

Organic Solvent Nanofiltration and Adsorbents; A Hybrid Approach to Achieve Ultra Low Palladium Contamination of Post Coupling Reaction Products

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Abstract:

Due to potentially toxic contamination of pharmaceutical products, effective removal of palladium from post-reaction solutions is of great importance, especially in the pharmaceutical industry. This work addresses this challenge by combining organic solvent nanofiltration (OSN) with adsorbents in a hybrid process. Post-reaction solutions resulting from acylation and Suzuki reactions were subjected to OSN, the catalyst was retained by the membrane, and the product was collected in the permeate. Palladium levels in the permeate were reduced further by using adsorbents. This technique achieved ultralow palladium concentration (<10 mg Pd kg product⁻¹) for post-reaction solutions with toluene and ethyl acetate as solvents. The results obtained using the hybrid OSN–adsorbent process were compared to those using selected adsorbents only. When palladium was removed from a post-Suzuki reaction solution, using polystyrene-bound trimercaptotriazine as the adsorbent, the hybrid process, while using 10 times less adsorbent than the adsorbent-only process, was able to reduce the product contamination to an 8.5 times lower level. It is thought that the membrane stage of this technique removes bulky ligated palladium along with palladium nanoparticles, species that are hard to remove by adsorption only. The residual palladium in the permeate stream comprises well-dissolved, smaller molecules, and these are removed very effectively by the adsorbent. This allows high-purity products to be achieved by treatment of the OSN permeate with low amounts of adsorbents. Therefore, this hybrid process is recommended for separations where adsorbent-only treatment can result in significant product losses, or where strong ligand–palladium interactions compete with adsorbent active sites, keeping palladium in solution.

1. Introduction

During the design of processes for manufacture of active pharmaceutical ingredients, chemists have access to an extensive toolbox of reactions for molecular construction. A survey of the most practised reactions in the industry revealed acylation and carbon–carbon coupling reactions as being among the top

four most commonly performed reactions.¹ These types of reactions often utilise homogeneous palladium catalysts which frequently present major downstream separation challenges, particularly for the pharmaceutical industry where significant levels of heavy metals in the final product are wholly unacceptable. Guidelines from the European Medicines Agency have set the permitted daily exposure of patients to palladium, 100 $\mu\text{g}\cdot\text{day}^{-1}$ for oral doses and 10 $\mu\text{g}\cdot\text{day}^{-1}$ for parenterally administered drugs.² On the basis of these guidelines the pharmaceutical industry generally needs to achieve less than 10 ppm and 1 ppm, for oral and parenteral drug substances, respectively.

Organic solvent nanofiltration (OSN) is a pressure-driven membrane-based separation technique, which has demonstrated its proficiency for catalyst/product isolation in many studies. OSN is capable of removing around 95% of post-reaction palladium catalyst in an active form, and this provides improvements in mass and economic efficiency of processes by allowing the catalyst to be recycled.^{3–6} However, when the commercially available OSN membrane, Starmem 122 (Starmem is a trademark of W.R. Grace and Co.) was used for the separation of catalyst from post-Suzuki reaction solutions, the residual palladium in the product permeate stream remained above acceptable limits. Note that palladium content is herein defined

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Table 1. Summary of Recent Studies for Palladium Removal from Organic Solutions

