficult to extend the results to other sets of conditions (e.g., higher metals feed concentrations, differing adsorbent amounts) for purposes of breakthrough time estimation. It would thus be helpful to arrive at a systematic method for fixed-adsorber design, preferably based on physical insights such as the thermodynamics of the separation and column operating parameters.

The goal of this work is to devise a methodology that will allow estimation of the breakthrough time for fixed-bed adsorption applied to the removal of soluble organopalladium complexes and thus arrive at preliminary design procedures for such separations. The approach taken is to use a reaction mixture, representative of those encountered in practice, to characterize the adsorption quantitatively using adsorption isotherms and evaluate subsequently fixed-bed performance. Palladium adsorption is thus characterized in the presence of other species (e.g., reaction product, solvent, reagents, and possibly unconverted reactant and intermediates), which could impact metals removal instead of using either an organometallic catalyst or a model compound (e.g., $PdCl_2$) alone in solution. The Heck coupling (see scheme above) was selected as a representative reaction, as it was catalyzed by a soluble palladium complex and developed and run in-house on a large scale while giving a large Pd content in the untreated reaction product (see below).[13]

While investigation of a single reaction mixture cannot provide the necessary information for fixed-bed palladium adsorption from any reaction mixture, a systematic investigation using a representative reaction mixture should elucidate the key factors and challenges for process design for adsorption of organopalladium complexes.

While performing fixed-bed adsorption experiments, two palladium-detection methods by HPLC/UV were developed, which provided a quantitative estimate of palladium content at the fixed-bed exit. These methods were especially useful for determining breakthrough times much more rapidly (i.e., within 30 min) than typical palladium detection methods (e.*g*., AA and ICP/MS), which require tedious sample preparation lasting several hours as well as costly instrumentation and specialized analytical chemistry expertise.

Experimental Section

Chemical Reaction. The reaction was conducted on the basis of the procedure developed by Slade and Liu.[13] Experiments were conducted on various scales, ranging from 60−600 mL using jacketed glass vessels equipped with overhead

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(10) Reaxa.com, http://www.reaxa.com/images/stories/reaxa_quarapureuser-guide.pdf.
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(12) Hinchcliffe, A.; Hughes, C.; Pears, D.; Pitts, M. R. *Org. Process Res. Dev.* **2007**, *11* (3), 477–481.
(13) Slade, J.; Liu, H. personal communication, June, 2006.

agitators (retreat curve and pitched-blade impellers at the small and large scale, respectively). In a typical run conducted at a 600-mL scale, 183 g of aldehyde **1** (989 mmol), 1.11 g of $Pd(OAc)_2$ (5 mmol), 6.02 g of P(*o*-Tol)$_3$ (20 mmol), 467 g of CH_3CN (594 mL), 189 g of Bu_3N (1020 mmol), and 87.9 g of olefin **2** (1020 mmol) were charged to the reaction vessel. The reaction mixture was heated under a nitrogen purge to 75 °C over 20 min and held at that temperature for at least 16 h. Conversion was monitored by HPLC. Instrument and method details, as well as sources and purities of materials, are given elsewhere.[14]

Batch Adsorption Experiments. Isotherm determinations were carried out using an apparatus comprising six constant-temperature small baths, each with independent temperature and agitation control. Vials containing 15−20 mL of Heck coupling reaction mixture (transferred to each vial under nitrogen purge) were placed in a given bath, with varying amounts of adsorbent (0.025−2 g) added to each vial to determine the isotherm. Care was taken to minimize exposure of the Heck coupling reaction mixture to air, as extensive exposure to air sometimes resulted in formation of palladium black particles. The slurries were agitated with magnetic stir bars overnight to allow equilibration, with the vials were sealed to minimize solvent loss and ensure good material balance closure (typically >95%). The solids were filtered, and the filtrates were analyzed for Pd content using ICP/OES by Robertson Microanalytical Laboratories (Madison, NJ). Solid-phase Pd content was calculated by difference.

Three adsorbents that are commonly used as palladium scavengers in the pharmaceutical industry were investigated: (a) P1400 activated carbon (PICA),[11] (b) Smopex 110,[15] comprising thiourea-grafted polyolefin fiber (Johnson Matthey), and (c) QuadraPure TU,[10] consisting of thiourea bound to 0.5-mm resin beads (Reaxa Ltd.). All adsorbents were used as received.

Fixed-Bed Adsorption Experiments. The apparatus used for the fixed-bed experiments is depicted in Figure 2. The adsorbent was placed in a jacketed glass column of 1.5-cm internal diameter and 30-cm length (Ace Glass, part no. 5821-13). The reaction mixture was pumped through the column with a Cole Parmer 74900 syringe pump. The column effluent was collected in a flask placed on a datalogged balance to monitor the flow rate. The jacket of the column was attached to a temperature bath (Thermo Neslab model RTE740) filled with 50:50 propylene glycol/water. To avoid crystallization of the product in the reaction mixture, the syringes and transfer lines to the column were placed in a 40 °C chamber.

