

**TOWARDS PRODUCTION OF SECOND
GENERATION P84 OSN MEMBRANES AND
MODULES FOR PHARMACUETICAL
APPLICATIONS**

By

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Abstract

This thesis describes the developments that led to the first polymeric OSN membrane and modules for applications in harsh solvent environments (e.g. DMF and THF), commonly used in the pharmaceutical industries. The chemical crosslinking of integrally skinned asymmetric P84 membranes has been shown to significantly enhance the chemical stability of the membrane thus allowing stable performance in these solvents that solubilise P84. The main issues relating to the production of the membrane and membrane modules addressed in this thesis are:

(i) The impact of drying on membrane performance

It was concluded that air-drying of water- and solvent-wetted membranes is not desirable for maintaining functional performance and that they must be impregnated with a preserving agent to maintain their properties (chapter 3).

(ii) Development of highly solvent resistant adhesive systems for spiral wound module

It was found that the key parameters influencing solvent stability are the available free volume in the epoxy adhesive and the functional groups present in the final adhesive network (chapter 4).

(iii) Optimising the adhesive curing conditions for P84 OSN membrane modules

A compromise need to be made in the curing conditions to achieve a highly solvent resistant adhesive whilst maintaining the membrane's performance, and a novel curing technique is also invented (chapter 5).

Finally, chapter 6 describes how these solvent resistant P84 modules prepared using the knowledge gained from previous chapters can be applied to classic purification processes in the pharmaceutical industries.

Abstract

Overall, this thesis demonstrates a significant step forward in the knowledge and understanding of the formation and use of P84 based OSN membrane and membrane modules. This will open up more opportunities for applying this emerging separation technology in the pharmaceutical industry.

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- (2) The next generation of membrane separations – Organic Solvent Nanofiltration (OSN), The Institution of Chemical Engineers (IChemE) FSSG Annual Research Event, Stevenage (UK), 30 May 2008.
- (3) Nanofiltration membranes for polar aprotic solvents – DuraMemTM, International Congress on Membranes and Membrane Processes (ICOM), 12-18 July 2008, Hawaii (USA).
- (4) Polymeric nanofiltration membranes with engineered molecular weight cutoff for molecular separations in aggressive solvents, American Institute of Chemical Engineers (AIChE) Annual Meeting, 16-21 November 2008, Philadelphia (USA).
- (5) Membrane module, International Patent Application PCT/GB2009/051255, 2009.
- (6) Demonstration of molecular purification in polar aprotic solvents by organic solvent nanofiltration, *Organic Process Research & Development*, 14(3), 600-611, 2010.
- (7) Organic solvent nanofiltration (OSN) solutions to classic purification issues in pharmaceutical industries, in preparation, 2010.

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Abbreviations

AEW	Amine equivalent weight
API	Active pharmaceutical ingredient
ATS	Anti-telescoping device
CA	Cellulose acetate
DCM	Dichloromethane
DGEBA-R	Diglycidyl ether of bisphenol A
DGEBF-R	Diglycidyl ether of bisphenol F
DGEBF(n)-R	Multifunction diglycidyl ether of bisphenol F
DMD	Dual Membrane Diafiltration
DMF	<i>N,N</i> -dimethylformamide
DMSO	Dimethyl sulfoxide
DVS	Dynamic vapour sorption
EA	Ethyl acetate
EEW	Epoxy equivalent weight
GPC	Gel permeation chromatography
HBS	High boiling point solvent
HDA	1,6-hexanediamine
HPLC	High performance liquid chromatography
IPA	Isopropanol
LBS	Low boiling point solvent
MW	Molecular weight
MWCO	Molecular weight cut-off
NEP	<i>n</i> -ethyl pyrrolidone
NF	Nanofiltration
NMP	1-methyl-2-pyrrolidinone
ODA	1,8-octanediamine
OSN	Organic solvent nanofiltration
PA	Polyamide
PAN	Polyacrylonitrile
PDMS	Polydimethylsiloxane
PEG	Polyethylene glycol

Abbreviations

PES	Poly(ether sulfone)
PF	Pore flow
PI	Polyimide
PMP	α -methylstyrene dimer
Psf	Polysulfone
PVDF	poly(vinylidene fluoride)
RCM	Ring-closed metathesis
RO	Reverse osmosis
SD	Solution diffusion
SEM	Scanning electron microscopy
TEA.HCl	Triethylamine hydrochloride
TEPA	Tetraethylenepentamine
TETA	Triethylenetetramine
TFA	Trifluoroacetic acid
THF	tetrahydrofuran
UF	Ultrafiltration
XYL	<i>m</i> -xylylenediamine

Nomenclature

A	FTIR peak area (-)
A_{cs}	Cross sectional area (m^2)
A_m	Membrane area (m^2)
B	Permeability ($L.m^{-2}.h^{-1}.Pa^{-1}$)
C	Concentration ($kg.m^{-3}$ or $g.L^{-1}$)
C_p	Heat of capacity ($kJ.kg^{-1}.^{\circ}C^{-1}$)
c	PF concentration ($mol.m^{-3}$)
D	Diffusion coefficient ($m^2.h^{-1}$)
$D_{i,\infty}$	Diffusivity in dilute bulk solution ($m^2.s^{-1}$)
$d_{i,s}$	Diameter of solute i (m)
d_p	Average pore diameter (m)
E	Tensile module ($N.m^{-2}$)
E	Activation energy (kJ)
E	Electric field strength
f	Frequency (Hz)
F_c	Capillary force (N)
F_R	Deformation resistance (N)
ΔH	Heat of reaction ($J.epoxide^{-1}$)
I	Impurity level (wt%)
J	Diffusion flux ($kg.m^{-2}.h^{-1}$)
J	Solvent flux ($L.m^{-2}.h^{-1}$)
J_v	PF solvent flux ($L.m^{-2}.h^{-1}$)
K	Conductivity (Ω^{-1})
K	Kozeny constant (-)
k	Reaction rate constant (-)
L_p	PF solvent permeability ($L.m^{-2}.h^{-1}.Pa^{-1}$)
M	Mass (kg)
$M_{i,w}$	Molecular weight of solute i ($g.mol^{-1}$)
N	Diafiltration volume ($m^3.m^{-3}$)
n	Reaction order (-)

Nomenclature

P	Pressure (Pa)
P_B	Bulk porosity (vol%)
$P_{i,e}$	Peclet number (-)
R	Ideal gas constant ($\text{J.mol}^{-1}.\text{°C}^{-1}$)
R	Rejection (%)
r_p	Pore radius (m)
S	Ratio of surface area to volume ($\text{m}^2.\text{m}^{-3}$)
T	Temperature ($^{\circ}\text{C}$ or K)
T_g	Glass transition temperature ($^{\circ}\text{C}$)
T_p	Peak temperature ($^{\circ}\text{C}$)
T	Time (s)
V	Volume (L)
V_f	Free volume (m^3)
V_i	Molar volume ($\text{cm}^3.\text{mol}^{-1}$)
V_T	Total volume (m^3)
W	Weight (kg)
X	Diffusional length (m)
Δx	PF active layer thickness (m)
Y	Yield (%)

Greek letters

α	Conversion of epoxies (-)
β	Heating rate ($^{\circ}\text{C}.\text{min}^{-1}$)
γ	Surface tension (N.m^{-1})
δ	Hansen solubility parameter ($\text{MPa}^{0.5}$)
$\tan \delta$	Dielectric loss tangent (-)
ε_m	Membrane porosity ($\text{m}^3.\text{m}^{-3}$)
ε'	Dielectric constant (-)
ε^0	Permittivity of free space (Farads.cm^{-1})
ε''	Dielectric loss factor (-)
ζ	Extent of reaction (-)
λ	Ratio of solute to pore radius (m.m^{-1})
μ	Viscosity (Pa.s)

Nomenclature

v	Molar volume (mol.m^{-3})
θ	Contact angle (rad)
π	Osmotic pressure (Pa)
π	3.142
ρ	Density (kg.m^{-3})
σ	Geometric standard deviation (-)
Φ	Partition coefficient (-)
Φ	Dummy variable
Ω	Dummy variable

Subscripts and superscript

c	Curing agent
e	Epoxy resin
F	Feed
i	Compound i
$Me-OH$	Methanol
Obs	Observed
P	Permeate
PF	Pore flow
R	Retentate
R	Reaction
S	Solute
t	Time t
T	Total
x	Direction x
0	Time 0
1	Stage 1
2	Stage 2

Chapter 1

Overview and scope of thesis

The application of membranes to chemical manufacturing is a growing area of separation technology. In particular, the use of nanofiltration (NF) membranes (with nominal molecular weight cut-off in the range 200-1000 Dalton) in organic mixtures is an emerging technology area of significant interest to both industry and academia. The potential for using this type of membrane as a replacement for conventional separation or purification technologies (e.g. evaporation, distillation and liquid chromatography) and enhancing chemical manufacturing processes (e.g. Active Pharmaceutical Ingredient (API) purification, solvent exchange, catalyst recovery, etc.) is significant, and is as yet not exploited to any significant extent by industry. As well as the general reluctance of the chemical industries to invest in emerging technologies, one of the main reasons for the delayed breakthrough of membrane technology is the lack of suitable membranes and membrane modules. Most commercial organic solvent nanofiltration (OSN) membranes and modules have limited solvent stability and unpredictable separation characteristics. The central challenge remains to develop membranes and integrating these membranes into modules that are stable in a wide range of organic solvents with controlled separation performance within the NF range, ideally satisfying all the regulatory demands for application in the pharmaceutical, nutraceutical and food industries (e.g. US FDA 21 CFR). Overall, this thesis presents work tackling the scale up issues faced in membrane and membrane module production.