entry	adsorbent	scavenger loading	conditions	feed Pd level (ppm)	final Pd level (ppm)	% Pd removal	solution	ref
1 ^a	trimercaptotriazine, charcoal and diatomaceous earth	0.1 g ads g prod ⁻¹	23 °C, 1 h and 3 °C, 1 h	600–650	20–60	83–97	post-indolization	7
2 ^a	polystyrene bound-ethylenediamine	1 g ads g prod ⁻¹	23 °C, 17 h	2683	103	96.2	post-Suzuki	8
3	polystyrene-bound trimercaptotriazine	4.8 mol equiv	23 °C, 24 h	47.4	0.045	99.9	Pd(OAc) ₂ (THF), 1 M acetic acid	9
4 ^a	activated carbon	75 wt %	22 °C, <1 h	86	<10	>88.4	post-amination	10
5 ^b	glass bead sponges	100 wt %	23 °C, 10 min	–	0.05	–	post-allylic rearrangement	11
6	Smopex 110	1.1 wt %	23 °C, packed bed, 1 pass	2370	9.48	99.6	Pd(OAc) ₂ (toluene)	10
7	thiol-functionalised silica	4 mol equiv	23 °C, overnight	395	3	99.2	post-coupling	12
8 ^b	multifunctionalised sulfur-based silica	10 g ads g prod ⁻¹	110 °C, 1 h	1000	<10	>99.0	Pd(OAc) ₂ (DMF)	13
9 ^b	polystyrene-bound diphenylphosphine	10 mol equiv	23 °C, 14 h	–	–	98.5	post-Buchwald–Hartwig	14
10	thiol-functionalised mesoporous silicate	4.42 mol equiv	23 °C, 1 h	530	0.0011	99.9	PdCl ₂ (THF)	15

^a Adsorbent stage applied to API molecule, ^b Adsorbent stage applied to model reaction product.

as a palladium loading per amount of product, expressed as mg (Pd) kg⁻¹ (product), not as the absolute concentration of mg·L⁻¹.

Use of adsorbents for sequestration of heavy metals has also demonstrated very efficient removal of palladium from post-reaction solutions (summarised in Table 1). However, when this technology is applied, active pharmaceutical ingredients (APIs), which offer complex structures containing multifunctional groups, may also bind to the adsorbent, thus reducing process yield, sometimes by up to 35%.¹⁶ Another problem associated with APIs is the ability of the functional groups present to anchor palladium to the product molecule itself.¹⁷ Palladium–API binding can have a severe effect on the efficiency of certain adsorbents, e.g. in entry 1 of Table 1, treatment of a post-reaction mixture with charcoal and diatomaceous earth, followed by filtration through a 0.22 μm filter, failed to sufficiently lower palladium levels.

To minimise problems associated with palladium–API and API–adsorbent binding, extensive screening of different adsorbents is required before the full-scale process can proceed. Screening can identify adsorbents capable of achieving regulatory-acceptable levels in challenging, functionality rich APIs without associated product loss. Additives such as ligands or ionic liquids, which can be used in a reaction to stabilise palladium catalysts, may also adversely affect the efficiency of the adsorption stage. These ligand functionalities can compete to keep the metal in solution rather than bound to the adsorbent.¹⁸ It has also been suggested that it would be more challenging for the adsorbents to remove any metal nanoparticles, commonly seen to form during palladium-catalysed reactions as a result of the catalytic cycle,¹⁹ than palladium species dissolved into a truly homogeneous solution.

This work presents a study assessing the feasibility of a hybrid process to remove palladium from post-reaction solutions resulting from acylation and Suzuki couplings. The majority of the palladium is first removed via OSN, and then palladium levels are further reduced using adsorbents. The OSN stage presents an opportunity for the removal of large post-reaction species which can include catalyst, ligands, metal colloids, and ionic liquids.^{6,20–23} The palladium concentrations achieved by the hybrid process are compared to those obtained by using each technology independently, for two model reactions.

2. Experimental Section

The two reactions used in this work are the Suzuki coupling reaction between bromoacetophenone and phenyl boronic acid to produce acetyl-biphenyl, see Figure 1a, and the formation of hexanophenone using an acylation coupling of phenyl boronic acid with hexanoic anhydride, see Figure 1b. The Suzuki coupling was performed using 5 mol % catalyst loading, and bromoacetophenone was the limiting reagent. A catalyst loading of 6 mol % was used in the acylation coupling, where hexanoic anhydride was the limiting reagent.

The post-reaction solutions were diluted and split into three aliquots to run three parallel purification processes (see Figure 2). Process 1 comprises two consecutive nanofiltrations to assess the feasibility of using OSN technology only to achieve a high-purity product. Process 3 assesses the feasibility of using adsorbent technology only to achieve the same goal. These technologies are combined in process 2, where the second nanofiltration is replaced by an adsorbent stage using lower adsorbent loadings than those of process 3.

