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Molecular separation with an organic solvent nanofiltration cascade – augmenting membrane selectivity with process engineering

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HIGHLIGHTS

- Developed an automated cascade utilising organic solvent nanofiltration membranes.
- Concurrently concentrated an API and recovered organic solvents with the cascade.
- Validated the process model, which is intuitive and simple to use.
- Process saves energy compared to flash-condensation.
- Process becomes economical with moderate improvements to membrane performance.

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ABSTRACT

While it is known that organic solvent nanofiltration (OSN) can be used to recycle solvents, most commercial membranes do not retain active pharmaceutical ingredients (API) sufficiently to enable solvent recovery in a single stage membrane process. A multistage membrane cascade might be used to augment the overall rejection. However there have been no examples shown, to date, of this approach to concurrent API enrichment and organic solvent recovery. In this work, the development of a membrane cascade design is described. The use of this automated multistage cascade, for the concentration of a dilute API product solution and concurrent solvent recovery downstream of a chromatographic process, was demonstrated. The 3-stage cascade was able to achieve an effective rejection of 80% compared to a single pass rejection of 55%. Control of the cascade was simple and its operation was stable. Furthermore, the low permeation selectivity of one solvent over another across the membrane meant that solvent composition did not change significantly in the cascade. As a result no additional heat needs to be applied to keep the solutes in solution if such a system were to be used for solvent recovery. This is especially advantageous for processing of thermally sensitive API.

1. Introduction

Organic solvents usage efficiency in the pharmaceutical industry has much room for improvement though solvents are widely used in the industry (Hellweg et al, 2004). In fact solvent use accounts for an estimated 80–90% of mass utilisation in a typical pharmaceutical batch chemical operation, but recovery rates of organic solvents are low with GlaxoSmithKline (GSK) quoting that $<50\%$ of their solvents are recycled and reused (Constable et al., 2006). Improving organic solvent recycling rates can be part of the strategy to reduce solvent wastage and organic solvent nanofiltration (OSN) might help realise this strategy.

While OSN membranes have made significant advances in terms of membrane performance, groups that have worked with the concentration of API with OSN have been unable to achieve total rejection of any API (Darvishmanesh et al., 2011; Geens et al., 2007; Székely et al., 2011). Vandezande et al. (2008) suggested that membranes with high rejections tend to have lower fluxes and vice versa, implying that the concentration of an API using a single membrane stage will likely require large membrane units, limiting such an application to costly APIs or solvents. An economical solution would involve the use of membranes with high fluxes which tend to have moderate rejections. However this requires a process engineering solution to overcome the problem of moderate rejections.

Abbreviations: API, active pharmaceutical ingredient; *f*, function placeholder, f; *h*, function placeholder, h; MeOH, Methanol

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We have identified a continuous chromatographic process at UCB Pharma S.A. which could potentially benefit from the use of a membrane cascade in solvent recovery and API concentration, and this will be used as a case study in this work. Several possible synthesis routes were investigated for the production of a small developmental API molecule with a molecular weight below 300 Da. In one of these routes, a continuous chiral chromatographic process is used to separate the API from its racemic mixture. The chromatography employs a solvent mixture, containing methanol and ethyl acetate, as the mobile phase. As large amounts of mobile phase are utilised, they need to be recovered after the separation. The recovery process involves 2 stages. Firstly the product solution, containing either the API or its enantiomer at $10\,g\,L^{-1}$ in concentration, is concentrated with an evaporator to $90\,g\,L^{-1}$. The resulting vapour stream is then sent to a total condenser to recover the solvent, which is continuously recycled back into the chromatographic process. Secondly, the product concentrate from the evaporator is sent to a crystalliser where the remaining solvent is evaporated, with the vapours once again sent to a total condenser for solvent recovery. A stringent design concentration specification has been set for the recovered solvent at $0.005\,g\,L^{-1}$ in an attempt to minimise impurity effects on the chromatographic separation.

The phase changes from liquid to gas and from gas to liquid require the input of significant amounts of energy, even if heat integration can be used to reduce the amount substantially. Furthermore the difference in volatility of the solvents in the mobile phase means the mobile phase composition changes as the product solution is concentrated. The solution becomes less polar as it gets concentrated via evaporation. A consequence is a decrease of API solubility, which needs to be mitigated by keeping concentrate temperature high via heat input to prevent premature crystallisation.