A bed of glass beads (diameter 0.5 mm) was placed at the column inlet to ensure plug flow and attainment of the desired temperature at the adsorbent bed entrance; a bed of glass beads was also placed at the adsorbent bed exit. In some cases, the resin particles were diluted with glass beads to a give a sufficiently long bed to minimize axial dispersion (bed length/particle diameter of at least 200). To obtain an accurate measure of bed temperature, a thin Pt100 resistance temperature detector (RTD) was placed inside a 1/8-in. diameter tube, which was sealed on one end and attached to the bottom of the column

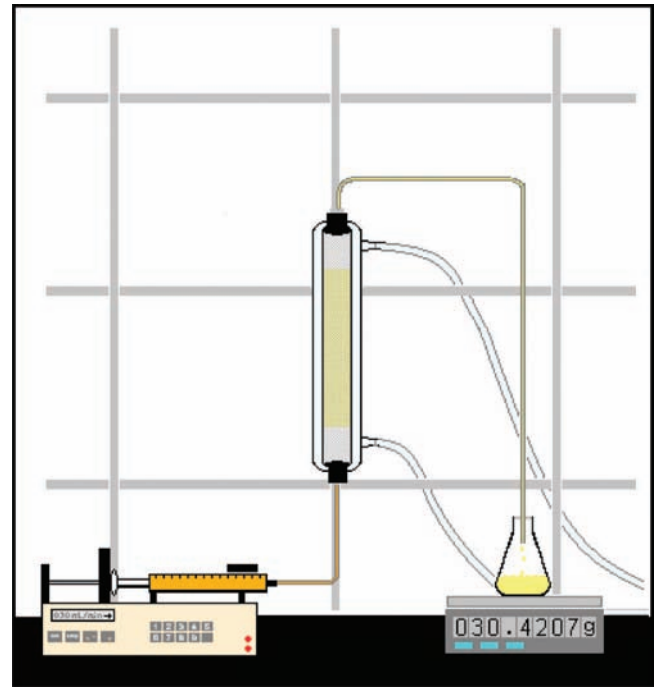

Figure 2. **Schematic diagram of laboratory fixed-bed adsorption apparatus.**

inlet; the RTD could be moved inside the 1/8-in. tube to verify that the axial temperature was constant. With the 0.5-mm diameter adsorbent particles used, the bed diameter was greater than 15 particle diameters, ensuring plug flow, even in the zone with the 1/8-in. tube present. A diagram detailing the fixed bed is given elsewhere.[14]

The column and transfer tubing were filled with acetonitrile solvent before introducing the reaction mixture. Thus, the system was hydraulically full before reaction mixture introduction to give a well-defined start of adsorption. Small (ca. 1-mL) samples of column effluent were taken for HPLC analysis to follow palladium breakthrough.

HPLC Methods for Palladium Detection. In initial fixed-bed experiments (see Figure 10), an HPLC method was developed comprising a modification of the one used for reaction monitoring.[14] This method was based on the finding from LC/MS analyses that a peak in the reaction-monitoring chromatograms was associated with palladium-containing species. The method is described elsewhere.[14] Additional experience indicated that this method was not sufficiently sensitive to allow detection of palladium levels below ca. 10 ppm.

A much more sensitive palladium-detection HPLC method was subsequently developed. The latter was adapted from a literature method [16,17] and is based on the formation of UV-detectable complexes between soluble palladium species and sodium diethyldithiocarbamate (Na-DEDTC). The structure of the complexes is unknown but may involve coordination of a palladium cationic species with two diethyldithiocarbamate anions. Sample preparation involved combining 0.1 mL of Pd-containing solution with 0.1 mL of a 0.02 M Na-DEDTC solution and 0.5 mL of acetonitrile. Chromatographic conditions are given in Table 1. Using this method, a well-resolved

(14) Supplemental Information, available online.
(15) http://www.smopex.com/page-view.php?page_id=122&parent_page_id=3.

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Table 1. **Second HPLC method for palladium detection**

instrument	Agilent series 1100 HPLC, Model G1311A quaternary pump, model G1315B photodiode array detector						
column	Zorbax SB-C18, 150 × 3 mm, 3 μm						
column temperature	25 °C						
mobile phases	A: 0.02 M sodium acetate buffer (pH = 6)/acetonitrile = 40/60 (v/v) B: 0.02 M sodium acetate buffer (pH = 6)/acetonitrile = 5/95 (v/v)						
flow rate	0.8 mL/min						
injection volume	10 μL						
detection wavelength	298 nm						
gradient elution	time, min	0	9	12	20	21	26
% B	0	0	100	100	0	0	

chromatographic peak corresponding to the palladium complex was obtained.[14]

Results and Discussion

Chemical Reaction and Palladium Content of Untreated Mixture. Conversion of aldehyde **1**, which is the limiting reactant, was almost complete (i.e., >99%) after 16 h at 75 °C; representative kinetics are shown elsewhere.[14]

To obtain a base case for product palladium content, coupling product **3** from one run was isolated without adsorptive treatment, based on a procedure developed earlier.[13] After cooling the reaction mixture to room temperature, 0.5 N HCl (104.1 g) and water (680 g) were added to produce a slurry of product **3**. After filtration and drying, the product was recovered in 89% yield, with a Pd content of 2100 ppm. This large value, being in excess of drug substance palladium content specifications by more than 2 orders of magnitude, and the observation that palladium is preferentially taken up by the solid during precipitation (as the calculated reaction mixture Pd content is only 570 ppm) are a further indication of the suitability of this Heck coupling for investigating palladium removal.

