Separation of Pharmaceutical Process-Related Impurities via an Organic Solvent Nanofiltration Membrane Cascade

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Introduction

The control of impurities is a critical issue in pharmaceutical industry and very strict regulations related with this issue have been introduced by ICH (International Conference on Harmonisation)[1-3]. The drugs impurities in general are classified into two types[4]: (1) impurities associated with the Active Pharmaceutical Ingredients (API) production and, (2) impurities generated during formulation and or with aging or that are related to the formulated forms. According to ICH guidelines, impurities associated with API are either organic, inorganic ones or residual solvents. Organic impurities include unreacted starting materials, intermediates, byproducts, degradation products, reagents, ligands, and catalysts. The undesirable chemicals that remain with the APIs during manufacturing so called process-related impurities, could be generated at any of the synthetic steps in variant solvents.

One of the common process-related impurities in pharmaceutical manufacturing process is coloured byproduct. Because they normally present at a trace level (<<0.1%) and have structural similarities with the API substance, colour impurities are not easy to separate by conventional processes and affect the product quality apparently. Muller et al.[5] pointed out a major hurdle in API process development is to separate an organic synthesis intermediate (I7) from a mixture comprising multiple components, including inorganic salts, polymers, isomers, and coloured byproducts. The last two items were found to be the most challenging task in purification as the first two could be separated by quench and charcoal treatment respectively. In addition, a yellowish colour was never observed during the synthesis of a pain relief drug until it was manufactured at a pilot plant scale in Merck Research Laboratories[6]. This trace amount coloured impurity was characterized by LC-MS-MS (liquid chromatography- tandem mass spectrometry) after enrichment by a preparative HPLC. The yellow byproduct (relative molecular mass, r.m.m. 711) was then confirmed it was resulted from its precursor (r.m.m. 626) derived from a starting material (rofecoxib, r.m.m. 314) for the coupling reaction. Another yellow impurity was observed at a level of 0.15% during the development of a drug substance candidate in Pfizer Inc.[7] According to the ICH guidelines, impurities exceeding 0.1% need to be structurally identified. Two structure-related impurities, i.e. $C_{38}H_{41}N_5O_9S$, (r.m.m. 775) and $C_{39}H_{44}N_4O_{10}S_2$, (r.m.m. 792), were therefore by LC-MS and LC-NMR (nuclear magnetic resonance spectrometry) with solid-phase extraction pretreatment. The two impurities were generated after crystallization of the API, and were assumed not easily removable by conventional processes, as they are pseudo-dimers of the API product, i.e. $C_{39}H_{44}N_4O_{10}S_2$, (r.m.m. 404). Thus there is a substantial need for further development of separation technologies able to coup efficiently with APIs purification.

Nanofiltration (NF) membranes have been developed well during the last two decades and the current main applications are water/wastewater treatment, food and dairy industries. In pharmaceutical industry, NF membranes have been used for recovery heterocyclic drug derivatives[8] and antiviral drugs derivatives[9] from aqueous waste streams and treatment of pharmaceutical plant wastewater[10, 11]. However, most pharmaceutical syntheses are solvent-based processes. Although conventional NF membranes can effectively separate solutes at nanometer scale in aqueous solution, the instability of

most membranes in organic solvents limits their applications in drug manufacturing processes. Organic solvent nanofiltration (OSN) membranes have recently emerged on the market. They are fabricated from solvent resistant materials and number of applications closely related to pharmaceutical processes have already been proposed, such as solvent exchange[12, 13], organic synthesis catalysts recovery[14, 15] and ionic liquids recycling[16].

Application of OSN membranes for API separations have been discussed by Witte[17] and Geens and Van der Bruggen[18] at two recent conferences, however up to date there is no real systematic study dealing with process-related impurities in the API production process. In addition most of the current OSN membrane studies were performed using a single stage nanofiltration unit, which normally is not able to show the capability of this process to simultaneously achieve real industrial requirements, e.g. continuity, high yields and purity. This work presents a comparison of different purification schemes of OSN membrane processes for impurities removal, i.e. a three-stage configuration and diafiltration. The different configurations are compared in terms of product purity and productivity.