Chapter 1 – Overview and scope of thesis

Following on from previous works and experience gained within Evonik Membrane Extraction Technology (MET) Ltd. and this research group, the key objective presented in this thesis is to improve the chemical stability of P84 polyimide based membranes to allow their further application in a wider range of solvents via chemical crosslinking. P84 polyimide is chosen as the core polymer in forming OSN membranes since it has been demonstrated to be a potential substrate for the development of integrally skinned asymmetric OSN membranes with good chemical stability and controlled separation characteristics. From an academic point-of-view it is often sufficient simply to produce a membrane with particular chemical resistance/cut-off characteristics, however from the industrial point-of-view the membrane has to be viewed as simply one component of an overall package (e.g. membrane module) containing many components. In translating these integrally skinned asymmetric polyimide (PI) membranes into membrane modules, inappropriate and uncontrollable preservation of the membrane structure after it is formed via phase inversion (e.g. where the pores of the membranes are filled with the non-solvent after formation) can cause the loss of the membrane's separation characteristics. To date, this preparation step for OSN membranes remained unexplored. Chapter 3 focuses on identifying the parameters that influence this preparation step and a suitable preserving agent for P84 PI membranes is developed in this work. Further understanding and control of the process parameters for introducing the preservation agent will enable production of membranes with reliable and consistent separation performance.

Apart from the membrane itself, another major issue in the development of OSN modules is the resistance of commercially available adhesives to organic solvents, particularly polar and polar aprotic solvents. The second objective of this thesis is to develop an adhesive that is resistant to all types of organic solvents, ranging from apolar solvents through polar to polar

aprotic and chlorinated solvents. The core of chapter 4 is to identify the formulation parameters in epoxy-aliphatic amine adhesives that influence the chemical interactions with a wide range of organic solvents. Epoxy-aliphatic amine adhesives are favoured over other epoxy systems (e.g. anhydride and catalytic curing agents), although these systems are also capable of providing excellent chemical resistance. One of the distinct advantages of epoxy-aliphatic amine adhesives is that they can be cured at lower temperatures ($< 100\text{ }^{\circ}\text{C}$) and even at room temperature.

The cure cycle and duration of the cycle is highly important to obtain a stable adhesive, but it also has significant ramifications for the membrane itself as the membrane is also cured in-situ in the module. Chapter 5 further investigates the effects of curing temperature and time on (i) the functional performance of membranes manufactured from P84 polyimide, both before and after chemical crosslinking, and (ii) the chemical stability of epoxy-aliphatic amine adhesives in organic solvents. As an alternative to thermal curing, microwave curing was also studied as a potential technique for curing due to the selective nature of microwave heating. This microwave technique markedly reduces the curing process time and maintains the performance of commercial polyimide membranes, StarmemTM (trademark of W.R. Grace) fabricated from P84 and Matrimid, whilst maintaining the chemical resistance of the epoxy-aliphatic amine adhesive in organic solvents.

Finally, chapter 6 integrates the work presented in the preceding chapters to examine the potential uses of the OSN membranes and modules produced from this work in several classic purification processes in the pharmaceutical industry. Three different case studies are presented and case study C is of particular relevance as it is a real industrial problem encountered during the development of a potential drug for Hepatitis C.

Chapter 2

Literature background and research motivation

2.1 Introduction

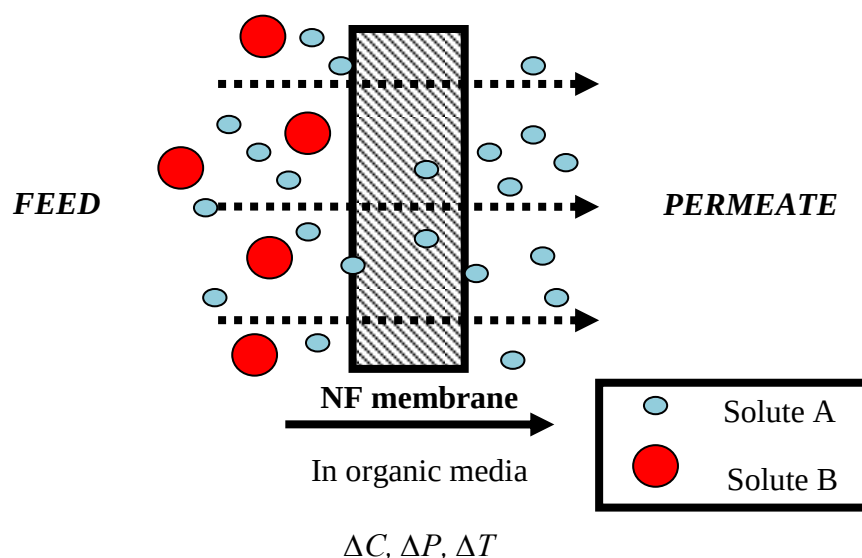


Figure 2.1: Schematic diagram of a nanofiltration separation process.

Organic solvent nanofiltration (OSN) is a form of filtration that uses membranes to separate organic molecules within the molecular weight range 200 – 1000 g.mol⁻¹ in organic solvents as illustrated in Figure 2.1. OSN is a pressure driven membrane process, situated between reverse osmosis (RO) and ultrafiltration (UF), that is used for the separation of small molecules such as sugars [1]. The pressures used are lower than that of RO and are in the region of 5 – 50 bar [1]. At present, nanofiltration (NF) membranes can be divided into two different application areas: aqueous systems and organic solvent systems. The former has been developed and researched in depth for a number of years but it is only recently that research and applications in solvent systems have become more prevalent. The demonstration

of several commercial membranes for use in organic media presents new possibilities for the use of NF membranes in the separation of organic molecules within the fine chemicals [2,3], petrochemical [4,5], food [6-8] and pharmaceutical industries [9].

2.2 Membrane characterisation

Membranes are generally characterised on the basis of their performance and morphology. Morphological characteristics include both physical (e.g. pore size and pore size distribution, porosity, overall structure, skin layer thickness) and chemical properties (e.g. polarity, swelling) [1,10]. In OSN, performance parameters (flux or permeability and molecular weight cut-off (MWCO)) are usually used by both academia and industrial manufacturers to describe a membrane.

The flux (J) is defined as the volumetric flowrate (V_p) through the membrane per unit area (A_m) of the membrane per unit time (t):

$$J = \frac{V_p}{A_m t} \quad (\text{Equation 2.1})$$

Permeability (B) is sometimes used in the literature to normalise flowrate with pressure (P) to allow comparison between membranes without needing to know the filtration pressure and is given by the following equation:

$$B = \frac{J}{\Delta P} \quad (\text{Equation 2.2})$$

The effect of pressure on flux has been reported by several authors [2,11,12] using several OSN membranes. Scarpello et al. [2] observed a linear increase of solvent flux (tetrahydrofuran (THF), ethyl acetate) with pressure ranging from 0.5 – 30 bar with StarmemTM 122, StarmemTM 240 (both W.R. Grace, USA) and MPF-50 (Koch Membrane System, USA) membranes using dead end filtration equipment. A similar observation was

also reported by Whu et al. [12] using the MPF-60 (Koch Membrane System, USA) membrane in methanol. This reported phenomenon is in line with other pressure driven membrane processes and can be attributed to an increase in pressure driving forces for convective flow, or an increase in the chemical potential gradient in diffusive transport.

The observed rejection, R_i^{obs} of compound i can be calculated based on the following formula:

$$R_i^{obs} = \left(1 - \frac{C_{P,i}}{C_{R,i}}\right) \times 100\% \quad (\text{Equation 2.3})$$

where $C_{P,i}$ and $C_{R,i}$ are the concentrations of component i in the permeate and retentate respectively. MWCO is defined by plotting the rejection of compounds versus their molecular weight, and determining the compound molecular weight corresponding to 90 % rejection. The techniques and experimental conditions for obtaining the MWCO are often not disclosed, leading to inconsistencies in both academia and industry. Many different compounds have been chosen by different authors to define the MWCO of OSN membranes, ranging from a homologous series of alkanes [13], dyes [14,15], quaternary ammonium salts [16] and polymers [17,18]. Although molecular weight (MW) gives an indication of the expected rejection, the variability in the structure (shape) and chemical functionalities (charge, polarity) of the compounds may result in differing compound-membrane interactions [19,20]. Also, the conformation of compounds is also highly solvent dependent and different molecules can also result in poor correlations between different membrane's performances. In most cases, a plot of rejection against compound length dimension gives a more accurate reflection of the MWCO. Van der Bruggen et al. [21] demonstrated a good correlation between different size parameters of compounds (e.g. MW, Stokes' radius, calculated molecular diameter) with their rejections.

Recently, See-Toh et al. [22] introduced a ‘standard’ MWCO characterisation method for OSN using styrene oligomers within the NF range (MW ranging from 236 – 1000 g.mol⁻¹) for tests in organic solvents. The method was shown to possess the following advantages over other techniques described above:

- determination of MWCO in a single filtration,
- covers NF range and able to give a comprehensive description of membrane performance in NF range (solutes with an increment of ≈ 100 g.mol⁻¹),
- able to evaluate the integrity of membrane and filtration equipment at the same time (e.g. leaks),
- oligostyrene soluble in many organic solvents (ranging from hydrocarbons to alcohols and ketones) making it a useful tool for cross comparison of membranes in different solvent systems,
- oligostyrene has no charge, non-polar and readily detected by UV absorbance (via a simple high performance liquid chromatography (HPLC) method where good separation between each oligomer is shown).

The authors demonstrated the feasibility of this technique by determining the MWCO of commercial OSN membranes, StarmemTM 122 and StarmemTM 240 (W.R. Grace) in toluene. The MWCO by this method is in good agreement with the values quoted by the manufacturer. Similarly, oligostyrene also corresponds closely to other markers such as n-alkanes and quaternary ammonium salts (quats). Drawbacks of this methodology include the cost of the oligostyrene standards and no coverage of the low molecular weight end of the NF range (50 – 200 g.mol⁻¹). The difficulty in accurately determining the absolute concentration of each oligomer also makes mass transport studies tricky.

Whilst the use of a single MWCO value for characterising OSN membranes is still arguable, a comprehensive understanding of the separation characteristics of OSN membranes is attainable using the oligostyrene method. The simplicity and effectiveness of this method makes it an attractive choice as a standard method to define NF membranes in organic solvents. The oligostyrene and alkanes methods will be used in this work for the determination of membrane separation characteristics.