Adsorption Isotherms. The adsorption isotherms at room temperature for the three adsorbents examined (Figure 3) indicate that QuadraPure TU had the greatest affinity for palladium by far, with the equilibrium solid-phase concentration being 1 order of magnitude greater than those of the other adsorbents at a given liquid-phase concentration in equilibrium with the solid. It is likely that palladium exists in solution in various chemical forms; for purposes of isotherm determination, all palladium-containing species are lumped into one pseudocomponent. The shape of the isotherm with QuadraPure TU is consistent with a Langmuir form, with the solid-phase concentration approaching a constant value at high liquid-phase concentrations; the convex-upward shape of the isotherm with QuadraPure TU implies that it may be characterized as type I favorable.[18]

The much greater palladium affinity of QuadraPure TU motivated its further evaluation. As shown in Figure 4, even greater palladium affinity was obtained at higher temperature, the cause of which is unknown. Two possible reasons for the greater affinity include (a) a possibly activated adsorption, with higher temperature needed for a selective interaction between thiourea functional groups on the resin and soluble palladium species and (b) a greater availability of adsorption sites because of resin swelling at higher temperature. The adsorption also follows the Langmuirian form at higher temperatures, with good fits obtained when fitting the data to the Langmuir isotherm (Figure 4):

$$q = \frac{NKc}{1 + Kc} \tag{2}$$

where q = solid-phase Pd concentration in ppm, (g of Pd/g of solid) × 10^6; c = liquid-phase Pd concentration in ppm, (g of Pd/g of liquid) × 10^6; N = constant representing the number of adsorption sites, (g of Pd/g of solid) × 10^6; K = constant representing the adsorption equilibrium constant, (g of liquid/g of Pd) × 10^{-6}.

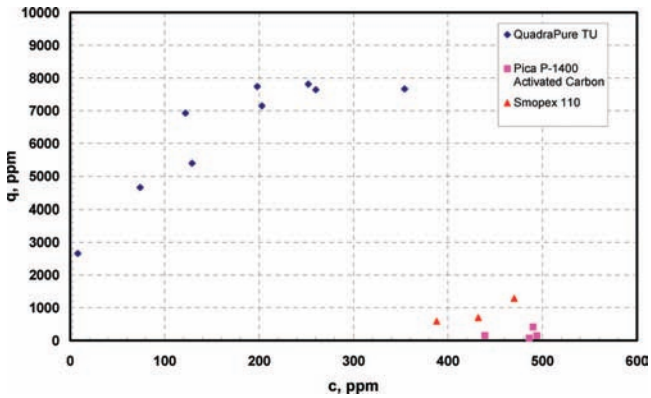

Figure 3. **Equilibrium isotherms for three adsorbents with Heck coupling reaction mixture at room temperature.**

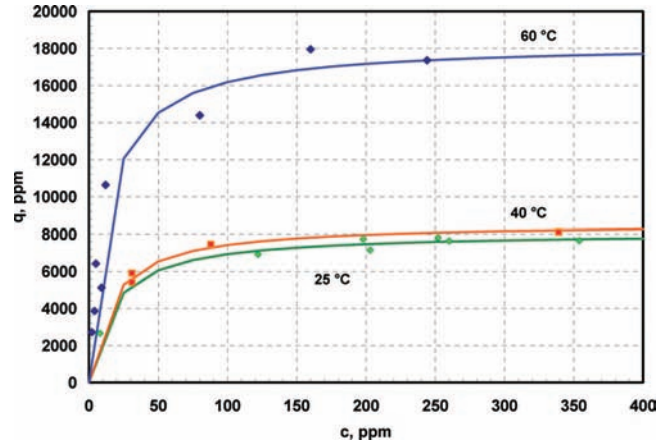

Figure 4. **Adsorption isotherms for QuadraPure TU at three temperatures with Heck coupling reaction mixture.**

Table 2. **Fitted Langmuir isotherm parameters**

temperature (°C)	*N* (g of Pd/g of solid) × 10^6	*K* (g of liquid/g of Pd) × 10^{-6}
25	8090	5.96×10^{-2}
40	8586	6.37×10^{-2}
60	18270	7.75×10^{-2}

The values of the parameters fitted are given in Table 2. The fit indicates that both the number of sites and the adsorption strength increase with temperature but that the N parameter increases more with temperature (viz., by a factor of >2.2 versus an increase of only 11% for K). The small change in K (which might be constant within experimental error) suggests that the greater adsorption capacity at higher temperature might be due predominantly to an increase in the concentration of active adsorption sites.

The selectivity of the adsorption was also characterized. After equilibration with the adsorbent and subsequent filtration, selected liquid-phase samples were assayed for content of product **3**. Despite some scatter in the data, the results indicate that the adsorption was more selective at higher temperature (Figure 5).