The adsorbent loadings used in this work are based within the typical ranges seen in literature, with 0.04 g (adsorbent)·g⁻¹ (product) (4 wt% based on product) and 0.4 g (adsorbent)·g⁻¹ (product) (40 wt % based on product) used in processes 2 and 3 respectively for the Suzuki coupling. The acylation coupling used 2.30 g (adsorbent)·g⁻¹ (product) (230 wt % based on product)

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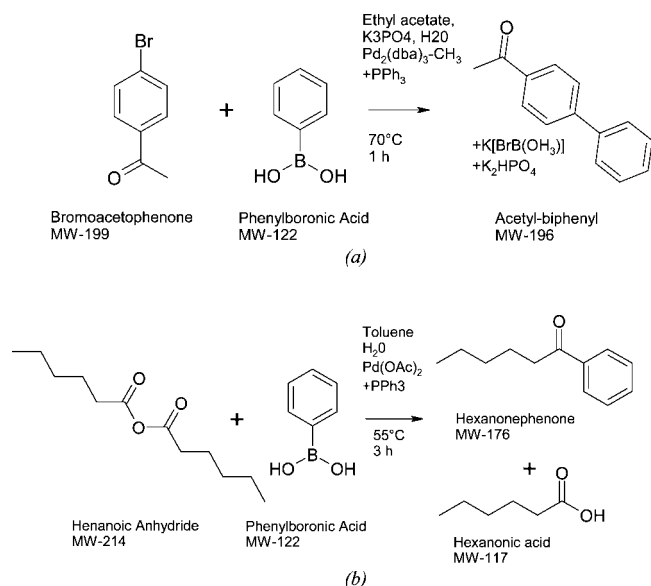


Figure 1. (a) Suzuki coupling reaction. (b) Acylation coupling reaction.

for process 2 and $6.80 \text{ g (adsorbent)} \cdot \text{g}^{-1}$ (product) (680 wt % based on product) for process 3. The palladium and product concentrations were monitored at the start and finish of the various treatment stages, using inductively coupled plasma (ICP) and gas chromatography respectively. Following successful performance in industrial applications¹⁰ and their commercial availability, the following four adsorbents with various functionalities were used for the acylation reaction: activated carbon (AC, Darco KB-B), macroporous polystyrene-bound trimercaptotriazine (TMT), Smopex 234 (S234, containing thiol functionality) and Smopex 105 (S105, containing pyridine/pyridinium functionalities). AC, Silica and TMT adsorbents were used for the Suzuki coupling. All reactants and adsorbents were purchased from Sigma-Aldrich, except for the Smopex samples and TMT which were obtained from Johnson Matthey and Argonaut Technologies respectively.

A water wash prior to the OSN stage is carried out for the Suzuki coupling, to remove the base and the palladium black from the system. This stage is not required for the acylation coupling, since no base is required to activate the boronic acid, this role being played by the acetate ion provided by the palladium acetate.²⁴

Finally, to confirm the membrane is indeed retaining the palladium nanoparticles, transmission electron microscopy (TEM) is used to observe palladium solids in the feed and permeate of an OSN stage. Palladium nanoparticles can be formed by allowing a solution of tris(dibenzylideneacetone)dipalladium(0) in ethyl acetate

to decompose in air. Visible precipitation of palladium black indicates the presence of nanosized species which cluster to form the precipitate.²⁵

3. Results and Discussion

3.1. The Hybrid Process (Process 2). The lowest palladium levels achieved in this work were obtained with the hybrid approach, particularly using TMT and S105 for the Suzuki and acylation coupling reactions, respectively, i.e. process 2 in Figure 2 (see results in Figure 3). OSN combined with a low TMT loading of $0.04 \text{ g (adsorbent)} \cdot \text{g}^{-1}$ (product) resulted in a product stream containing $4 \text{ mg (Pd)} \cdot \text{kg}^{-1}$ (product) for the post-Suzuki coupling solution. Even when adsorbent loadings were 10 times greater than those used in the hybrid process, the process using only the selected adsorbents was not able to meet the regulatory specification for palladium levels.