2.3 Commercial OSN membranes and modules

Commercial OSN membranes are produced from both polymeric [23-25] and inorganic materials [26,27]. In terms of physical and chemical properties, inorganic membranes are superior in comparison to polymeric membranes. However, their large scale production and module construction is often complicated and expensive to handle. Inorganic NF membranes [28], which are generally made from SiO_2 and TiO_2 , are largely provided by Inopor (Germany). Due to the statistical nature of these inorganic membranes, the reproducibility of the membrane properties and performance is not easy to obtain. In addition, the intrinsic hydrophilicity of SiO_2 and TiO_2 surfaces also prohibits permeation of organic solvents across these membranes and makes them less versatile for OSN applications [29]. Furthermore, for applications in organic solvents, these inorganic membranes must be post treated to make them hydrophobic. However, the post treatments compromise the chemical stability of the membranes.

Polymeric membranes can be classified based on their overall structure; (i) integrally skinned asymmetric membranes [30-32] ((Figure 2.2 (A)) made from a single material formed via phase inversion and (ii) composite membranes (Figure 2.2 (B)) consist of several layers of

different materials with the active layer formed by either interfacial polymerisation [33,34] or by deposition from a solution [35]. Composite membranes are often viewed as being more flexible as each individual layer of the membrane can be optimised independently to obtain the desired membrane separation selectivity and permeability. However, differential swelling between the layers or incompatibility of any layer can also render membrane failure. Both types of membranes are often prepared on porous non woven backing (commonly polyester and polypropylene) to enhance their mechanical strength.

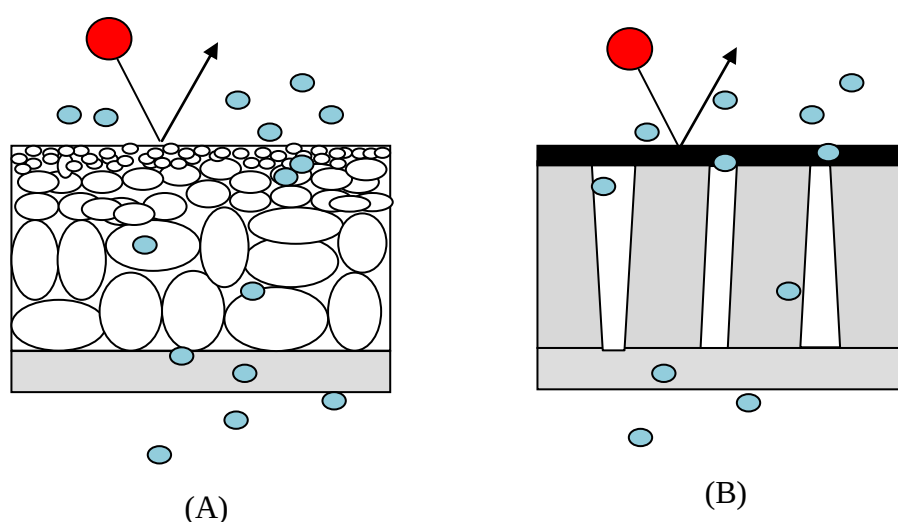


Figure 2.2: Schematic representation of the cross sections of (A) an integrally skinned asymmetric membrane and (B) a thin film composite membrane [30,32,34].

Table 2.1 lists the commercially available OSN membranes and their characteristics. Some membranes such as Desal-5, Desal-DK from GE Osmonics (Switzerland) [36] and NF010, NF030 from Microdyn-Nadir (Germany) [37] were specifically designed for aqueous applications, but found to be effective for use in OSN with a limited range of solvents.

StarmemTM series membranes (StarmemTM 120,122, 228 and 240) [23] are a trademark of UOP (formerly Grace Davison Membranes, a W.R. Grace &Co.-Conn. company) (USA) and

are distributed by Evonik Membrane Extraction Technology (MET) Ltd. (UK). These asymmetric polymeric hydrophobic membranes are formed from PIs and were designed for petrochemical industry applications [4]. These membranes and their modules have been reported to be stable in a wide range of solvents including apolar solvents [5,13,38,39], alcohols [16,40,41] and some ketones [5] and are available in several MWCOs, 200, 220, 280 and 400 g.mol⁻¹. However, these PI membranes have limited stability in many common industrial solvents such as tetrahydrofuran (THF) [23] and dichloromethane (DCM) [39], and readily dissolve in *N,N*-dimethylformamide (DMF) [42] and 1-methyl-2-pyrrolidinone (NMP) [43]. Furthermore, extensive study within Evonik MET has established that StarmemTM modules compromising other components (e.g. adhesive) are not suitable for use in solvents including acetone, methanol, THF and DMF for extended periods. Pictures in Figure 3.3 presents the failure of adhesives in StarmemTM modules after exposure in acetone, which then led to the failure of the module's performance.

Koch Membrane Systems (USA) was the first company to introduce OSN membranes to the market. SelRO MPF-60, MPF-50 and MPF-42 are all composite multi-layered membranes consisting of a crosslinked polydimethylsiloxane (PDMS) separating layer supported on a crosslinked polyacrylonitrile (PAN) UF support [20,44]. GMT Membrantechnik (Germany) also distributes a range of PDMS composite NF membranes on various types of supports (PAN, polyether imide (PEI) and poly(vinylidene fluoride) (PVDF)) [45,46]. Despite the broad chemical stability of these membranes and their frequent use in research studies, the extensive swelling of PDMS in organic solvents limits their utility to solvents like hydrocarbons, aromatics, ketones and alcohols. Extensive studies have been carried out by Gevers et al. [33,34] and Aerts et al. [47] to overcome this swelling issue with PDMS membranes. SelRO membranes are supplied as flat-sheet and spiral modules soaked in their

preserving solution, 50 vol% ethanol in water. Minimal swelling of MPF-60 and MPF-50 has been reported in liquids with ≤ 2 % of organic solvents [48-50]. However, extended testing of these membranes by Van der Bruggen and co-workers [20] found that they are only semi-solvent stable with the membranes showing visible damage after ten days of exposure to ethyl acetate, ethanol and acetone. Vankelecom et al. [51] showed swelling of up to 70% when these membranes were immersed in *t*-butanol. Similarly, Silva et al. found that the MPF-50 membrane was unable to give reproducible results in methanol, toluene and ethyl acetate [19]. The MPF-60 and MPF-50 membranes have been discontinued by the manufacturer due to the poor reproducibility of the membrane performance.

Five NF membranes with different MWCOs are produced by Solsep (The Netherlands). The stability and application of these membranes have not yet been explored to a significant extent by researchers or industrially. They are reported to be stable in some solvents such as ethanol, isopropanol, hexane, and heptane [41,52].

Whilst both integrally skinned asymmetric and composite membranes constitute areas with research potential, this thesis will focus on the development of polymeric - integrally skinned asymmetric OSN membranes.

Table 2.1: Commercial OSN and NF membranes.

Membrane and (Type)	Manufacturer	Claim to be stable in class of organic solvents	MWCO (g.mol⁻¹)	Available in	Regulatory Compliance	Ref.
Starmem TM 120,122,228 and 240 – PI asymmetric membranes	W.R. Grace-Davison (USA)	Hydrocarbons, alcohols, aromatics, ethers, ketones and esters	200, 220, 280 and 400	Flat sheets and spiral modules.	Not available	[23]
SelRO MPF-60, MPF-50, MPF-44 and MPF-42 – composite membranes (PDMS skin layer on PAN support)	Koch Membrane System (USA)	Aqueous mixtures and pure solvents of alcohols, aromatics and ketones	400, 700, 250 and 200	Flat sheets and spiral modules, stored in solutions.	Not available, but applied in food industry.	[24]
GMT/GKSS membranes – composite membranes (PDMS skin layer)	GMT Membrantechnik (Germany)	Hydrocarbons, aromatics and alcohols	350 to 400	Flat sheets and spiral modules	Not available	[45,46,53]
Solsep 010206, 010306 and 030306 – unknown type of polymeric membranes	Solsep (The Netherlands)	Hydrocarbons, alcohols, esters, ketones, and aromatics	500 to 1000	Spiral modules	Not available, but applied in food industry.	[25]
Sepa TM Desal-5 and Desal-DK – unknown type of composite membranes	GE Osmonics (Switzerland)	Aqueous application, but effective in some organic solvents, e.g. hexane, acetonitrile	300 to 1000	Flat sheets and spiral modules	Available	[36]
Nadir NF010 and NF030 - PES and PSf asymmetric membranes	Microdyn-Nadir (Germany)	Aqueous application, but effective in some organic solvents, e.g. ethanol, hexane,	Not available	Flat sheets and spiral modules	Available	[37]
SiO ₂ and TiO ₂ membranes -Unknown	Inopor (Germany)	In all class of solvents including polar aprotic solvents.	220 to 750	Tubular and monolith modules	Available	[54,55]

2.4 Membrane formation

2.4.1 Phase inversion

Phase inversion is a controlled transformation process of a polymer solution to a solid state. Solidification is initiated when the polymer solution is subjected to liquid-liquid demixing, which can be induced by [1,9]:

- *Immersion precipitation:* Immersion of cast polymer into a coagulation bath of the non-solvent. The solvent exchange leads to the precipitation of the polymer.
- *Thermal precipitation:* The solvent quality decreases when the temperature is lowered. After demixing is induced, the solvent is removed by extraction, evaporation or freeze drying.
- *Solvent evaporation:* Polymer is dissolved in a mixture of volatile solvent and a less volatile non-solvent. As the solvent evaporates the concentration of polymer in the non-solvent increases and eventually leads to the precipitation of the polymer. In solvent evaporation, an important aspect is the temperature of the casting solution.
- *Precipitation from the vapour phase:* Casting the polymer solution in an environment saturated with the non-solvent. This prevents evaporation of the solvent and precipitation takes place when the non-solvent vapour penetrates into the solution.