Approach to Equilibrium Determination. The isotherm determinations and selectivity data allowed selection of the optimal adsorbent (QuadraPure TU) and the best temperature for that adsorbent (60 °C) for the Heck coupling reaction mixture. To test the hypothesis of rapid equilibrium attainment between fluid and solid phases in the fixed bed and thus guide selection of fixed-bed experimental conditions, a batch adsorption experiment was conducted in which QuadraPure TU was added to the Heck coupling reaction mixture in a vessel equipped with an agitator. Several liquid samples were taken and analyzed for palladium content to quantify the approach to equilibrium as a function of time.

As indicated in Figure 6, up to 6 h of contact was required to reach equilibration between the resin and the Heck coupling reaction mixture. The high agitation in the batch adsorption experiment suggests that mass transfer resistance between fluid and solid phases is not high. Thus, the long equilibration time is consistent with a slow chemical reaction between dissolved palladium species and thiourea functional groups on the resin surface. Comparison of the rate of disappearance of palladium at early times based on Figure 6 with a conservatively low estimate of the mass transfer rate reveals that the latter exceeds

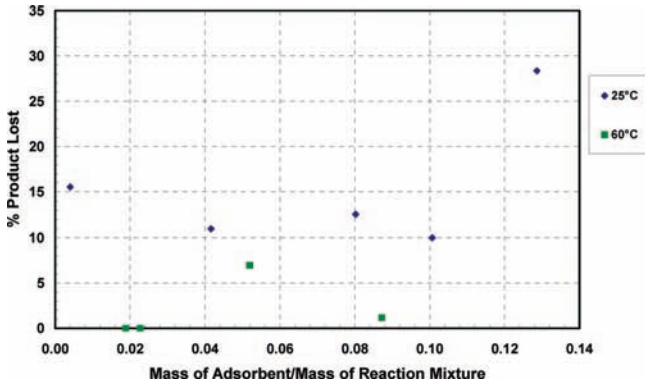

Figure 5. **Improved adsorption selectivity at 60 °C with QuadraPure TU.**

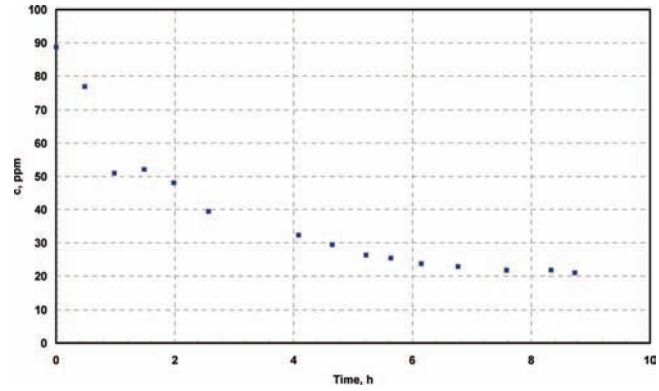

Figure 6. **Batch adsorption experiment results.**

the observed rate of disappearance by at least 2 orders of magnitude, consistent with a slow reaction.[14]

Fixed-Bed Experiments. The results of Figure 6 suggest that a ca. 6-h bed residence time is needed to approach fluid–solid equilibrium. However, because such a long bed residence time gives low throughput (viz., <0.2 bed volumes processed per hour), it is useful to quantify the tradeoff between throughput and extent-of-approach to equilibrium, as it may then be possible to determine if acceptable throughput can be obtained within a reasonable residence time range.

A systematic methodology was employed in the fixed-bed experiments in which independent variables (key inputs) were specified. Based on these variables, outputs, comprising column operating variables and performance (i.e., breakthrough time), were calculated. The input and output variables, including their method of computation, are given in Table 3. The variables are categorized as either column parameters, thermodynamic properties, or adjustable parameters. With the apparatus used (Figure 2), bed density, porosity, and cross-sectional area were fixed. The palladium feed solution concentration for the Heck coupling reaction mixture was 570 ppm, and based on the QuadraPure TU isotherm at 60 °C (Figure 4, Table 2), the equilibrium value on the solid was calculated to be 1.8×10^4 ppm. A value of 17.3 g for the resin mass was selected to give a 20-cm long bed.

A suitable residence time based on the batch adsorption results was then chosen, thus specifying the flow rate and allowing calculation of a theoretical breakthrough time as shown in Table 3. The actual breakthrough time would then be determined experimentally. An adsorption efficiency η, defined as the ratio of experimental to calculated breakthrough times, is calculated. The tradeoff of efficiency with residence time would be quantified from experiments at various bed residence times.