There are many advantages of using membranes in solvent recovery and API concentration following the continuous chromatographic separation. Firstly, there is the potential for energy savings through the elimination of phase changes. Furthermore the potential savings in energy mean an API producer is less exposed to the volatility of energy prices that have characterised the last decade (Kojima, 2009). Lastly, mildly athermal conditions can be used, which decrease the chances of thermal degradation of a high value API.

When recovering solvent mixtures, the use of an evaporation–condensation solvent recovery setup can result in solvent composition changes when volatility differences between the constituent solvents are significant. This is especially disadvantageous if a certain composition is essential for the process. The use of a nanofiltration membrane that is unable to discriminate between the solvents in the mixture means the solvent composition can be preserved while concentrating the API.

Multistage membrane processes can be used to implement a membrane process despite the constraints of moderate rejection OSN membranes. Such processes have been used for product concentration and solvent recovery (Katraro et al., 1997), reagent purification (Abejón et al., 2012), binary solute separation (Mayani et al., 2010) and solvent exchange (Lin and Livingston, 2007). With the exception of the cascade used for solvent exchange, these previous cascades had no simple way of changing the flows into and out of each stage independently of solute rejection, short of changing the area of each stage. Hence these cascades are unlikely to be robust enough to adapt to changing feed conditions. The differences in areas of the stages also increase the complexity in designing such a cascade.

Process models, originating from the design of the corresponding membrane cascades, have been developed for membrane cascades used for gas treatment (McCandless, 1994) and liquid fraction separations (Avgidou et al., 2004; Keurentjes et al., 1992). However, these models are mostly incompatible with solute rejection, the commonly used membrane performance parameter in OSN. On the other hand, Lightfoot et al. (2008) and Gunderson et al. (2007) have developed a set of equations, derived from the constant volume diafiltration process model, to describe cascade behaviour. However this equation set is incompatible with our process because it ignores the solvent balance and is unable to account for solvent recovery. While Caus et al. (2009) and Vanneste et al. (2012) have developed process models that can possibly be used for a solvent recovery and solute concentration cascade, their processes differ from the eventual cascade proposed in this work. The configuration by Caus et al. (2009) lacks a "stripping" section essential for a high solute enrichment capacity (see Section 2.4) while the process proposed by Vanneste et al. (2012) was designed for batch operation, as opposed to the continuously operated cascade presented in this work.

2. Development of a membrane cascade system

This work proposes a new cascade configuration that is easy to design, and is both robust and flexible in operation. In this study, due to the low solute concentration, we ignored the partial molar volume effects of the solute in solution. Hence the concentrations of the solute were expressed in terms of $g\,L^{-1}$. In doing so, material balance calculations were simplified, as volumetric flow readings could be used without conversion to mass flow readings. Three configurations of membrane cascades, of increasing complexity, were examined and compared.

Note that in the comparisons, the rejection of solute i over a membrane in stage j was defined as

$$R_{i,j} = 1 - \frac{y_{i,j}}{x_{i,j}} \tag{1}$$

Using this definition of solute partitioning, we assumed perfect mixing in each membrane stage. As a measure of the effectiveness of a cascade in augmenting the separation capability of a membrane, we used the overall rejection as a standard of comparison.

$$R_{i,o} = 1 - \frac{y_{i,product}}{x_{i,product}} \tag{2}$$

In this work, we evaluated the possibility of using a membrane cascade to replace the first step in solvent recovery process as described in Section 1.

2.1. Batch permeate multipass cascade

The simplest batch nanofiltration unit operation involves the filtration of a solution until the solute concentration of the retentate reaches the target concentration level. A series of such unit operations forms a batch permeate multipass cascade, in which the permeate stream from stage j is sent for further filtration in stage $j+1$. This can be done until the desired permeate solute concentration, $y_{i,n}$, from the final stage is achieved. The schematic of such a cascade is shown in Fig. 1.

The control of product quality in such a cascade is not as straightforward as it might seem. For each stage, the filtration results in the increase of solute concentration in the retentate which causes an increase in solute concentration in the permeate stream, if solute rejection is assumed to be constant. Obtaining the exact product quality would require detailed understanding of the process dynamics in this cascade. Modelling such a dynamic system is challenging as one will never be sure of the evolution of solute concentration over the filtration time, unless there is firm control over the permeate flux through the membrane. Such a