Case Study

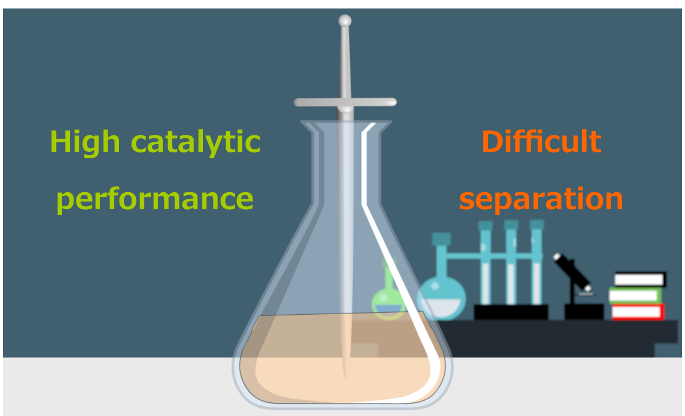
ETERNAL

MEMBRANES FOR HOMOGENEOUS CATALYST RECOVERY

ENERGY EFFICIENT REUSE

The high reaction efficiency and selectivity they afford to key chemical transformations such as cross-coupling and asymmetric hydrogenation make homogeneous catalysts a popular choice in the pharmaceutical and chemical industries. Separating them from the reaction mixture once their job is done however is inherently challenging because, unlike heterogenous materials, they cannot simply be filtered out. Since the catalysts contain precious metals like palladium, ruthenium, and rhodium however, patient safety, process economics, and environmental sustainability all dictate that finding efficient methods for their recovery and reuse is of critical importance.

Traditional separation methods, like distillation, extraction, and adsorption, can't solve all the challenges. Distillation for example, requires phase changes and high energy input, making it unsuitable for heat-sensitive catalysts and products. Solvent extractions entail cumbersome biphasic operations, whilst using scavengers to adsorb impurities risks both loss of product via undesired adsorption and potential introduction of the scavenger as a new impurity should it not be effectively removed.



Uniform dispersion is a double-edged sword: having both the catalyst and reactants in solution contributes to the high performance of homogeneous catalysts but presents significant challenges for catalyst separation and recycling.

Context

Homogeneous catalysts are frequently used in the pharmaceutical industry but separating them from the reaction mixture for subsequent reuse is problematic. Removal of these toxic catalysts is crucial to ensure patient safety. Additionally, their high costs make their recovery and reuse essential for both economic viability and environmental sustainability.

Challenge

Separating homogeneous catalysts is inherently challenging because they exist in the same phase as the product. Traditional separation methods often lead to high energy consumption and waste generation.

Innovation

AstraZeneca has developed a process using organic solvent nanofiltration (OSN) membrane technology to efficiently recover and reuse palladium catalysts during the synthesis of an important oncology drug. This minimizes energy consumption and waste production, promoting a more sustainable approach to catalyst management in pharmaceutical manufacturing.

Next Steps

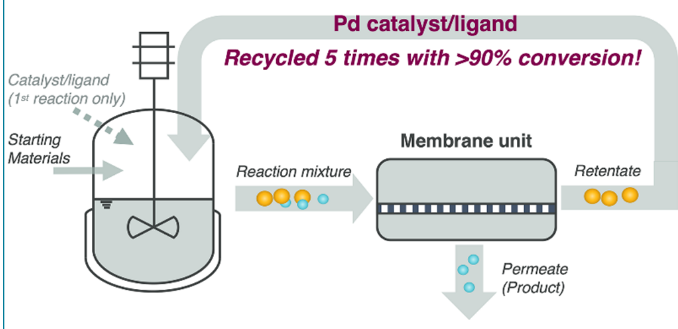
To further enhance sustainability, AstraZeneca is optimizing the OSN process by integrating solvent recovery techniques. They also aim to apply membranes to other pharmaceutical syntheses, which will broaden its impact and contribute to greener practices in industry.

Organic solvent nanofiltration (OSN) presents a promising new alternative way of addressing these challenges as it can selectively separate catalysts from the product without thermal or phase transitions and biphasic operation, making homogeneous catalyst recovery easier and greener.

Features and Advantages

OSN membrane technology utilizes membranes that are stable in organic solvents to separate solutes with molecular weights ranging between 200-1000 Da, which encompasses many small molecule drugs. Unlike traditional separation methods such as distillation, OSN operates without phase changes and under mild conditions, making it particularly suitable for heat-sensitive catalysts and products. The technology allows selective separation of palladium catalysts and associated ligands from product mixtures. Additionally, separation is non-destructive allowing the catalysts and ligands to be reused in future reaction batches.