This work will mainly focus on integrally skinned asymmetric membranes obtained from immersion precipitation, which is the most common phase inversion method used to produce commercial NF membranes. The thermodynamic behaviour of a polymer solution subjected to immersion precipitation may be represented by a ternary phase diagram as illustrated by Figure 2.3. In general two mechanisms are well known during liquid-liquid demixing: nucleation growth and spinodal decomposition. Nucleation growth occurs when the polymer system departs from the homogeneous stable region to the metastable region which is located

between the spinodal and binodal lines in the phase diagram (following red pathway). Spinodal decomposition, the less frequent mechanism occurs, when the system enters an unstable region within the spinodal (following blue pathway). As a result, two different phases are formed leading to a bicontinuous morphology [1,9].

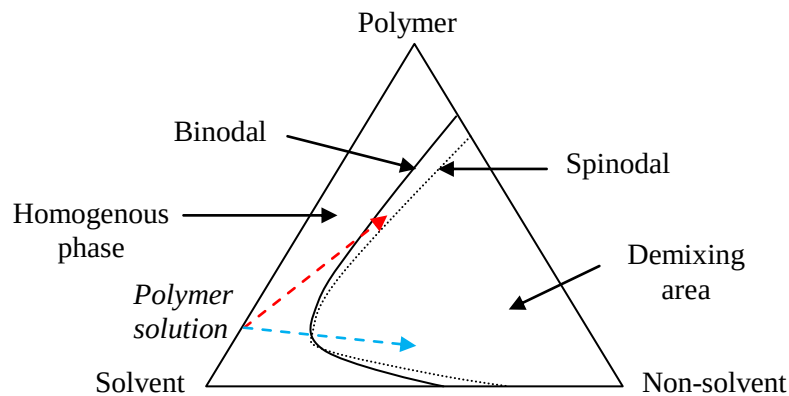


Figure 2.3: Schematic representation of the phase transition mechanism for an isothermal ternary polymeric mixture consisting of polymer/solvent/non-solvent [1,9].

2.4.2 Post treatment

Many process parameters during phase inversion (e.g. coagulation bath temperature [56,57], composition of bath [56,58], composition of polymer solution [11,31,32,56,59-61]) and the addition of additives [9,62,63] into the polymer solution are reported to play a role in influencing the final membrane morphology and performance. However, in order to produce a reliable and reproducible membrane as well as a consistent end product, post treatments such as membrane drying [64,65] and thermal annealing [32,64] are also crucial to control the membrane performance. These steps are often over-looked in research publications and have not been explicitly reported in literature.

Membrane drying/storage

When asymmetric membranes are removed from their coagulation bath and dried at ambient conditions, the membranes become fragile, brittle and develop cracks which render them unsuitable for further use. This is thought primarily to be due to the differential shrinkage of the polymer and non woven support, resulting in membrane defects. At present, attempts to prepare wet-dried immersion precipitation membranes by thermal drying are successful for making dense membranes for application in RO [66] and gas separation [67].

Several patents have been published reporting two techniques, (i) multiphase solvent exchange [68-71] and (ii) the use of preserving agents [13,72] or non-ionic surface agents [72], used to preserve the structure of asymmetric gas separation and reverse osmosis membranes. Multiphase solvent exchange is a process where the non-solvents present in the membrane after immersion are replaced by a first solvent which is miscible with the non-solvent. This solvent is then replaced by a second, more volatile solvent, which can be removed easily by evaporation to obtain a dry membrane. The last solvent used is often an aliphatic hydrocarbon (e.g. hexane) or halogenated hydrocarbons (e.g. trichloroethane), since the surface tension of these liquids are relatively low. This method claims to minimise pore collapse upon drying, but still does not offer flexibility and makes handling difficult.

In principal, the preserving agent acts as a plasticiser allowing the membrane to be handled in a dry state by increasing the flexibility of the polymer chains. Several preserving agents (or conditioning agents) have been reported in the literatures and include hydrophobic oils [64] and hydrophilic glycerol and ethylene glycol [72-74]. The impregnation of preserving agents normally involves a solution containing the conditioning agent and a volatile solvent. The membrane is allowed to soak in the solution for a period of time to allow the preserving agent

to be incorporated into the polymer matrix. The membrane is then removed and dried to remove the solvent. Membranes prepared via this technique claim to offer unaltered membrane performance with improved flexibility and handling properties [73]. However, the limited understanding and undisclosed information from manufacturers have led to inconsistencies in flux and rejection data obtained for several commercial OSN membranes. This has prompted studies on membrane pre-conditioning by several researchers. Both Whu et al. [75] and Machado et al. [50] have concluded that the inconsistencies may be due to the differences in the pre-conditioning condition of the membrane prior to tests. Commercial membranes are often supplied in preservation liquid (e.g. mixture of ethanol and water in MPF-50) or are impregnated with plasticisers (e.g. mineral oil in StarmemTM).

The theoretical detail of wet drying will be further discussed in chapter 3.

Thermal annealing

Thermal annealing of PI based membranes has been studied by several authors for application in gas separation [76,77] and pervaporation [78,79]. This step has been shown to improve the performance in these processes by densification of the membrane films to remove defects and suppress plasticisation. This usually results in increased selectivity at the expense of permeability. In these cases, this observation has been attributed to the re-organisation of the polymer chains at elevated temperatures to a thermodynamically favoured structure and the simultaneous densification of the membranes.

See-Toh et al. [30,32] also observed a decline in permeability of PI OSN membranes upon heating at 100-150°C for 30 minutes, whilst the MWCO remained largely unaltered. A gradual loss of the nano-porosity in the separating top-layer was noticed, with the typical

nodular structure being replaced with a continuous, non-porous layer interspersed with nodules. In OSN, this phenomenon of transforming the membrane into modules is highly undesirable as the membrane will be cured thermally in situ with adhesive in a module format. It is important to note that temperature curing is often required to provide a highly resistant adhesive for applications in organic solvents.

2.5 Membrane transport

Currently, there is no universal model accepted that describes the transport phenomena across OSN membranes although several approaches have been reported in the literature. Two different approaches, based on solution diffusion (SD) and pore flow (PF) models, have been frequently used to describe OSN processes and provide the basis for various further adaptations reported in the literature [49,75,80]. Figure 2.4 compares the transport mechanism of both SD and PF models.

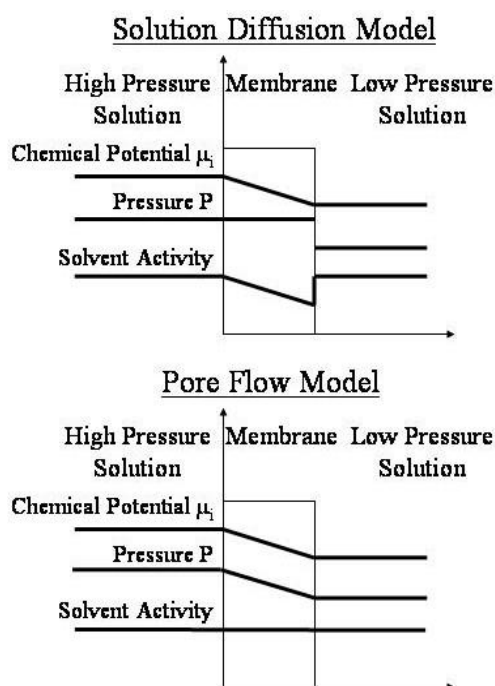


Figure 2.4: Schematic representation of the transport mechanism of a component solution through a membrane following (A) solution diffusion model and (B) pore flow model [1,81].

Solution diffusion (SD) model

The SD model was initially developed by Lonsdale et al. and further improved by Wijmans and Baker [81] to describe transport mechanism across gas separation and reverse osmosis membranes. In the literature, membranes that are best described by the SD mechanism possess free volume that is present as statistical fluctuations that appear and disappear together with the motions of the permeants cross the membrane. Following the SD mechanism, the concentration gradient acts as the driving force across the dense separation layer and there is no pressure drop across the membrane. This model has been successfully applied to describe the transport of OSN membranes, mainly integrally skinned asymmetric membranes [19,80,82,83]. Membranes with a high tendency to swell in organic solvents (e.g. rubbery polymeric membranes like PDMS) require that the effects of solvent-polymer interactions considerations be considered [84,85].

Peeva et al. [80] applied a combined solution diffusion model and film theory model. This model combined the solution diffusion model for membrane transport with the resistance in series model for transport across the liquid film adjacent to the membrane. This is necessary to mimic the concentration polarisation effects present if such membranes were to be used industrially. The overall mass transfer coefficient and ratio of activity coefficients were experimentally determined to obtain inputs to the model. The model fits the data reasonably well and the experimental data is markedly improved by allowing the activities of the solution components to vary, indicating that these systems are non-ideal.

Pore flow (PF) model

The PF mechanism assumes a permeation process whereby the compounds are separated by size exclusion during pressure driven convective flow through the pores. Phase inverted

membranes commonly have a structure similar to a system of closely packed spheres. In such cases, the Hagen-Poiseuille equation is modified for spheres to give the Carmen Kozeny equation:

$$J_v = \frac{\varepsilon^3}{K\mu S^2 (1-\varepsilon)^2} \frac{\Delta P}{\Delta x} = L_p \Delta P \quad (\text{Equation 2.4})$$

In this equation J_v is solvent flux, K the Kozeny constant, ε the porosity, S the surface area per unit volume, ΔP the differential pressure across the membrane, μ liquid viscosity and Δx the membrane thickness. In OSN, very few membranes possess such structure [86] and furthermore solute pore interactions [87,88] have also to be taken into account. Detailed descriptions of this model will be presented in chapter 3.

The work reported by Silva et al. [19] utilises both SD and PF models to predict permeation of organic mixtures using permeabilities of pure solvents, and showed that both models can adequately provide an explanation to the observed transport behaviour across the integrally skinned asymmetric StarmemTM 122 membrane. The work also demonstrated that the SD model is more suitable than the PF model.