Methodology

A membrane cascade, consisting of three flowthrough stirred cells in series, was set up to test the feasibility of OSN membranes in the application of API impurity separation. Each membrane cell holds a circular flat sheet membrane with an effective area of 51 cm^2. The detail drawing and layout of this cell can be found in our previous work[11]. A makeup solution is fed into the cascade by a high pressure liquid chromatography pump (HPLC pump, Gilson 302) as shown on **Fig. 1**. Since permeates of the second and the third cell are both recycled by the other two pumps to each previous cell, only two product streams generated in the system, i.e. permeate of the first cell and retentate of the last cell. The system pressure was controlled by a pressure release valve located at the end of the final retentate stream. Pressure of each cell was monitored by individual pressure gauge.

In another way, constant volume diafiltration (CVDF) set-up were used to compare the performance with the three-stage cascade. The set-up comprised of a single flowthrough stirred membrane cell, two HPLC pumps and one pressure release valve, as shown on **Fig. 2**. OSN membranes were preconditioned until steady permeate flux achieved. Initial make-up solution was fed into the testing cell from a reservoir by one pump, while fresh pure solvent was added by another one to keep the reservoir constant volume, i.e. 250 ml.

One commercial available OSN membrane, i.e. STARMEM^{TM,1} 228, was chosen in this study. STARMEM 228 is a polyimide based membrane with nominal molecular weight cut-off (MWCO) of 280 $g \cdot mol^{-1}$. Methanol was used in this study as it is a common solvent in pharmaceutical process. Due to the relative molecular mass (r.m.m.) or molecular weight (m.w.) of colored impurities are normally twice larger than the target APIs in above two cases, two dyes with similar molecular weights were chosen as a model system to demonstrate here. Martius Yellow (MY, 2,4-Dinitro-1-naphthol sodium salt, m.w. 274.16 $g \cdot mol^{-1}$) and Brilliant Blue R (BBR, m.w. 826 $g \cdot mol^{-1}$) were respectively represented color impurity and API product in manufacturing process. All chemicals are obtained from Sigma-Aldrich UK.

The concentrations of model API product and impurity were analyzed by UV spectrophotometer. Maximum absorption peaks of each dye were firstly scanned by a UV-VIS scanning spectrophotometer

[1] STARMEM is a trademark of W.R. Grace & Co. (USA), and supplied by Membrane Extraction Technology, Ltd. (UK)

(Shimatzu UV-2101 PC) to make sure they did not interfere each other in the mixtures. Calibration curves of Martius Yellow and Brilliant Blue R in methanol were then made at their maximum absorption wave length, i.e. 431 and 588 nm, respectively. Solute concentrations of feed, permeates and retentate were analyzed by another spectrophotometer (UNICAN).

The performances of OSN membrane processes are evaluated by impurity level, productivity and rejection, which are defined as follow:

$$\text{Impurity level} = \frac{\text{g (impurity)}}{\text{g (product)}} \text{ or } \frac{\text{g (Brilliant Blue R)}}{\text{g (Martius Yellow)}}$$

$$\text{Pr}oductivity = \text{C (concentration)}\,[\text{g}\cdot\text{L}^{-1}] \times \text{J (flux)}\,[\text{L}\cdot\text{m}^{-1}\cdot\text{h}^{-1}] \quad \text{or} \quad \frac{\text{C (concentration)}\,[\text{g}\cdot\text{L}^{-1}] \times \text{Q (flowrate)}\,[\text{L}\cdot\text{h}^{-1}]}{\text{A (membrane area of each process)}\,[\text{m}^2]}$$

$$\text{R}ejection = 1 - \frac{\text{C}_\text{p}\ \text{(permeate concentration of each cell)}}{\text{C}_\text{R}\ \text{(retentate concentration of final cell)}}$$

Results and discussions

STARMEM 228 membranes discs were placed in each cell of the three-stage cascade and preconditioned with pure methanol until a constant permeate flux was reached. As shown in **Fig. 1**, the model mixtures were then fed into the first stage of a three-stage cascade constantly (average feed flowrate is 0.34 $L\cdot h^{-1}$). Each permeate flux was measured and samples were collected from the permeate streams and the final retentate in 15 minutes intervals. The filtration was performed at room temperature and 30 bar pressure. Good system stability was shown on **Fig. 3(a) & (b)** since flux and rejections of impurities were stable. Average rejections of model impurity (i.e. Brilliant Blue R) in the first, second and third stage are 99.6, 99.1 and 100%. The performance of the OSN membrane configuration is evaluated by the impurity level and productivity according to above definitions. The product and impurity are eventually separated into two streams, i.e. the first stage permeate (Permeate 1) and the final retentate. The productivity of product is increasing from 2.87 to 4.86 $g\cdot h^{-1}\cdot m^{-2}$, while the productivity of impurity in retentate is slowly increased as well (from 0.216 to 0.476 $g\cdot h^{-1}\cdot m^{-2}$).