A 2-h bed residence time was first selected, as the curve in the batch adsorption experiment begins to flatten at about this time (Figure 6). As a result of limitations of reaction mixture availability, it was necessary to decrease the flow rate late in the experiment by 21% (i.e., from 0.115 to 0.09 cm^3/h) after 55.3 h. This flow rate change increases the bed residence time by a factor of 1.25. Examination of Figure 6 shows that increasing the bed residence time from 2 to 2.5 h does not increase the approach to equilibrium significantly. Thus, the breakthrough time can be reasonably approximated as 70.5 h

Table 3. **Process variables in fixed-bed adsorption**

parameter	category	symbol/method of determination and units	value of input variables set by feed properties, equipment and adsorption isotherm
bed porosity	input: bed property	ε, cm^3 liquid/cm^3 bed volume	0.4 cm^3/cm^3 (measured)
bulk density	input: bed property	ρ_B, g solid/cm^3 bed volume	0.50 g/cm^3 (measured)
cross-sectional area	input: column property	A, cm^2	1.69 cm^2 (known)
feed palladium content	input: feed solution	c_0, (g Pd/g liquid) $\times$ 10^6	570 ppm (calculated)
solid Pd concentration in equilibrium with feed	input: solid-fluid thermodynamics	q_0^*, (g Pd/g solid) $\times$ 10^6	1.8×10^4 ppm (calculated from isotherm)
resin mass in bed	input	M_{res}, g	17.3 g (measured)
bed residence time	input	τ, h	adjustable
bed length	output	$L = (M_{res}/\rho_B)/A$, cm	20 cm, set by selection of M_{res}, ρ_B, and A
volumetric flow rate	output	$Q = (M_{res}/\rho_B)(\varepsilon/\tau)$, cm^3/h	set by selection of τ and other input parameters
interstitial velocity	output	$v = Q/A\varepsilon$, cm/h	
breakthrough time	output	$t_{brkthru} = L/v\,[1 + (\rho_B/\varepsilon)(q_0^*/\rho_f c_0)]$, h	
volume of solution processed at breakthrough	output	$V_{brkthru} = Q\,t_{brkthru}$, cm^3	

(Figure 7). Comparison of the latter with the calculated breakthrough time of 104 h gives an efficiency of 68% (Table 4).

Column effluent samples that were collected up to 70.5 h were combined, and the product was isolated by crystallization as described above. The isolated product contained 3.9 ppm of palladium (weighted average from 2 crops), well within guidelines for palladium content in APIs.[3]

A residence time of 1.25 h was examined subsequently, as the batch adsorption results indicate that slightly less product is adsorbed relative to the 2-h time (Figure 6). The breakthrough curve for this experiment (Figure 8) shows that samples taken at early times (viz., ≤ 20 h) contained some palladium, but the low content (<1 ppm) of these motivated continuing the run. A late sample terminating at 35.7 h contained 3.9 ppm of Pd, and thereafter the Pd content increased sharply. Taking the breakthrough time as 35.7 h, the efficiency in Table 5 is calculated, further demonstrating the importance of sufficiently long contact time to obtain good fixed-bed performance. The palladium-removal capability of the fixed bed was again evidenced by the low palladium content of the isolated solid (6.8 ppm, weighted average palladium content from two crops).

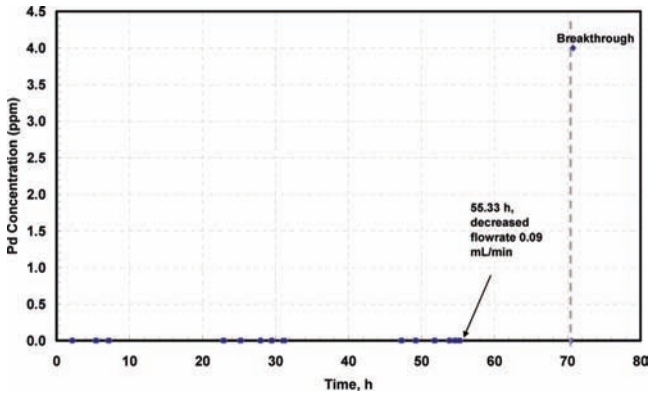

Figure 7. **Breakthrough profile with 2-h residence time. Zero time corresponds to the time at which the reaction mixture reached the bed entrance. Palladium detection in this figure and subsequent ones is determined using the more sensitive HPLC/UV method involving addition of Na-DEDTC before sample analysis.**

Table 4. **Results from fixed-bed adsorption run with 2-h bed residence time**

flow rate, cm^3/h	6.91
interstitial velocity, cm/h	10.2
calculated breakthrough time, h	103.7
actual breakthrough time, h	70.5
η	0.68

The latter results, in conjunction with those from subsequent experiments, were used to quantify the tradeoff between bed residence time and efficiency (Figure 9). Despite some scatter in the data, the figure indicates that the adsorption efficiency is not improved significantly by increasing the bed residence time above ca. 0.75 h.

The low residence time runs were based in part on adsorbent vendor recommendations. Examination of the vendor literature indicated that a flow rate corresponding to 4−6 column volumes/h was recommended.[10,12] A more conservative value, namely 1 column volume/h, was used in a representative run shown in (Table 6). On the basis of the vendor-specified resin capacity of 20 mg Pd/g resin[10] and the Pd feed content of 570 ppm, the resin mass given in Table 6 should have been sufficient to process about 107 mL of reaction mixture, giving a breakthrough time of 5.9 h at the flow rate employed.