Other Adapted Transport Model

Machado et al. [49] used a viscous model that is loosely based on the pore flow model. It considers a composite NF membrane made up of a NF surface layer, a UF sub-layer and a porous support layer. The model was tested using the composite MPF-50 (Koch Membrane System, USA) membrane and showed a good fit to the tested systems.

Bhanushali et al. [85] and Koops et al. [89] used the Spielger-Kedem model [90] to consider the coupling between the solute and solvent as it transports through the membrane. The

model considers convective transport of the solute together with the diffusive flux. In the Spielger-Kedem model, the membrane is represented by a series of thin layers which are in equilibrium with other segments that make up the membrane. The deficiency of the Spielger-Kedem model is that it does not consider interactions between the solute and the membrane. This is better represented by the pore flow model in which the surface potentials (ϕ) may be calculated or measured.

In summary, the PF model allows the prediction of membrane performance (solvent flux and solute rejection) once base membrane characteristics such as pore size and porosity are known. Whereas, for the SD model measurements of the solute and solvent permeability across the membrane are required to postulate the membrane performance for a given solvent/solute system. Therefore, the PF model is more relevant in many cases as it allows the transport behaviour across a membrane to be explained without the need for experimental data.

2.6 Applications of OSN

OSN has a distinctive advantage over conventional separation and purification techniques especially high energy consumption technologies such as distillation and crystallisation. Purification technologies such as liquid chromatography and solvent extraction that are not generally regarded as requiring high energy consumption can also have ‘hidden’ high energy consumption through downstream processing to concentrate the target product and recycle the process solvents. The American Institution of Chemical Engineers Vision 2020:2000 Separations Roadmap [91] shows that separation processes account for 40-70% of total operating/capital costs and energy use of the chemical process industries. This equates to > £100 billion in costs globally and ~3.5 million tonnes of oil equivalent annual energy use in

the UK alone. Recovering solvents using conventional thermal processing, uses half of this energy, so if we assume that OSN may be relevant to 10% of all solvent recycle operations, then the commercial market and carbon reduction potential is huge, potentially > £1 billion per annum and hundreds of thousands of tons of carbon per annum. The unique selling point of this technology is the ability to separate and purify chemical materials without phase transition, resulting in a low energy means of separation. Both distillation and evaporation have been used for the past century, however they are energy intensive, e.g. up to 2.2 GJ of energy can be required to recover one ton of methanol in a batch distillation. Consider the case of recovering 1tonne of a dilute solution of solute in methanol.

- Using *distillation*, $\Delta H_{fg} = 1100 \text{ MJ ton}^{-1}$
 - Evaporation requires 1100 MJ heating
 - Condensation requires 1100 MJ cooling via refrigeration

- Using *OSN*, the filtration pressure = 30 bar
 - Pump energy required = 3 MJ
 - Even if we assume the real energy use is 5-10 times higher than this calculated amount this is still a maximum of 30 MJ per tonne processed.

If we assume that fuel oil costs £0.03 per kWh and electricity costs are £0.12 per kWh, then the cost of evaporation is $1100 \text{ MJ per tonne} \times 0.278 \text{ kWh per MJ} \times £0.03 \text{ per kWh} = £9.174$ per tonne and the cost of refrigeration is $1100 \text{ MJ per tonne} \times 0.278 \text{ kWh per MJ} / 5 \text{ (kW refrigeration/kW compressor power)} / 0.8 \text{ (compressor efficiency)} \times £0.12 \text{ per kWh} = £9.174$ per tonne - a total of £18.35 per tonne. The cost of carrying out the recovery with OSN = $30 \text{ MJ per tonne} \times 0.278 \text{ kWh per MJ} \times £0.12 \text{ per kWh} = £1.00$ per tonne. The net saving is £17.35 per tonne.

For the case of an OSN unit treating 250,000 tonne per year [92], the energy cost saving through using OSN could be as high as $£17.35 \times 250,000 = £4,337,500$ per year. This volume could be treated by an OSN plant containing 500 m^2 of membrane area – the capital spend on a unit for this membrane area would be approximately £2,500,000 and the cost of replacing membranes per year would likely be in the range £200,000-£1,000,000 (depending on the lifetime and type of membrane). Even in the worst case, this gives a payback time of less than a year!

In 2001, 7.7 million tons oil equivalent of energy (24.8 million tons of CO_2) was used overall by the UK chemical process industries, of which 8% was used by the Pharma industry (2 million tons of CO_2) [93]. Approximately, 25% of the total energy was used to recover solvents, which releases ~ 6 million tons of CO_2 per year from the UK chemical process industries and $\sim 500,000$ tons of CO_2 from Pharma per year. As a base case for CO_2 reduction by OSN, take an EU country that recovers 250,000 tonne of solvent per year [92] and assume that 2,200 MJ and 30 MJ of energy are required to recover each tonne of solvent via batch distillation and OSN respectively. This equates to $\approx 42,000$ and ≈ 600 tonne of CO_2 emissions by batch distillation and OSN respectively. OSN adaption not only brings economic benefits, the carbon reduction is clearly shown to increase dramatically. If OSN was used for 1/3 of all solvent recovery operations in the UK then 2 million tonne less CO_2 would be emitted per year.

Table 2.2 presents an overview of proposed OSN applications in various industries. Many of these proposed applications involve the using of aqueous NF, RO and gas separation membranes. Whilst many potential applications have been demonstrated, they are still often

relying on perfunctory testing of membrane coupons in dead end cells over short periods (< 1 day). The commercial viability of such applications are often over looked without going further and testing them in systems (e.g. modules) that can be readily scaled or applied for commercial use. To date, the majority of these reported applications are not applied industrially. The largest industrial success so far is the Max-DewaxTM process at the ExxonMobil refinery in Beaumont (Texas) for recovering dewaxing solvents from lube oil filtrates with spiral-wound modules of StarmemTM 240 membranes [5]. This plant has a net benefit of >\$6 million per annum and had a payback time on the project cost of less than a year's time, whilst handling 11,000 m³ of solvent per day.

Table 2.2: Overview of successful OSN application in various industries.

Industry	Membrane	Solvent	Application
Petrochemical	Cellulose acetate (CA)	NMP, phenol, fufural	Recovery of solvents [94]
	PI, Starmem TM (W.R. Grace)	Aromatic hydrocarbons, ketones	Lube oil dewaxing [4,95,96] Recovery of solvents [5,64]
Food/ Nutraceutical	CA, PVDF, polyamide (PA)	Ethanol, isopropanol	Solvent recovery in edible oil processing [97]
	Crosslinked PDMS (GMT membrane)	Hexane, <i>i</i> -octane	Solvent recovery in edible oil processing [18]
	Desal-5 (GE Osmonics), NTR-759 (Nitto Denko)	Methanol	Deacidification of edible oil extracts [98]
		Ethanol	Deacidification of edible oil extracts [7]
	PI (W.R. Grace)	Methanol	Recovery of unreacted amino acid derivatives from synthesis of dipeptides [99]
	Commercial PI, PA, CA		
	Desal-DK	Ethanol	Purification of natural active compounds from solvent extracts [100]

Table 2.2 (Continued): Overview of OSN applications in various industries.

Industry	Membrane	Solvent	Application
Pharmaceutical	MPS-44 (Koch)	Methanol/DCM	Recovery of API intermediate [9]
	PI	Butyl acetate	Solvent removal and API concentrate [101]
	Starmem TM 122 (W.R. Grace)	Methanol	Microfluidic purification [102]
	Starmem TM (W.R. Grace), MPF (Koch)	Methanol, toluene, ethyl acetate	Solvent exchange of high boiling point solvent to low boiling point solvent, solvent mixtures forming an azeotrope [103]
	Starmem TM (W.R. Grace)	Hexane, toluene	Chiral separation [38,104]
	MPF (Koch)	Preparative HPLC solvents	Purification of solvent to HPLC grade [24]
Fine chemical	MPF-50 (Koch) Zeolite filled PDMS MPF-60 (Koch)	THF [105] Chloroform [106] DCM [107]	Homogenous catalyst recovery
	MPF-50 (Koch)	Butyraldehyde, acetone [108], methanol [109]	Catalytic reactions coupled with membrane separations
	Starmem TM (W.R. Grace), various	DCM, EA, THF [2], methanol [110] various	Catalyst recovery (PTC, Mn-Jacobsen, Pd-BINAP, Rh-Wilkinson, CYPHOS IL 101, etc.)

2.7 Potential of OSN for pharmaceutical industries

The use of organic solvents is prevalent in the pharmaceutical industry [111]. The ability to carry out selective separations in solvent based solutions using NF membranes would enable the recycling of solvents, the concentration and purification of products, and recovery of valuable pharmaceutical ingredients. Before a membrane system is accepted by commercial users, many requirements must also be fulfilled. The main requirements present technological challenges to be solved for the current OSN membranes and modules. A brief overview of the requirements and technological challenges are described in Table 2.3.

Table 2.3: Overview of crucial aspects required for OSN membranes and modules before applying the technology in the pharmaceutical industry.

Requirement	Technological challenge
Long term stability	➤ Chemical stability in common industrial organic solvents (e.g. THF, DMF, dimethyl sulfoxide (DMSO), NMP, DCM, toluene, acetone). ➤ High selectivity and competitive permeability for over a long period. ➤ Mechanical stability under cyclic temperature and pressure regimes.
Reliability	➤ Reproducible fabrication processes. ➤ Long-term storage properties. ➤ Easy scale-up of application processes from laboratory to production installations.
Applicability	➤ Regulatory compliance of materials and components (e.g. US FDA 21 CFR). ➤ Low cost production including modules and installation cost.

