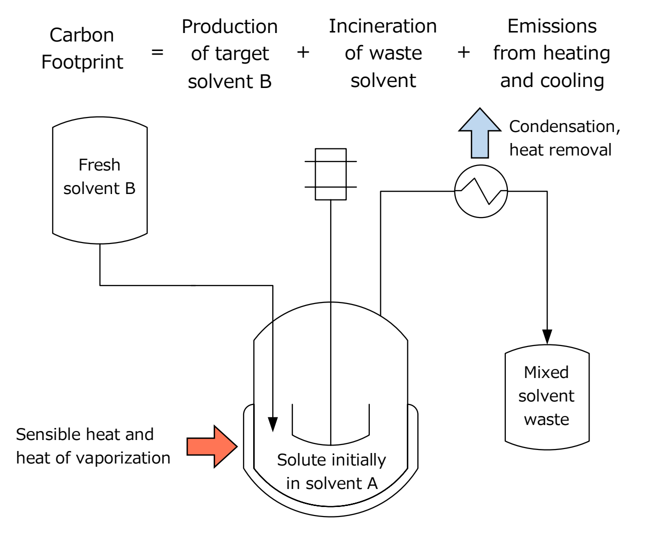
Case Study

ETERNAL

MEMBRANES FOR STREAMLINED SOLVENT EXCHANGE

SUSTAINABLE SEPARATIONS

Pharmaceutical manufacturing processes often involve numerous, sequential batch reactions, carried out in different organic solvents. This necessitates frequent exchanges of solvent, so that the intermediate solutes are presented in the appropriate solvent for the next reaction stage. Conventionally, solvent exchange is achieved by distillation, which requires significant amounts of solvent and energy to achieve. Moreover, distillation is only effective when exchanging from a solvent of lower boiling point to another with higher boiling point, and the thermal conditions may well be less than ideal for heat-sensitive molecules. With the stringency of environmental regulations applicable to the pharmaceutical industry only likely to increase, it is vital for the sector to integrate more sustainable and environmentally friendly ways of swapping solvents into their processes.



Solvent exchange by distillation involves elevated temperatures and energy intensive phase changes, generating a large carbon footprint.

Context

Pharmaceutical manufacturing processes often involve complex batch reactions and frequent solvent exchanges. These are typically achieved with energy-intensive distillation. As environmental regulatory pressures increase, the industry is being compelled to adopt more efficient, sustainable separation technologies.

Challenge

Distillation is inefficient when exchanging from a high- to a low-boiling-point solvent and are unsuitable for heat-sensitive compounds. The challenge is to find a more sustainable approach to solvent exchange that minimizes energy consumption and solvent waste while ensuring compliance with stringent regulatory standards.

Innovation

Organic solvent nanofiltration (OSN) offers an energy-efficient alternative to distillation, using membrane technology to achieve low temperature, low energy solvent exchange. Coupled with inline Fourier Transform infrared spectroscopy (FTIR), solvent composition can be monitored dynamically, enhancing the overall process efficiency.

Next Steps

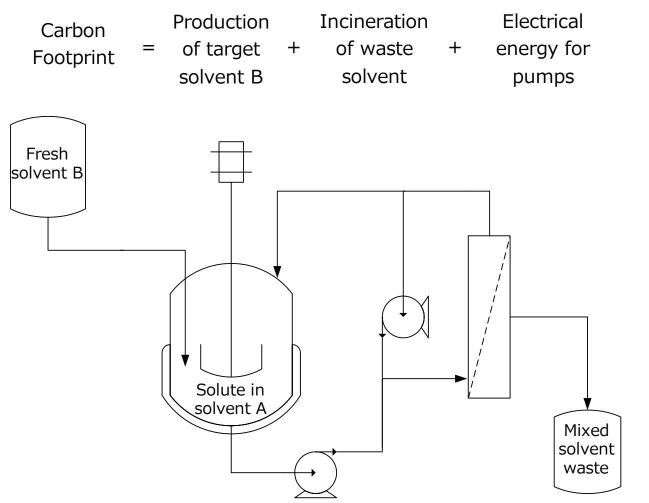
With further optimization and targeting towards suitable industrial applications, the identified OSN stages are being scaled up and validated at pilot scale, to promote sustainability and enable broader benefits across the industry.

Organic solvent nanofiltration (OSN) has emerged as a promising, energy-efficient technology for the separation of organic compounds at a molecular level. OSN works by by applying a pressure gradient across a membrane surface at ambient temperature. Provided sufficiently high flux (permeability) and rejection (selectivity) can be achieved, OSN provides an attractive and realistic alternative means of achieving solvent exchange.