Constant volume diafiltration experimental set-up is shown in **Fig. 2.** In this single stage configuration the retentate was recycled to the feed and the volume in the feed reservoir was kept constant (250 ml) via continuous addition of fresh solvent. This experiment was also carried out at room temperature and 30 bar pressure, but monitoring in a longer period (11 hour). There are also two streams as the same as previous three-stage scheme. The productivity of product in permeate reached to a peak at the 50th minute, then decreased gradually from 5.32 to 1.21 $g\cdot h^{-1}\cdot m^{-2}$. The same trend obtained in a previous shorter period (2.12 hr) CVDF testing, which the productivity of product in permeate also reached to a peak at the 50th minute, then decreased gradually from 6.51 to 3.17 $g\cdot h^{-1}\cdot m^{-2}$.

Both experimental results show OSN membranes capable to control impurity even only tiny amounts existing in the feed mixture (5.04 wt.% and 5.37 wt.% respectively for the three-stage configuration and the CVDF testing). Impurity levels of all permeate streams are always nearly zero whether different configuration or scheme. At the same feed volume (250 ml), the product productivity of the CVDF set-up (5.25 $g\cdot h^{-1}\cdot m^{-2}$ at the 40th minute) showed better performance than three-stage

configuration (3.45 $g \cdot h^{-1} \cdot m^{-2}$). However, the advantages of the cascade including no fresh solvent needs to be added and the process can be operated continuously.

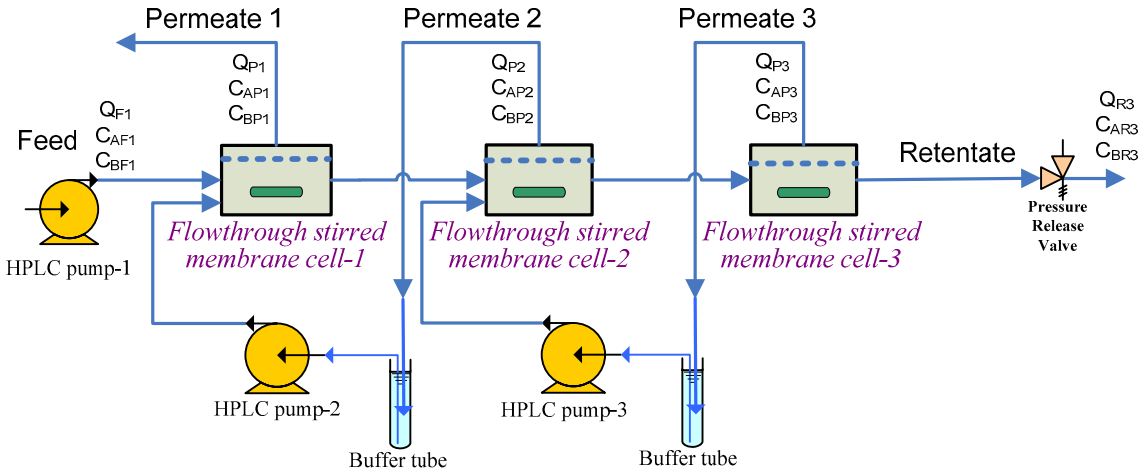

Figure 1 Schematic of API impurity separation set-up in a three-stage membrane cascade (fed to the first cell, permeate recycling configuration)