2.8 Summary and research motivation

Despite the clear potential of OSN as an economical and environmentally sound separation and purification technology in the pharmaceutical industries, the uptake of OSN by industry is slow. A primary reason is the lack of commercial OSN membranes and modules available for applications in common industrial solvents. Aprotic solvents especially are demanding and require an extremely high chemical stability from the whole membrane system. This include the adhesives required for assembling membrane module, which are often forgotten

by academia, and additionally the adhesive have to be compliant or acceptable to regulatory authorities (e.g. EMEA and FDA) due to the potential for components to leach or extract into organic solvents. In recent years, OSN has advanced in many areas including new applications and the development and understanding of transport mechanisms for the few commercially available membranes. However, much of the reported work has been performed in dead end experiments and/or in relatively short term studies using membrane coupons rather than membrane modules. Furthermore, the limited understanding of the required pre-conditioning steps of the commercial OSN membranes and other aspects mentioned earlier often leads to inconsistency in comparing results reported by various researchers. The ability to relate the functional membrane/membrane module performance to every step involved in the fabrication process will further enhance the ability to control membrane performance and allow membranes and modules tailored to their specific applications to be produced reproducibly. For further development of OSN, it is first necessary to address the major limitation of the commercially available membranes and modules, i.e. the chemical stability. Taking the challenges described in Table 2.3 into account this led to a research programme addressing:

- (a) improvements in the chemical stability of OSN membranes and understanding the influence of process steps on preparing them for production – the research methodology is to establish a theoretical understanding of these process steps based on pragmatic observations in the literature (mainly patents) and experimental observations (chapter 3),
- (b) improvement in the chemical stability of an important component used to fabricate the membrane system, i.e. the adhesive system – the research methodology initially involved developing a fundamental understanding of the base chemistry of the

adhesive and subsequently relating this developed knowledge to the adhesive's resistance in organic solvents (chapter 4),

- (c) optimisation of the adhesive curing conditions focussing on the compromise between chemical resistance and membrane performance when they are cured in-situ using conventional thermal energy and the development of a microwave radiation curing technique– an experimental approach was used to establish the relationship between key thermal curing parameters and stability of adhesive and membrane functional performance, and through theoretical understanding a novel curing technique of polyimide membrane module is invented (chapter 5).

To demonstrate that the learning from chapters 3-5 can be used to produce a commercially viable membrane and membranes modules, a series of case studies on pharmaceutical relevant applications were carried out (chapter 6).

Chapter 3

Second generation polyimide OSN membranes: Towards production

3.1 Abstract

In this chapter, an improved second generation PI OSN membrane prepared through chemical crosslinking of integrally skinned P84 (PI) membranes using aliphatic diamines has been demonstrated. Operation in DMF and THF for 120 hours showed that these membranes have stable fluxes and consistent separation performance throughout the testing period in harsh solvent environments. The ease of preparation makes this membrane easily scalable. This chapter further reports the study of the post preparation step – drying via solvent exchange to solvents that have low surface tension (e.g. IPA, toluene and hexane) and impregnating with preserving agents to prepare this membrane for module fabrication. The experimental transport data upon drying of water- and solvent-wetted membranes was interpreted using the intrinsic membrane parameters of bulk porosity and pore size distribution estimated from a pore flow model. Preserving agents, polyethylene glycol 400 (PEG 400) and undecanone were found to be suitable for maintaining the performance of the chemically crosslinked PI membranes in a ‘dry’ state due to their easy impregnation into the membranes and their good solubility in most of the application solvents of this membrane type.

3.2 Background and introduction

Commercial PI membranes, StarmemTM, are known to provide good performance in mainly apolar solvents such as toluene, ethyl acetate and hydrocarbons [2,5,13,38,83,103,104]. These are henceforth referred to as the first generation of PI OSN membranes. But, PIs generally have poor and irreproducible performance in many common industrial solvents used in pharmaceutical synthesis like THF, acetone [112], DMF, DMSO, NMP and DCM [39]. This is because most PIs are soluble or soften substantially in these solvents. At the time this work was undertaken, there were no reports of OSN in these solvents with polymeric membranes.

Two approaches, (i) post-casting modification (e.g. crosslinking) and (ii) using highly chemical resistant polymers (e.g. Kevlar distributed by DuPont [113] is stable in polar aprotic solvents) were considered as means of imparting improved chemical stability to polymeric membranes. The latter approach can be difficult, as it may be impossible to dissolve the polymer to form membranes via phase inversion. Therefore, it is logical to further investigate the feasibility of the former option. Crosslinking of polymeric membranes has been shown to increase their chemical and thermal stability [114-116]. However, this is often at the expense of a decrease in permeability [116,117]. Several crosslinking strategies for PI have been proposed including the use of radical initiated (thermally or via the use of UV) and chemical crosslinks [115,116,118]. Post casting modification of polymer films allows the desired morphology of the membranes to be attained via phase inversion followed by crosslinking the pre-formed membrane to maintain this morphology under aggressive conditions. In OSN, where membrane stability of the under-layer is as critical as the separating layer, effective and uniform crosslinking of the whole membrane structure must be achieved. This precludes the use of radical initiated methods which would have difficulty achieving crosslinking throughout the whole membrane. Instead, chemical crosslinking was chosen as the preferred

method to achieve uniform crosslinking throughout the membranes. Several chemical crosslinking strategies for use in PI membranes have been proposed and include the use of di/poly-amines in a ring opening reaction [119,120] and the inclusion of condensable crosslinking sites during polymer preparation [121,122].

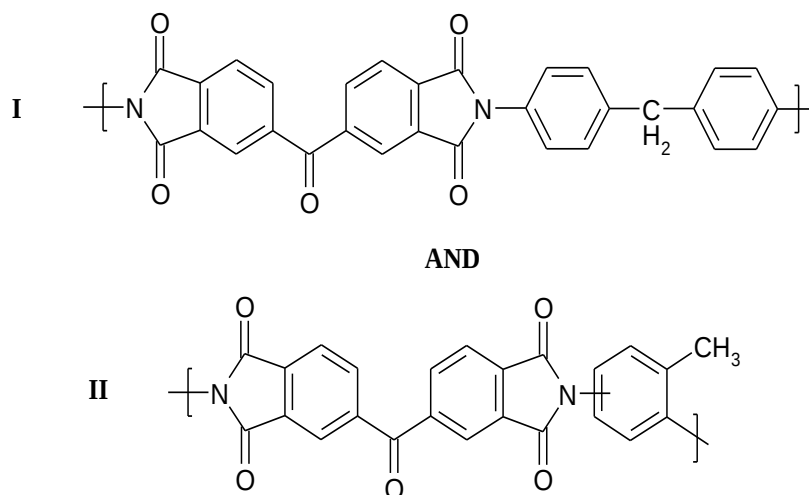


Figure 3.1: Chemical structure of P84 co-polyimide.

P84 (HP Polymer GmbH, Germany) is a BTDA based co-polyimide produced from 3,3',4,4'-benzophenone tetracarboxylic dianhydride and 20/80% toluenediamine and methylphenylenediamine with a T_g of 315°C (See Figure 3.1). The polymer is aromatic, fully imidized, highly polar and insoluble in most organic solvents. It is soluble in many polar aprotic solvents such as DMF, DMSO, DMAC, NMP [74] and in mixtures with 1,4-dioxane [83] and THF. It has been reported that P84 shows better chemical resistance than other PIs such as Matrimid and Sixef [74], making it a prime candidate for use in OSN. White et al. [13,83] has previously demonstrated the use of P84 in the manufacture of OSN membranes. Here, we describe integrally skinned asymmetric OSN membranes made of P84, which is post modified via chemical crosslinking with diamines [30].

P84 PI membrane that was post treated chemically with 1,8-octanediamine (ODA) (M1, refer to Table 3.1) showed good stability across a range of solvents including polar aprotic solvents such as DMF that is used as a solvent in the initial preparation of the integrally skinned asymmetric membrane. Figure 3.2 shows the flux and MWCO of these membranes in THF and DMF at 30 bar and 30°C. Continuous testing was carried out over 120 h with flux and rejection measurements taken intermittently. The membrane showed fluxes of $100 \text{ L m}^{-2} \text{ h}^{-1}$ and $70 \text{ L m}^{-2} \text{ h}^{-1}$ in THF and DMF respectively. The membrane also shows a MWCO of 200 g mol^{-1} in THF and 300 g mol^{-1} in DMF. The data unequivocally demonstrates the stability over an extended test period of the membrane in harsh polar aprotic solvents. Figure 3.3 shows the end flux and MWCO of M1 in different organic solvents tested in a dead-end filtration cell. Remarkably, in addition to solvents already commonly used in OSN applications such as methanol, toluene and acetone, the membrane was also usable in solvents such as DCM, DMF and n-ethyl pyrrolidone (NEP) and gave good separation within the NF range of $200 - 1000 \text{ g mol}^{-1}$, whilst providing solvent permeability $\geq 0.2 \text{ L.m}^{-2}.\text{h}^{-1}.\text{bar}^{-1}$ at 30 bar and 30 °C.

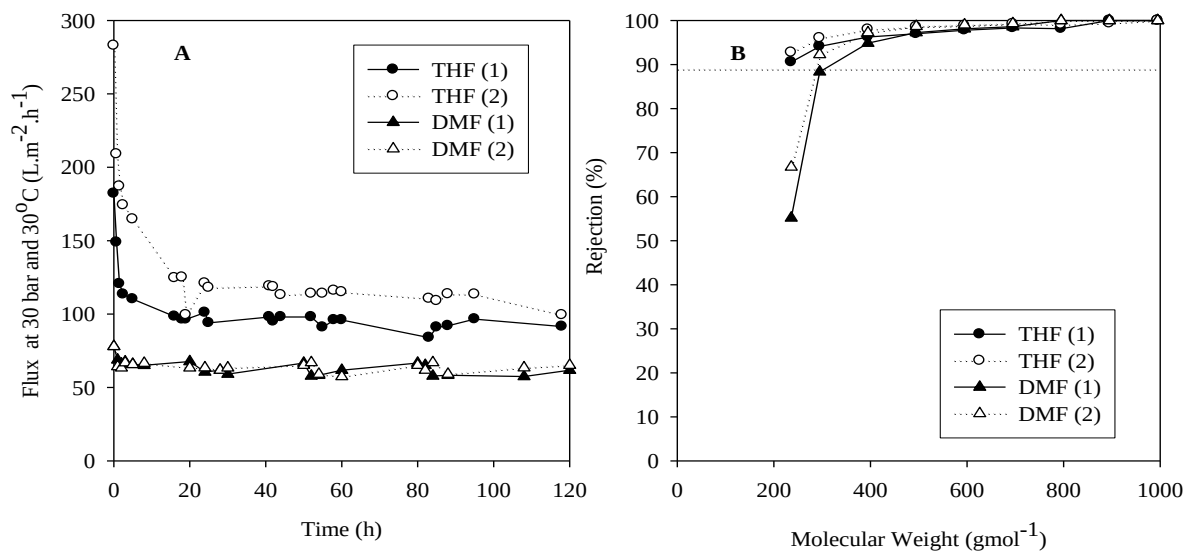


Figure 3.2: Flux and MWCO of M1 in THF and DMF determined in cross-flow (A) showing fluxes over time, (B) showing MWCO curve determined after 120 hrs at 30 bar and 30°C.