As the catalyst undergoes the oxidation/reduction cycles involved in the coupling reactions, a spectrum of homogeneous palladium species are produced, the larger of which includes palladium complexes with multiple, strongly bound, PPh_3 ligands. A majority of these larger homogeneous palladium species, as well as any heterogeneous species that may have formed during the reaction, can be removed in the OSN stage of the hybrid process. With the majority of the PPh_3 ligands bound to the palladium remaining in the retentate, the hybrid process allows the residual amounts of palladium in the permeate to be easily scavenged by the adsorbents, without having to compete with the PPh_3 ligands.

The hybrid process uses the OSN membrane Starmem 122, which has a molecular weight cut-off of 220 Da (Molecular weight cut-off (MWCO) of the membranes used here was obtained from a plot of the rejections of a series of *n*-alkanes dissolved at 2 wt % in toluene, versus alkane molecular weight. MWCO is defined as the molecular weight (MW) for which rejection by the membrane is 90%) and displays a low rejection (*R*) for the reaction products, around 10%.²¹ In this work, in order to transport a majority of the product from the retentate into the permeate, each filtration stage is carried out via a two-stage batchwise diafiltration. On the basis of 10% rejection, this filtration procedure results in a 4.7% product loss. However, by adding a third and then a fourth filtration stage the product losses could be reduced further to 1% and 0.2%, respectively. Product losses are easily reduced through further diafiltration to recover product in the permeate, while in the case of adsorbents, product losses can only be minimised through extensive screening of different adsorbents and adsorption conditions.

3.2. The Two-Stage OSN Process (Process 1). The initial palladium concentration of the post-reaction mixture, before any post-reaction treatment, was highest for the Suzuki coupling; however, OSN permeate streams in process 1 exhibit lower palladium concentrations for this reaction than for the acylation coupling (see Figure 3). Although the transport of palladium is positively related to the concentration difference across the membrane (i.e. in the retentate and permeate), the nature of palladium species present also plays an important role. The acylation coupling utilises a significantly lower molecular weight catalyst precursor of palladium acetate (224.5 Da) than

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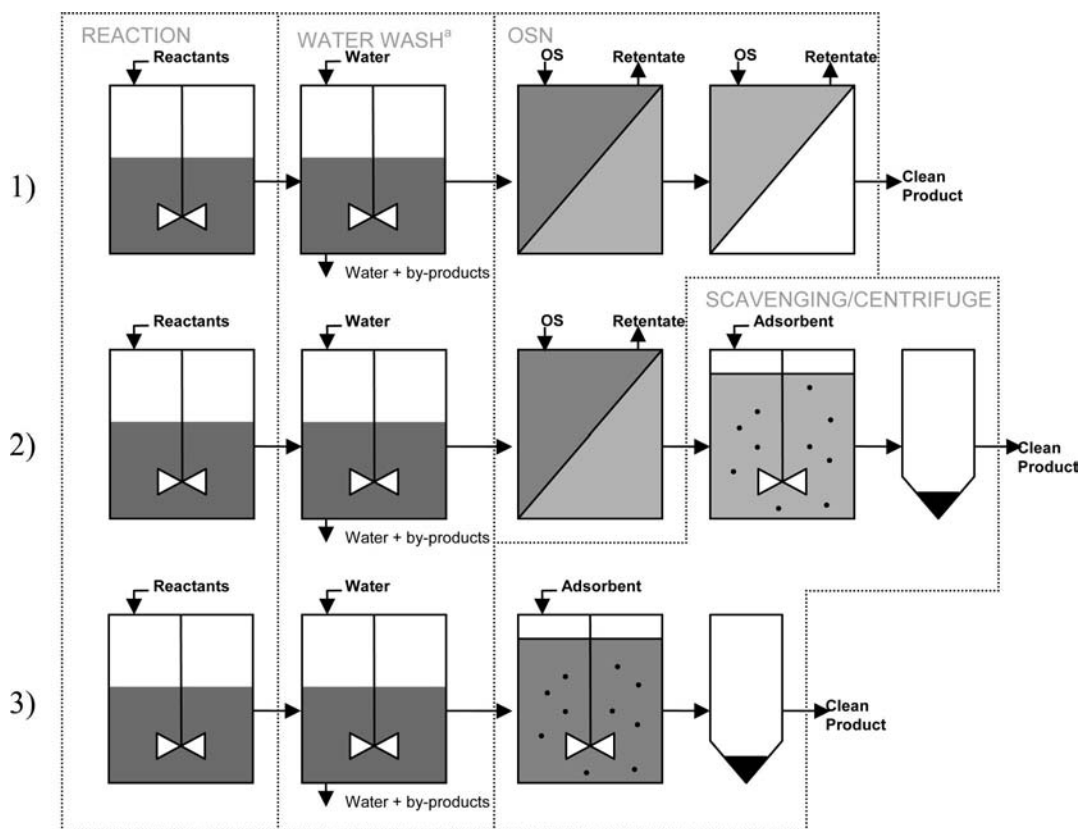