The result from this representative run is shown in Figure 10 with samples of the column effluent taken periodically and analyzed for Pd using ICP/OES and the first short-cut HPLC method

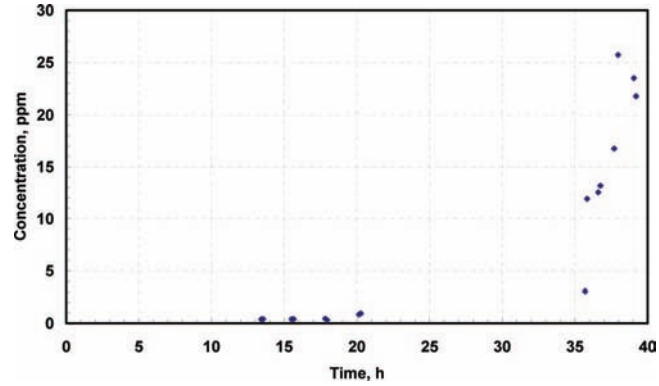

Figure 8. **Breakthrough data for fixed-bed adsorption run with 1.25-h bed residence time.**

Table 5. **Summary of run with 1.25-h bed residence time**

flow rate, cm^3/h	11.0
interstitial velocity, cm/h	16.2
calculated breakthrough time, h	65.3
actual breakthrough time, h	35.7
η	0.55

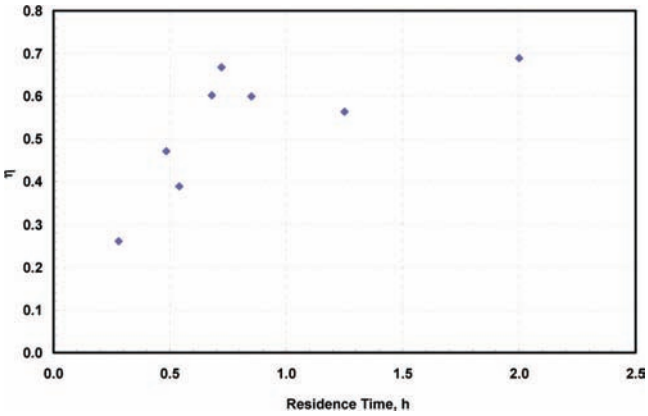

Figure 9. **Tradeoff of efficiency with residence time.**

Table 6. **Representative conditions for initial fixed-bed adsorption runs**

mass of QuadraPure TU resin in bed, g	2.4
mass of glass beads in diluted resin bed, g	20.2
diluted resin bed volume, cm^3	16.9
diluted resin bed height, cm	10
bed void fraction	0.48
flow rate, cm^3/min	0.3
residence time in diluted bed, min	28

mentioned above. In sharp contrast to expectations, breakthrough occurred in under 2 h, with only 11.5 g of reaction mixture treated before palladium was detected at the outlet. Based on the resin mass in the bed, the resin removed only 2.7 mg Pd/g resin, representing only 13.5% of the expected value of 20 mg/g.

The data from the fixed-bed adsorption experiments performed at various bed residence times (Figure 9) demonstrate that a sufficiently long bed residence time, and thus close approach to fluid−solid equilibrium, is key in obtaining good fixed-bed adsorption performance (i.e., $\eta > 50\%$). Considering that the interaction between dissolved palladium species and thiourea functional groups on the QuadraPure TU resin is likely to be selective (versus likely physical adsorption between adsorbents such as activated carbon), the long required residence time suggests that the adsorbent/adsorbate interaction behaves like a surface chemical reaction that requires a certain contact time to obtain sufficient conversion.

Investigation of Axial Dispersion and Bed Residence Time. Additional experiments were performed to determine if axial dispersion could adversely impact breakthrough time at the conditions examined. If axial dispersion effects were significant, plug flow would not occur, and the bed is not efficient because of a diffusive flux superimposed on bulk flow along the bed axis. Toluene tracer tests were performed in which acetonitrile was pumped through the column filled with either glass beads or resin particles, with a single 1-mL pulse of toluene injected near the column inlet at the start of each experiment. Samples were then taken at the column outlet and analyzed by HPLC to measure the temporal toluene concentration profile.

Key results of these experiments[14] showed that the toluene temporal profile was similar for various flow rates. Additional experiments demonstrated that axial dispersion was minimized with an undiluted bed. Thus, glass beads were not used to dilute the bed in fixed-bed experiments (see above). Adsorption column runs were then performed at the optimal conditions suggested by the toluene tracer experiments. Even under optimal conditions, the breakthrough time did not increase significantly, being comparable to that shown in Figure 10 at 0.25-h bed residence times. These experiments ruled out axial dispersion as the main cause for the early breakthrough time at such low bed residence times.