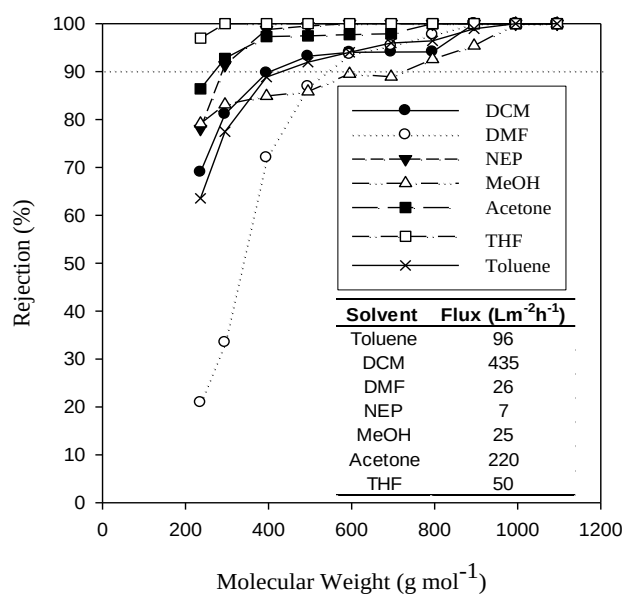


Figure 3.3: Flux and MWCO of M1 in different organic solvents tested in dead-end at 30 bar.

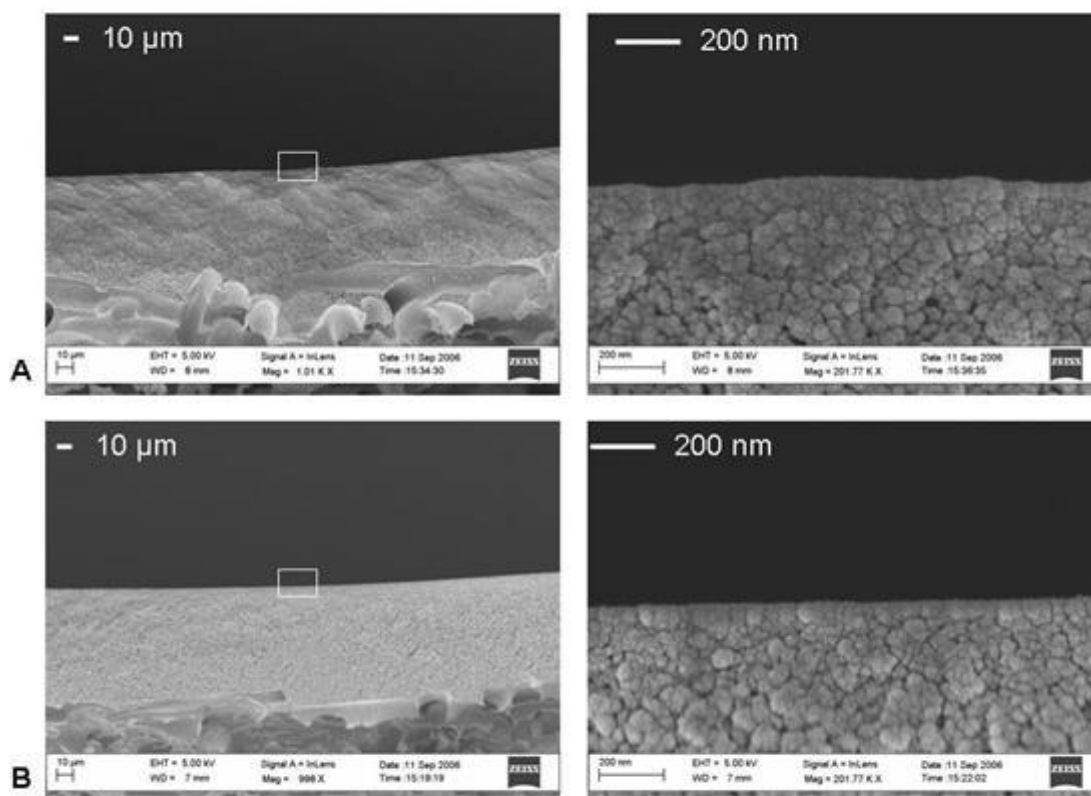


Figure 3.4: SEM pictures of the cross section and top separating layer of M1 membrane before (A) and after (B) crosslinking with 1,8-octanediamine (ODA).

The cross section and a magnified detail of the M1 membrane before and after crosslinking with ODA are shown in Figure 3.4 (A) and (B). The SEM pictures suggest that both membranes have a spongy asymmetric structure with a nodular top separating layer. The crosslinked membrane was observed to retain this structure even after immersion in DMF, and showed no indication of plasticisation or re-dissolution which would change the morphology of the membrane. The similarity in structural features suggests that crosslinking does not change the morphology of the membranes, but rather helps to preserve that morphology by introducing intermolecular bonds to hold the polymer chains together when exposed to polar aprotic solvents.

(The work from page 50-54, published in Journal of Membrane Science [30] has been carried out in collaboration with Yoong Hsiang See-Toh from the Department of Chemical Engineering and Chemical Technology, Imperial College London, UK.)

In order for this membrane to be seriously considered as a possible solution or alternative to the first generation PI OSN membranes, its performance has to be rigorously investigated to determine the limits of its operation. Prior to this, membrane has to be prepared reliably and in large quantities with minimal variation between membrane batches. For a membrane process to be viable, large areas of membranes need to be produced and fabricated into modules to maximise the membrane area, whilst providing the smallest possible footprint. Schipolowski et al. [123] describes differences in membrane material in lab scale tests and modules due to differences between production batches, variation within the flat sheets, storage, cleaning and pre-treatment protocols of membranes. In order to fulfil these requirements and for the membranes to be fabricated in modules, they must be dried first.

The typical morphology of an integrally skinned asymmetric P84 membrane is presented in Figure 3.5 [32]. The morphology observed within the top 100 nm of the P84 membrane consists of a matrix of tightly packed polymer nodules leaving small channels (<5 nm) between them. Some of these channels can be seen to reach the surface. Pores are thought to be formed by the interstitial spaces between the nodules. This morphological feature is frequently observed and reported in the top separation layer of UF and NF membranes [124]. The formation of polymer nodules on the surface layer has been described by Wienk et al. [125] and was also observed by Carruthers et al. [126] for other PI membranes (Matrimid). The formation mechanism and origins of nodules are however disputed and may be attributed to: (i) aggregates or micelles already present in the dope [127,128] and/or (ii) formation via

liquid-liquid demixing during phase inversion [129,130], or (iii) simply artefacts of SEM or sample preparation. The evident change observed in the nanostructure of P84 OSN membranes after thermal annealing via SEM by See-Toh et al. [32] has alluded that these features were artefacts of the technique.

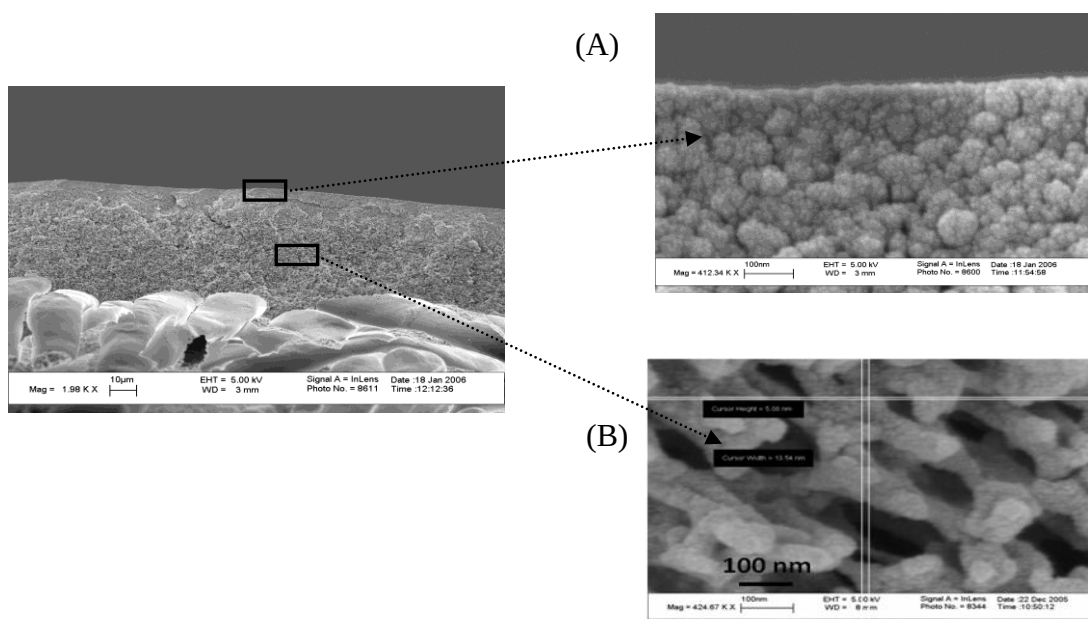


Figure 3.5: SEM pictures of the cross section of an integrally skinned asymmetric membrane formed via phase inversion, (A) top separating layer and (B) bottom sub-layer.