Figure 2. Processing routes used in this work for palladium removal from post-reaction mixtures (OS = organic solvent). (1) Double nanofiltration, (2) nanofiltration and adsorbents, (3) adsorbents only. (a) Water wash was used for the removal of base and insoluble byproduct, for Suzuki reactions only, and any palladium black was also removed by this wash. Centrifugation was used to remove palladium black for acylation post-reaction solutions.

	REACTION	OSN	ACYLATION		SUZUKI COUPLING					
			Pd Content ^a		Pd Content ^a					
1)			Pd Content ^a	36200	Pd Content ^a	56000				
			Membrane	SM122	Pd Content ^a	257	Membrane	SM122	Pd Content ^a	72
			Membrane	SM122	Pd Content ^a	103	Membrane	SM122	Pd Content ^a	58
2)			Adsorbent loading: 2.30 gadsorbent.gproduct ⁻¹		Adsorbent loading: 0.04 gadsorbent.gproduct ⁻¹					
			Adsorbent	S234	Pd Content ^a	11	Adsorbent	AC	Pd Content ^a	18
			Adsorbent	S105	Pd Content ^a	<3	Adsorbent	Silica	Pd Content ^a	9
3)			Adsorbent loading: 6.80 gadsorbent.gproduct ⁻¹		Adsorbent loading: 0.40 gadsorbent.gproduct ⁻¹					
			Adsorbent	S234	Pd Content ^a	84	Adsorbent	AC	Pd Content ^a	100
			Adsorbent	S105	Pd Content ^a	41	Adsorbent	Silica	Pd Content ^a	72
			Adsorbent	TMT	Pd Content ^a	18	Adsorbent	TMT	Pd Content ^a	34

Figure 3. Product purity summary for all three process routes (see Figure 2) for purification of post-reaction mixtures.^a mg (Pd)·kg⁻¹ (product).

the Suzuki coupling, which uses Pd₂(dba)₃ (1035.1 Da). This may lead to an increase in the presence of smaller post-reaction palladium species for the acylation coupling, leading to a higher proportion of post-reaction palladium being able to pass through the membrane during the OSN

stage. As a result, in spite of the acylation post-reaction solutions presenting a lower palladium concentration than those from the Suzuki coupling, we see that the permeate stream arising from the acylation coupling is significantly more contaminated. Smaller palladium species, less well