Design for Large Scale. For design purposes, eq 1 is modified to read

$$t_{\mathrm{brkthru}} = \eta \frac{L}{v}\left[1 + \frac{\rho_{\mathrm{B}}}{\varepsilon}\frac{q_0^*}{\rho_{\mathrm{f}} c_0}\right] \tag{3}$$

where η is determined experimentally (Figure 9) and is assumed to be a function of the residence time alone and scale-independent. Then the equation above implies that

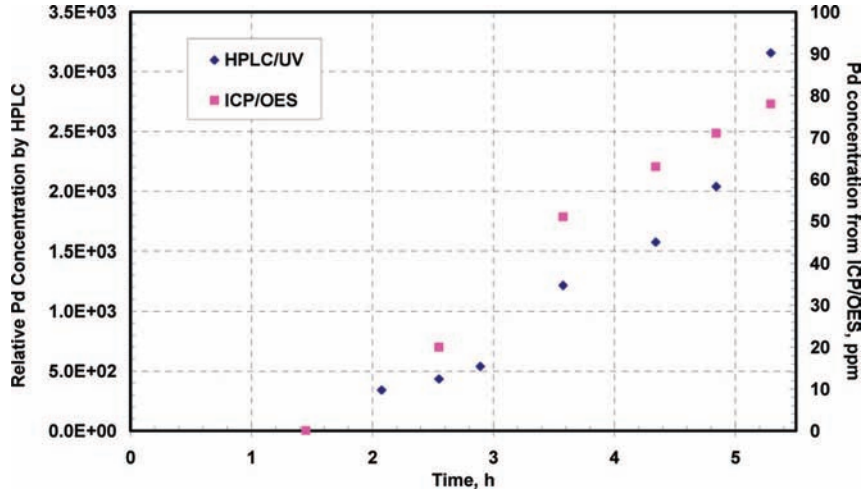

Figure 10. **Representative result of palladium breakthrough at column exit in initial runs. The palladium content was determined using a HPLC/UV method (based on modification of the reaction monitoring method; see above) and by ICP/OES (Robertson Micronanalytical Laboratories). The HPLC/UV results are expressed in terms of a relative concentration equal to the actual concentration divided by the undetermined response factor.**

$$\frac{t_{\text{brkthru}}}{L/v}_{\text{plant}} = \frac{t_{\text{brkthru}}}{L/v}_{\text{lab}} \tag{4}$$

where the subscript "lab" refers to an actual laboratory experiment and the subscript "plant" refers to a large-scale design case.

If a volume of V liters of solution with a Pd concentration of c_0 is to be processed, one can proceed two ways:

(a) Assume $t_{\text{brkthru|plant}}$ equals $t_{\text{brkthrullab}}$.

Then the volumetric flow rate Q is fixed and calculated from:

$$Q = \frac{V}{t_{\text{brkthru}}} \tag{5}$$

The resin mass is determined from (Table 3)

$$M_{\text{res}} = \frac{Q\rho_{\text{B}}\tau}{\varepsilon} \tag{6}$$

(Note that that one would operate at the same η value on both scales and that Figure 9 implies that selection of η fixes τ).

Once a large-scale column is specified, the cross-sectional area is fixed, allowing calculation of the required bed length:

$$L = \frac{M_{\text{res}}/\rho_{\text{B}}}{A} \tag{7}$$

The bed length L must obviously be shorter than the actual length of the selected column; otherwise, a longer column must be found. Alternatively, one can use a different breakthrough time on scale-up (see below).

(b) Assume a different $t_{\text{brkthru}|_{\text{plant}}}$

In this case, the quantity F is defined as the ratio of the large-scale breakthrough time to that in the laboratory:

$$F = \frac{t_{\text{brkthruplant}}}{t_{\text{brkthrulab}}} \tag{8}$$

The flow rate Q is then specified from

$$Q = \frac{V}{F * t_{\text{brkthrulab}}} \tag{9}$$

allowing calculation of the resin mass and bed length, respectively, from

$$M_{\text{res}} = \frac{Q\rho_{\text{B}}\tau}{\varepsilon} = \frac{V}{F * t_{\text{brkthrulab}}}\frac{\rho_{\text{B}}\tau}{\varepsilon} \tag{10}$$

and

$$L = \frac{M_{\text{res}}/\rho_{\text{B}}}{A} = \frac{V}{F * t_{\text{brkthrulab}}}\frac{\tau}{A\varepsilon} \tag{11}$$

F can be increased until L is sufficiently below the actual length of the column chosen.

Thus, with specification of the equilibrium isotherm and an estimate of column efficiency, a design for a large-scale column can be made. In practice, solutions containing dissolved metals might oxidize with time, leading to variations in the isotherm, which can be difficult to predict. It is thus recommended that when a large-scale column is operated, the column effluent should be collected in fractions, each of which can be analyzed via a shortcut HPLC method, with only those fractions before breakthrough combined; this approach would compensate for isotherm variations. It might also be helpful to prepare a second column at the outset, connect it in parallel to the first, and redirect the feed solution to the second column in case breakthrough occurs unexpectedly early. Finally, for the sake of avoiding large differences in mass transfer resistance between small and large scales, it is advisable to operate at interstitial velocities that do not differ significantly on scale-up.