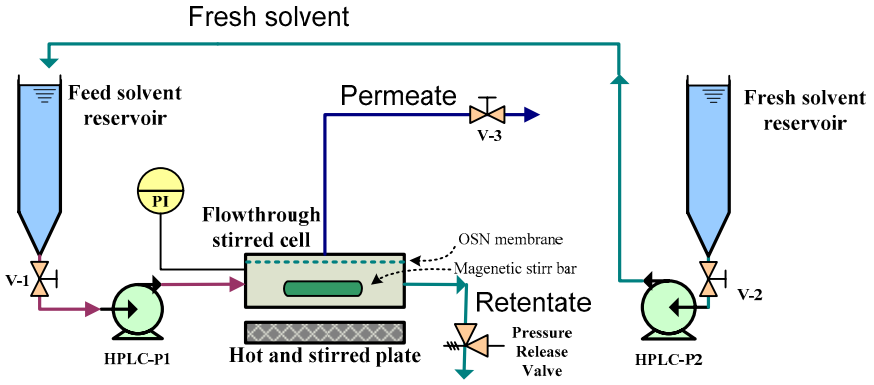

Figure 2 Schematic of API impurity separation set-up in a single-stage flowthrough stirred membrane cell for constant volume diafiltration (CVDF) testing

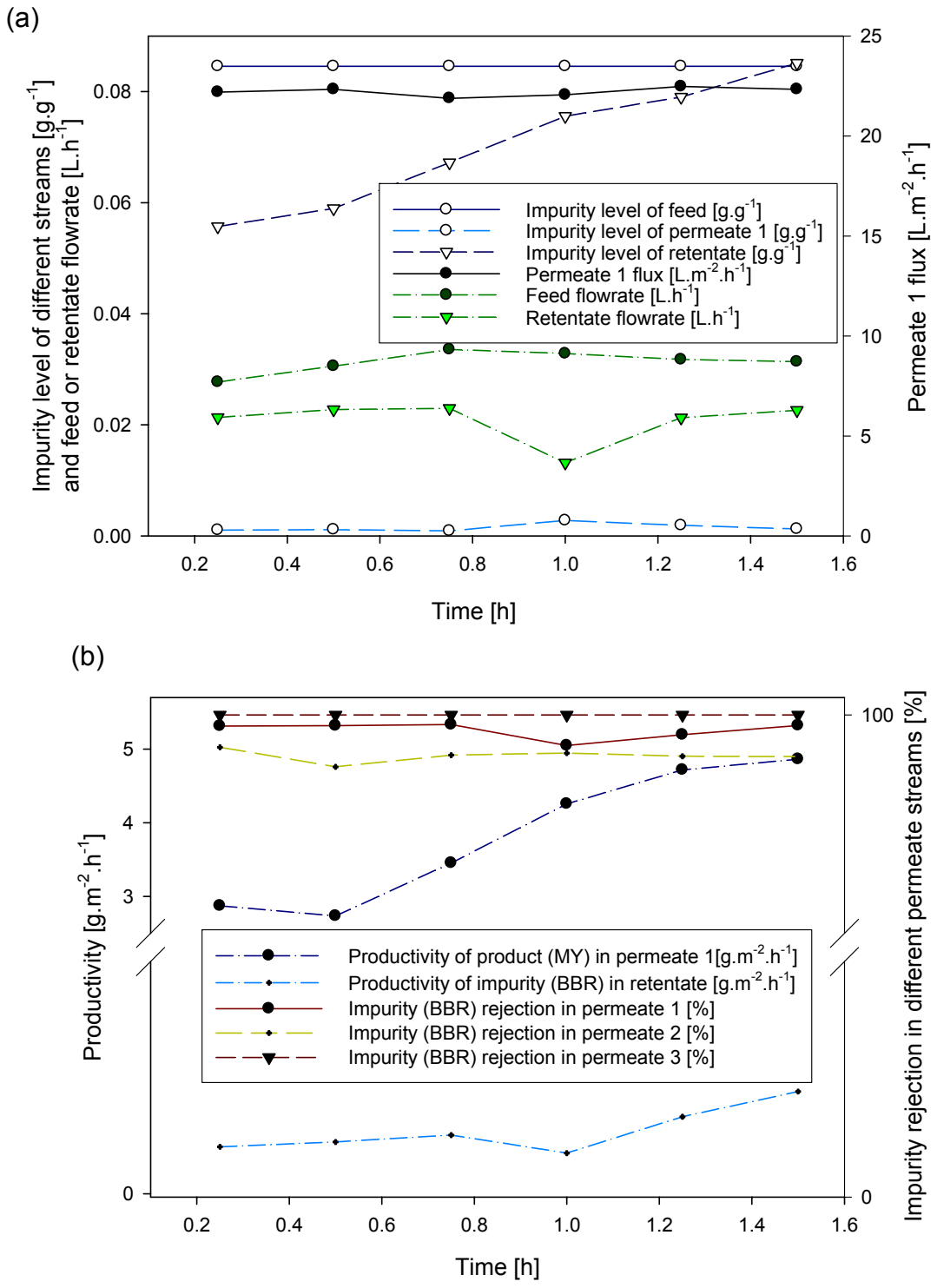

Figure 3 API impurity separation results in a three-stage membrane cascade (fed to the first cell, permeate recycling configuration) at 30 bar, room temperature with STARMEM 228 membrane: **(a)** Impurity level in