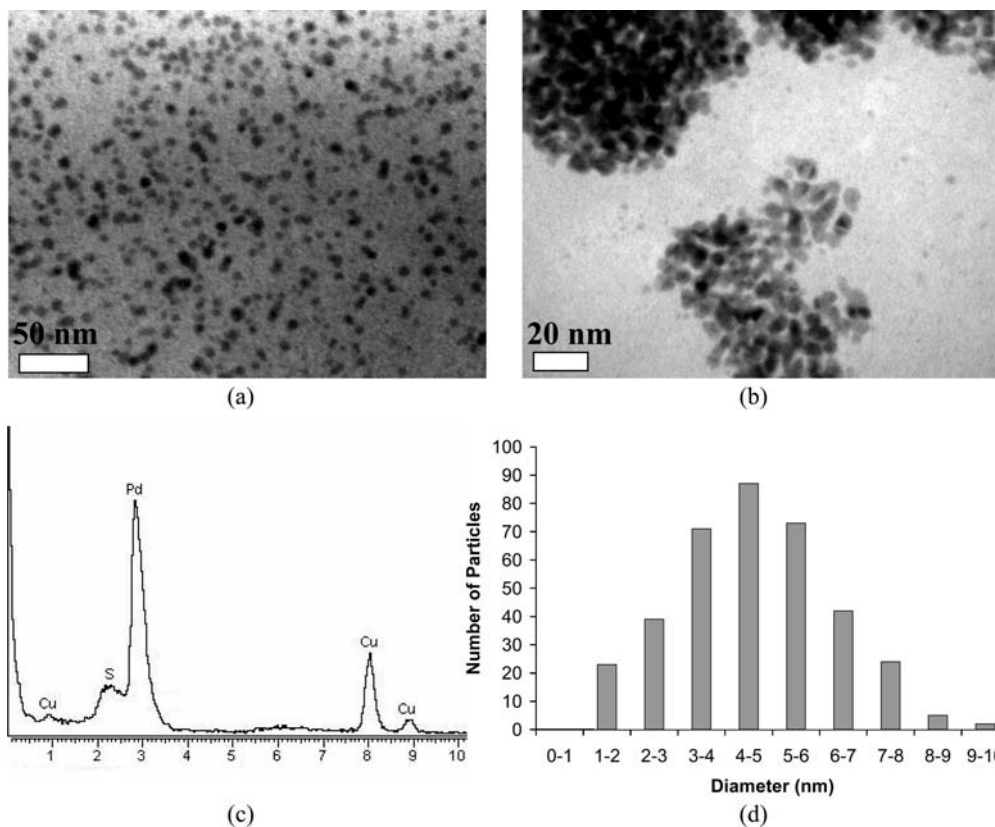


Figure 4. TEM images showing palladium nanoparticles formed from degraded tris(dibenzylideneacetone) dipalladium(0) (a) OSN feed solution, (b) higher magnification of possible palladium nanoparticles, around 1–2 nm, (c) conformation of palladium using in situ ED XRF for the area shown in (b), (d) nanoparticle size distribution, sampled from 366 random nanoparticles.

rejected by the membrane, can also explain the significant drop in palladium removal performance of the second OSN stage used in process 1. To see this, consider the following ratios of Pd levels, (initial feed/first OSN permeate) and (first OSN permeate/second OSN permeate). For the acylation reaction this ratio falls from 140.9 to 2.5, while for the Suzuki reaction, it falls from 777.8 to 1.2.

Palladium nanoparticles formed by the degradation of tris(dibenzylideneacetone) dipalladium(0) are shown in Figure 4. These palladium nanoparticles were seen in the feed samples subjected to nanofiltration; however, no sign of them was detected in the permeate samples, confirming their effective retention by the OSN membranes.

3.3. The Adsorbent Only Process (Process 3). Reducing palladium contamination of the product to levels below 10 ppm proved more challenging for the acylation post-reaction solution when using process 3. In an attempt to enhance palladium removal, higher adsorbent loadings were used. Moreover, the temperature dependence of the final palladium level and the adsorbent selectivity, α , (defined in eq 1,^{26–28}) were also investigated.

$$\alpha = \left(\frac{1 - x_{\text{Pd}}}{x_{\text{Pd}}} \right) / \left(\frac{1 - x_{\text{product}}}{x_{\text{product}}} \right) \quad (1)$$