Comparison with Batch Adsorption. In the 1.25-h residence time run, about 394 mL, or 310 g, of solution were treated with 17.3 g of resin, giving a solution mass L to resin mass S ratio of 17.9 g/g. Based on the equilibrium isotherm and a mass balance, it is possible to determine the amount of palladium removed using batch adsorption at the same L/S value.[19] Assuming that no palladium is present on fresh resin, a mass balance on a single stage of batch adsorption shows that

$$L(c_0 - c_1) = Sq_1 \tag{12}$$

where L = mass of solution treated; S = mass of adsorbent; c_0, c_1 = liquid-phase Pd concentration in feed and product, respectively; and q_1 = solid-phase Pd concentration after single-stage contacting. Solving for q_1 gives

$$q_1 = -\frac{L}{S}c_1 + \frac{L}{S}c_0 \tag{13}$$

On c,q coordinates (taking c as the horizontal axis), the mass balance corresponds to a straight line with slope $-L/S$ and horizontal intercept of c_0. If a batch adsorber is operating with a feed palladium concentration of 570 ppm and with L/S = 17.9 g/g, the equilibrium concentration after a single-stage of contacting can be determined graphically by reading the ordinate at the intersection of the mass balance line (i.e., also called the operating line) with the isotherm (Figure 11). A more accurate determination can be done algebraically, giving a value of 15 ppm for the liquid-phase palladium concentration after a single-stage batch adsorption. Assuming that the palladium concentration in the isolated solid would be 3.7-fold greater (as seen in at least two cases; see above), a value of 55 ppm would be obtained, more than 7-fold greater than the actual palladium content of the isolated solid (7 ppm, see above).

To obtain a palladium content of 7 ppm in the isolated solid (or 1.9 ppm in the liquid-phase reaction mixture, based on the assumption listed above) with a single batch adsorption stage, calculations based on the analysis above indicate that a L/S value of 4.13 is needed, or 4.3 times the resin required in the fixed-bed with 1.25-h residence time and 55% efficiency.

If a second stage of batch adsorption is used, it can be shown that in the optimal case, only a slightly lower resin amount can

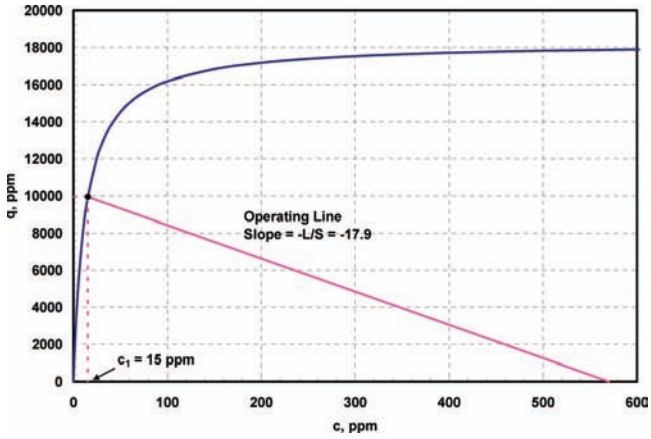

Figure 11. **Graphical depiction of single-stage batch adsorption.**[19]

be used to obtained the same degree of palladium removal relative to the fixed-bed case with 1.25-h residence time and 55% efficiency. Summing the material balance equations across both stages gives

$$S_1 + S_2 = L(c_0 - c_1)\frac{1 + Kc_1}{NKc_1} + L(c_1 - c_2)\frac{1 + Kc_2}{NKc_2} \tag{14}$$

where the subscripts correspond to the two stages.

An iterative calculation can be performed to estimate the minimum adsorbent amount required for the two stages by (a) estimating a value for S_1, (b) calculating c_1 from the stage 1 mass balance, (c) calculating S_2 from the stage 2 mass balance (with c_2 set to 1.9 ppm), (c) calculating $S_1 + S_2$, and (e) varying S_1 to minimize the latter sum. In this manner, we find that the minimum adsorbent amount for the two stages results when $S_1 = 12.7$ g and $S_2 = 4.10$ g, giving a total adsorbent amount that is slightly smaller than the 17.3 g case with the fixed bed adsorber operating at 1.25-h residence time and 55% efficiency. Note, however, that the throughput would be decreased significantly owing to a second batch adsorption stage for only a slight decrease in adsorbent amount.

Conclusions

Removal of soluble palladium complexes from a Heck coupling reaction mixture was investigated using fixed-bed adsorption, with the goal of devising a methodology for removal of dissolved metals species from reaction mixtures. The adsorption was first characterized quantitatively by determining adsorption isotherms for three commonly used adsorbents. The isotherms showed that QuadraPure TU had the greatest affinity for dissolved palladium and indicated its optimal adsorption temperature. The unexpectedly short breakthrough times in small residence time experiments were attributed to insufficient approach to equilibrium in the fixed bed rather than axial dispersion effects. Subsequent experiments, in which bed residence times were selected to approach equilibrium on the basis of batch adsorption results, gave much better performance, with bed performance exceeding 55% of the theoretical degree of palladium removal based on the assumption of local fluid−solid equilibrium. These experiments were also used to develop a design methodology in which actual breakthrough time could be estimated from experimental determination of the tradeoff between bed efficiency and residence time. To arrive at the same level of palladium removal, fixed-bed adsorption was shown to require less than one-fourth the resin amount relative to a single stage of batch adsorption. HPLC methods for detection of soluble palladium allowed for quasi real-time monitoring of adsorption column performance.

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Supporting Information Available

Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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