Features and Advantages

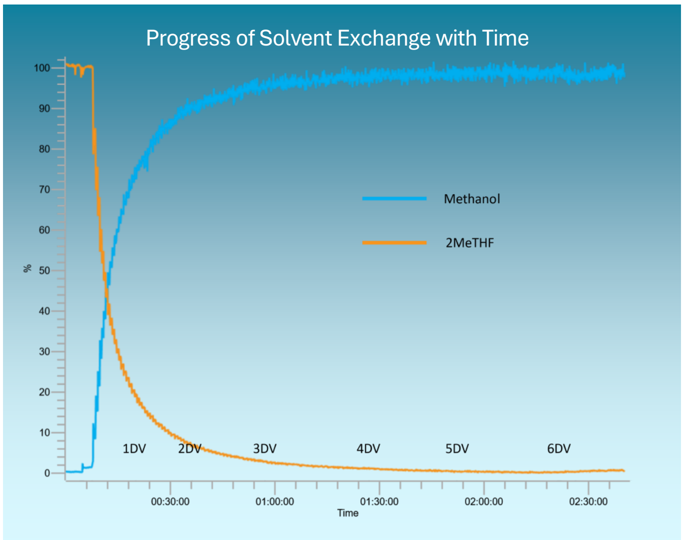
A key feature of OSN is energy efficiency. Membrane-based separation processes typically operate at ambient temperatures and without phase changes, reducing overall energy requirements compared to distillation. Coupling the membrane technology with advanced monitoring, through integrated FTIR-based Process Automation Technology (PAT), allows for real-time solvent compositional analysis. This facilitates immediate process adjustments where required. The ability to tailor membrane performance, targeting high permeability and selectivity for a given application, enables effective separation.

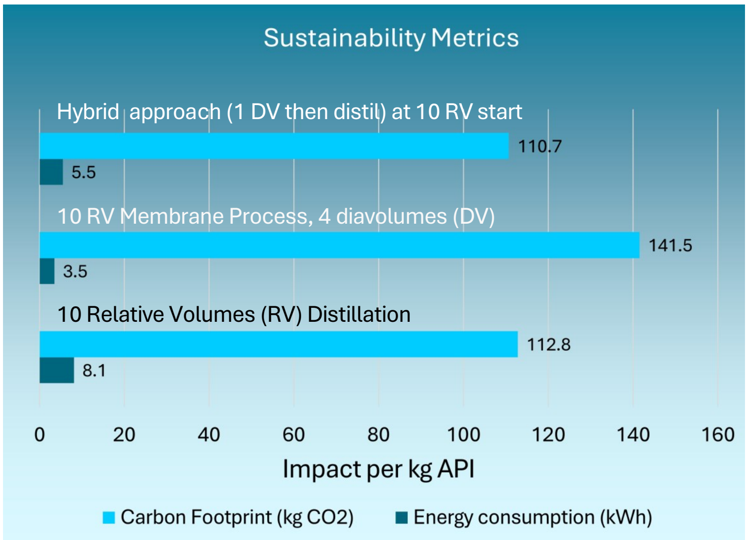
The combination of these features lead to operational efficiency, cost savings, and reduced environmental impact. Streamlining solvent exchange reduces downtime and enhances productivity. Energy consumption is reduced, leading to reduced operating costs. Finally, minimizing waste and the carbon footprint associated with physical separation can help manufacturing align with organizational sustainability goals.



OSN offers the prospect of achieving the same solvent swap under milder conditions and without the need for heating and cooling duties.

Operational efficiency, cost savings, and reduced environmental impact





Results and Benefits

Researchers from the ETERNAL team at AstraZeneca have identified and tested six different commercially available membranes, determining optimal conditions for solvent exchange between 2-methyl THF and methanol in one of the steps to synthesise AZD4625, a drug candidate for treatment of $KRAS^{G12C}$ positive tumours. Results indicate that OSN can significantly lower energy demands and solvent waste compared to traditional methods. In this specific example, a hybrid approach, which uses OSN to reach the azeotropic solvent composition and then continues with distillation, provides results indicating that a significant reduction in CO_2 footprint and energy can potentially be achieved.

Applied to suitable solvent exchange duties, this innovation will improve the sustainability of pharmaceutical processes, directly contributing to cleaner production that aligns with regulatory standards. Ultimately, this could lead to safer drugs with reduced environmental impacts, benefitting both manufacturers and consumers alike.

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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Find out more at: www.eternalproject.eu