Performing the adsorbent stage (process 3) at 90 °C resulted in increased palladium–adsorbent binding for the functionalised scavengers (see Figure 5). The selectivity of the adsorbents also increased with temperature except for TMT. For TMT, increas-

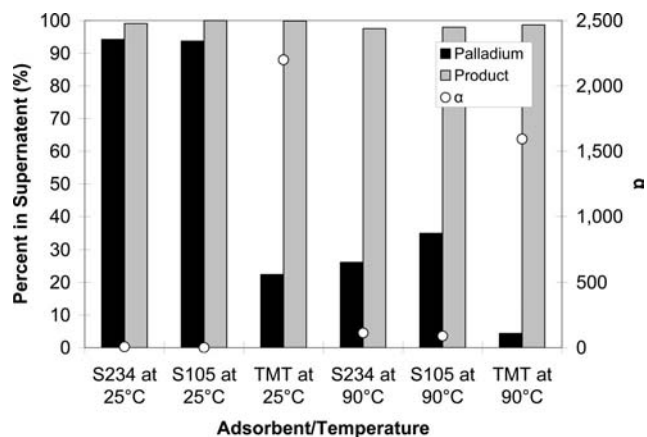


Figure 5. Effect of temperature on adsorbent selectivity using an adsorbent loading of 0.40 g adsorbent · g product⁻¹ (40 wt % of adsorbent based on product).

ing the temperature to 90 °C led to an increase in product lost due to adsorption. This reduction in product concentration outweighed the benefits, in terms of α , of the extra palladium removed by the temperature increase. However, this result also reflects the limitations of using α to compare the selectivity of high-performance adsorbents, since increasing the temperature resulted in only 1.2% product loss, which may be acceptable when considering the significant reduction in palladium contamination of 18.0%. Adsorbing residual traces of palladium requires a significant increase in adsorbent loading (see Figure 6). Selectivity of the adsorbents was highest for the intermediate adsorbent loading. This observation suggests the existence

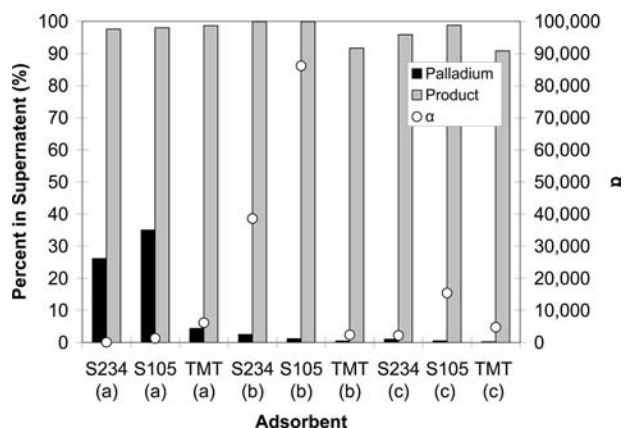


Figure 6. Effect of increasing adsorbent loading on palladium removal for the acylation coupling. Process 3, adsorption carried out at 90 °C. Adsorbent loadings: (a) 0.40, (b) 2.30, (c) 6.80 g adsorbent · g product⁻¹, or 40, 230, and 680 wt % of adsorbent based on product, respectively.

of an optimal adsorbent loading, where sufficient binding sites are available to remove a majority of the palladium while providing minimal vacancies for product loss. These results highlight one of the constraints of relying on adsorption only to achieve product purification, e.g. for TMT, increasing adsorbent loadings 17 times decreased the adsorbent selectivity from 6160 to 4730.

4. Conclusions

This study has presented a successful, novel approach to obtain post-reaction products which have ultralow palladium levels. The use of metal adsorbents, which can often result in significant product losses, are minimised in this OSN-adsorbent hybrid process which makes use of nanoporous OSN membranes to remove larger palladium species such as nanoparticles from solution by molecular filtration. It is suggested that this hybrid process maybe a useful technique to apply when confronted by a problematic API-catalyst separation. A variety of cross-flow and spiral wound membrane modules are commercially available; these can provide high membrane areas per liquid volume to be processed, leading to short processing times for large-scale applications. For example, the average flux of the post-acylation reaction using Starmem 122 was 46.8 L · m⁻² · h⁻¹; if we consider the use of 4 × 6 m² spiral wound membrane modules for the filtration of a 500-L post-reaction batch, typical of the pharmaceutical industry, the total filtration time for the reaction would be expected to be <30 min.