Compared to traditional separation technologies, membranes offer milder and more energy-efficient processes with minimal waste and seamless integration into continuous manufacturing. Beyond these direct advantages catalyst recovery and reuse can significantly reduce operational disposal and replacement costs, whilst lowering environmental impact. The potential for broader application across various pharmaceutical syntheses positions OSN as a key enabler in advancing greener practices within the industry.



Membrane choice in OSN seeks to combine a high degree of catalyst rejection with low solvent product, along with high membrane stability. A membrane which performs well in otherwise unmodified reaction conditions makes for a straightforward process substitution.

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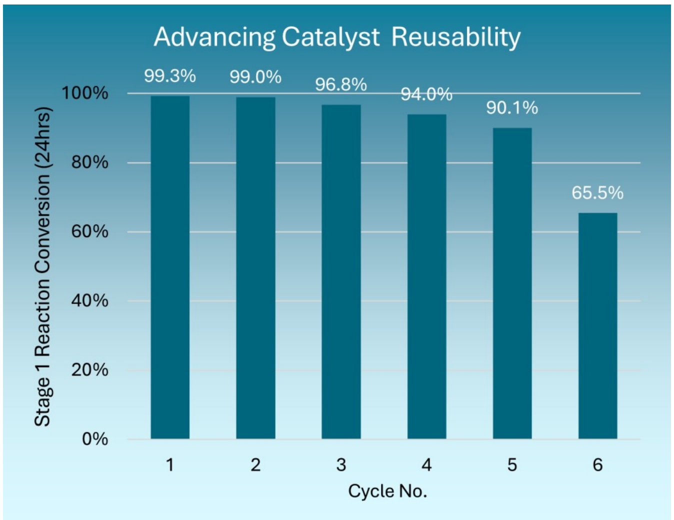

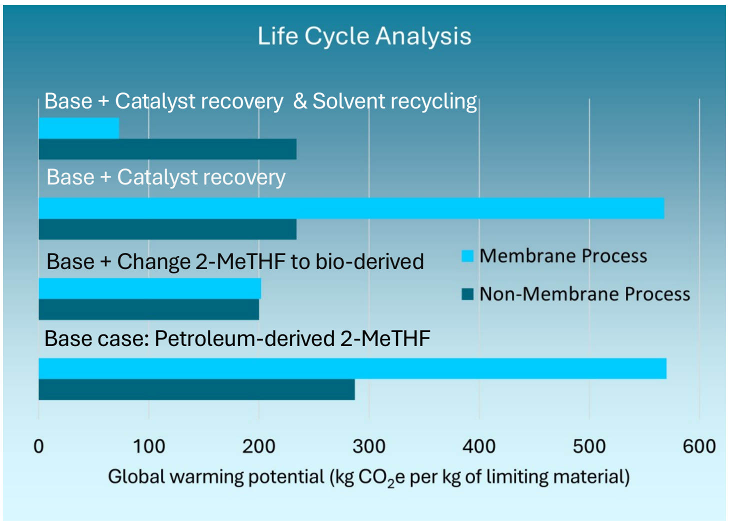

Results and Benefits

Published results[1] demonstrate the application of OSN for the efficient recovery and reuse of a homogeneous palladium catalyst in the synthesis of AZD4625.

- 98% of the product has been recovered with minimal catalyst contamination
- Recovered catalysts and ligands have been successfully reused for up to five reaction cycles, while maintaining conversion of more than 90%

Life cycle assessments indicate the sustainability of the OSN process could be further improved by using bio-derived solvents and solvent recovery techniques.

Catalyst recovery and reuse can help manufacturers reduce waste and reliance on costly catalyst replacements, benefiting both the economy and the environment. Positive impact extends to public health by facilitating the production of safe and effective medications while fostering a commitment to sustainability within the industry.

ETERNAL is contributing to the sustainable development of pharmaceutical manufacture, use and disposal, by using and promoting full life cycle approaches covering design, manufacture, use, and disposal through

- application-industry oriented R&D and scale-up;
- clear pathways to compliance;
- new scientific knowledge on the environmental fate and eco-toxicological effects of pharmaceuticals; and
- behavioural change for safe use and disposal.

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1. See doi.org/10.1039/D4GC06334A

Find out more at: www.eternalproject.eu