different streams, feed and retentate flowrates and permeate 1 flux; **(b)** Productivity and impurity rejections in different streams

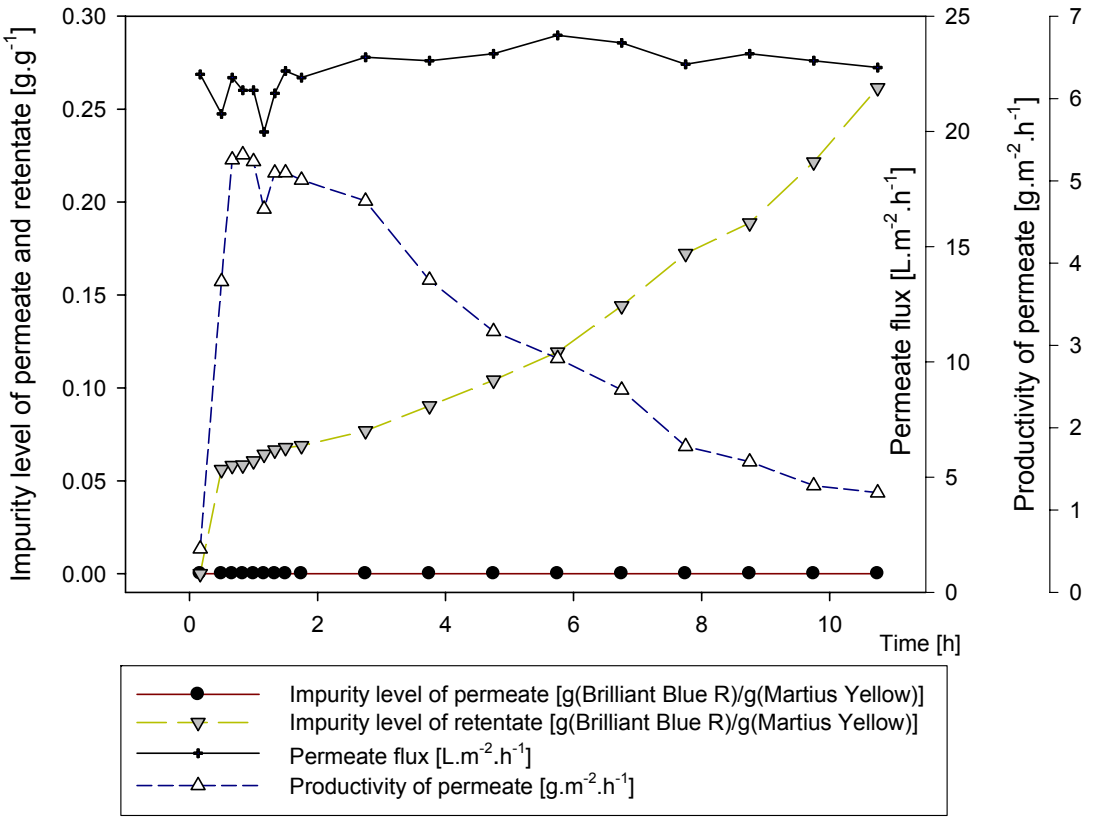

Figure 4 Constant volume diafiltration (CVDF) testing in a single-stage flowthrough stirred cell at 30 bar, room temperature with STARMEM 228 membrane: Impurity level of permeate and retentate, permeate flux and productivity

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