5. Experimental Procedure

All reaction solvents were degassed in a 250-mL volume, double-necked, round-bottom flask using the Schlenk technique (15 min under argon). All reactants were purchased from Sigma Aldrich.

5.1. Acylation Reaction. Hexanoic anhydride (2 mmol, 1.0 equiv), phenylboronic acid (2.4 mol equiv.), triphenyl phosphine (0.07 mol equiv), palladium acetate (0.06 mol equiv) were added to a carousel tube. Water (0.09 mL) and toluene (8 mL) were added to the reaction mixture, and the tube was connected to a Radley's carousel, stirring at 55 °C for 3 h under argon. Average product yield was 80.3%.

5.2. Suzuki Reaction Procedure. 4-Bromoacetophenone (1 mmol, 1.0 equiv) and phenylboronic acid (1.1 equiv) were added to a carousel tube. An atmospag was inflated and evacuated three times using argon. Inside, the triphenylphosphine (0.5 equiv) was dissolved in degassed ethyl acetate, and (1 mL) of tris(dibenzylideneacetone)dipalladium(0) (0.05 equiv) was weighed into the tube. Degassed ethyl acetate (1 mL) and 0.2 mL of the ligand solution was added along with the potassium phosphate (dried in an oven for an hour at 100 °C previously, 3.3 mmol 3.3 equiv) and 0.4 mL of degassed, purified water. The tube was then connected to the carousel, stirring started and was left for 1 h once the reaction mixture reached 70 °C. Average product yield was 76.9%.

5.3. Post-Reaction Treatment. Post-reaction mixtures were diluted and the solutions split between the three process routes.

5.4. Filtration Procedure. All filtrations were carried out in a dead-end Sepa ST pressure cell (Osmonics, U.S.A.) at 30 bar pressure and 30 °C. The cell was immersed in a temperature-controlled water bath, and the temperature was allowed to stabilise before any filtrations were started. The solution was agitated using a magnetic plate and a Teflon stirrer bar. Starmem 122 membranes (polyimide, asymmetric-type membrane) were supplied by Membrane Extraction Technology Ltd., UK. All membranes were preconditioned before use, using fresh organic solvent dictated by the reaction solution to be filtered. Filtration of post-reaction mixtures included two stages, the first initial separation allowed 80% of the 100 mL feed solution to permeate, the retentate of which was then diluted back to the original feed volume using fresh organic solvent before a second filtration of 80% commenced. Samples for ICP and GC analysis were taken from the combined permeates, as well as from the feed and retentate.

5.5. Adsorption Procedure. Aliquots of the diluted post-reaction mixture or permeate (10 mL) were placed in glass vials containing the appropriate adsorbent loading and agitated for 24 h. At the end of the adsorption stage, the solution was centrifuged for 15 min at 3600 rpm, and then the supernatant was analysed by GC and ICP.

5.6. Analytical Techniques. Gas chromatography was used to determine the concentration of 4-acetyl-biphenyl and bromoacetophenone using the 6850 series II from Agilent technologies, fitted with a flame ionisation detector

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and a HP-1 capillary column 30 m × 0.32 mm nominal diameter, 0.25 m film thickness 100% dimethylpolysiloxane phase.

ICP was used to determine metal concentrations (Pd, K, B) in the nanofiltration feed, permeate, and retentate. ICP analysis was carried out using a Perkin-Elmer 2000DV ICP OES. Each sample was analysed three times, and the coefficient of variation for the values obtained was estimated to be lower than 4%.

Images of palladium nanoparticles were made from dip-coated copper grids (300 mesh, carbon filmed) on a JEOL, JEM-FX2000 II TEM.

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