Wienk et al. [131] suggested that the highly entangled polymer structure collapses when brought into contact with non-solvent during the immersion precipitation process. This collapse results in polymer-rich phase domains (the nodules), with an interconnected structure which contains pores at regions where disentanglement of polymer chains has fully taken place. The disentanglement process takes place while solvent is still present in the nascent membrane which plasticises the polymer during the immersion precipitation. When most of the solvent has diffused into the non-solvent bath, the polymer will reach the glassy state, when its glass transition temperature (T_g) is well above the temperature of the coagulation bath. In the glassy state, the morphology is effectively frozen in a non-

equilibrium state, since the relaxation times for polymer movement in the glassy state are very large when compared to the rubbery and highly plasticised states.

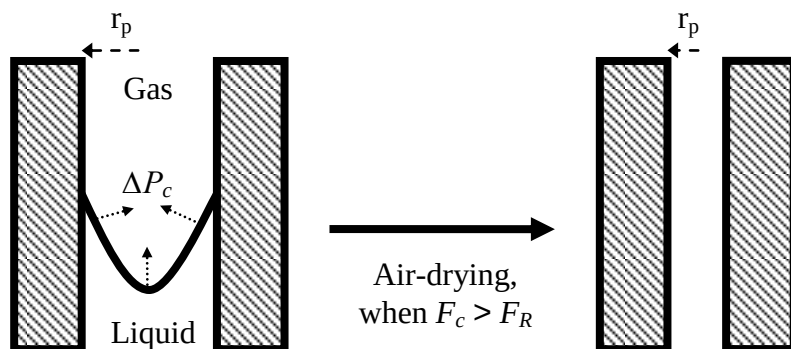


Figure 3.6: Schematic diagram illustrating the capillary pressure difference in a pore during the air-drying process, when $F_c > F_R$.

However, the structure of an integrally skinned asymmetric membrane prepared via phase inversion, which is wetted with non-solvent (e.g. water, in this work) can collapse if the capillary force (F_c) in the pores is larger than the membrane deformation force (F_R) when it is air-dried at atmospheric conditions [66,74]. This causes the membrane to suffer a non-recoverable loss in permeation rate and selectivity. Figure 3.6 describes the capillary pressure difference in a wetted pore of an immersion precipitated membrane during air-drying while the wetting agent (e.g. water, IPA and any other wetting agents) evaporates from the pore [74]. When $F_c > F_R$, the very small pores may decrease in pore radius or completely disappear. Therefore, if $F_R > F_c$, the collapse of the pores will not occur. Theoretically, the strong capillary force (F_c) present inside the liquid filled pores is represented by:

$$F_c = \Delta P_c \times A_{cs} \quad (\text{Equation 3.1})$$

where ΔP is the capillary pressure difference between the gas phase (atmospheric) and the liquid phase and A_{cs} is the pore cross sectional area. The capillary pressure difference in a cylindrical pore can be given by the Laplace equation [66]:

$$\Delta P_c = \frac{2\gamma}{r_p} \cos \theta \quad (\text{Equation 3.2})$$

where γ is the surface tension of the liquid interface inside the pores, r_p is the pore radius and θ is the contact angle between the liquid and the membrane material. The resistance of the matrix to deformation opposes the capillary pressure, as stated by Brown [74], and is defined as:

$$F_R = 0.37E \times A_{cs} \quad (\text{Equation 3.3})$$

where E is the tensile modulus of polymer material, and is a measure for the pore wall elasticity.

For $F_R > F_C$, researchers have used different techniques to lower F_C and/or increase F_R . The Laplace equation (equation 3.2) indicates that F_C is proportional to the interphase tension between the wetting agent and polymer ‘pore’ wall during drying. Attempts to decrease or eliminate F_C include:

- (i) replacing non-solvent (usually water) with low surface tension wetting agents such as hydrocarbons and FreonTM113 prior to air-drying [68,71,74,132],
- (ii) soaking the membranes in aqueous solution containing surfactant prior to air-drying [72],
- (iii) isolating the non-solvent interaction from the membrane polymer matrix by coating the membrane polymer surface with hydrophobic liquid additives such as

- polysiloxanes, hydrocarbons and chlorohydrocarbons; these components are added to the casting solution and migrate to the polymer surface as the membrane forms [133],
- (iv) via freeze-drying where water inside the membrane is frozen and dehydration of membrane is obtained by sublimation of ice in high vacuum without melting [66], and
- (v) replacing non-solvent with non-volatile compounds (usually referred to as preserving agents) such as mineral oil [64] and glycerol [72,73] prior to air-drying.

On the other hand, researchers have investigated increasing the F_R of the membrane matrix by reducing the potential for molecular packing rearrangement within the membrane structure upon drying through thermal annealing in sequential water baths from cold to hot water [133,134] and by introducing TiO_2 particles into the membrane matrix [135]. Although all the approaches listed are claimed and shown to reduce the effect of ‘pore collapse’ with various types of membranes, ranging from cellulose acetate to polyimide membranes and from RO to UF membranes, the influence of the techniques on the functional performance of different membranes are not well documented and leads to discrepancies between studies. To date, limited studies on the air-drying of NF membranes are available. Understanding the relationship between functional performance and membrane properties (e.g. pore size distribution, porosity and mechanical strength) of membranes made from the same type of polymer upon air-drying would help significantly in the formation and manufacturing of consistent membranes tailored to their specific applications.

Water and isopropanol (IPA) are the main process solvents used in the formation of P84 OSN membranes [30,32]. In this chapter, the effect of air-drying on water and/or IPA wetted P84 membranes with different physical properties will be investigated. This is attained by (i)

using membranes with MWCO from 200 (NF) to 70,950 g.mol⁻¹ (UF) [1,11] and (ii) by introducing chemical crosslinks between the polymer chains. Pore size distribution measurement is not straightforward and difficult to measure and directly analyse for NF membranes with the technologies currently available. Therefore, a detailed study of the membrane pore size distribution upon drying was performed by combining the pore flow model with experimentally determined solute rejections to calculate the pore size distribution.

Here, two main drying techniques (i) solvent exchange to a solvent that has low surface tension and (ii) impregnating the membrane with different types of low volatility preserving agents were studied. These techniques were chosen since they have no impact on membrane formation (the techniques are applied once the membrane has formed), the compounds are easy to remove from the membrane prior to use, and they also impose minimal extended leaching profiles.

3.3 Experimental

3.3.1 Chemicals

P84 co-polyimide was purchased from HP Polymer GmbH, Austria and used without any further post treatment. The solvents used for the preparation of membranes were DMF, dioxane, methanol, IPA, MEK and toluene. Analytical grade THF, water and DMF were used as solvents for analysing samples collected from membrane characterisation. All chemicals listed above including ODA, 1,6-hexanediamine (HDA), mineral oil, undecanone, and trifluoroacetic acid (TFA) were purchased from Sigma-Aldrich (UK). PEG 400 was purchased from VWR International, UK.

Two types of solutes were used to determine MWCO, (i) a homologous series of alkanes and (ii) styrene oligomers. The alkane solutes included decane, tetradecane, hexadecane, eicosane, tetracosane and hexacosane were purchased from Sigma-Aldrich (UK). A solution consisting of at least 0.1 wt% of each solute was used. The styrene oligomer mixture contained a mixture of 1g of PS580, 1g of PS1050 (GPC standards purchased from Polymer Laboratories, UK) and 0.1g of α -methylstyrene dimer (purchased from Sigma-Aldrich, UK) in 1 L of solvent(s) was used for testing NF membranes. Styrene oligomer standards with MW of 1200, 5120, 19 640, 38 100 and 70 950 g.mol⁻¹ were purchased from Polymer Laboratories, UK and used to characterise UF membranes. A solution mixture containing at least 0.1wt% of each solute was used. The organic solvents used for filtrations, including toluene, DMF and acetone, were purchased from Sigma-Aldrich (UK).

3.3.2 Preparation of integrally skinned asymmetric PI-OSN membranes

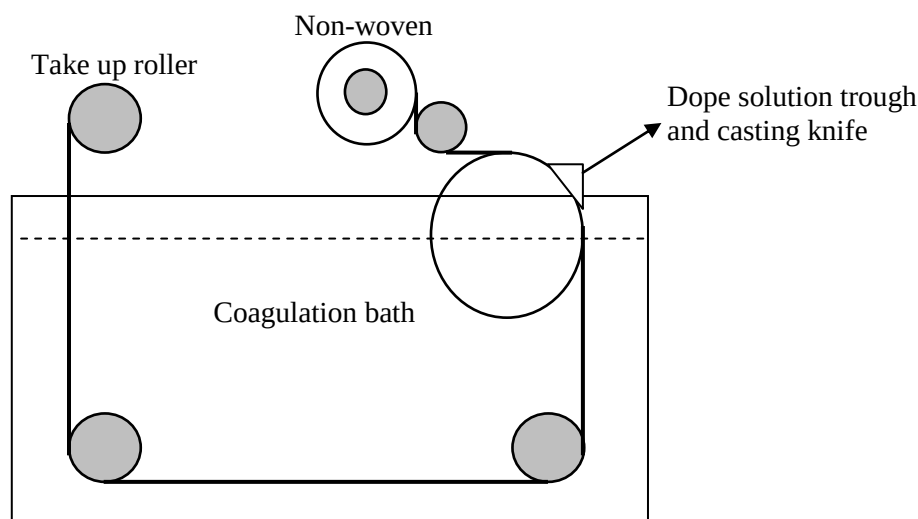


Figure 3.7: Schematic diagram of continuous casting machine used to prepare integrally skinned asymmetric membranes.

Dope solutions were prepared by dissolving P84 polymer into a solvent mixture of DMF and dioxane at 20 – 25 °C. Once a homogenous solution was obtained, the solution was left sitting at room temperature for degassing. The dope solutions were transformed into integrally skinned asymmetric NF membranes by casting a $200 \pm 50 \mu\text{m}$ film on a non-woven cloth (polyester (PET) or polypropylene (PP)) before precipitation in a water bath at 20 °C using a continuous casting machine. Figure 3.7 shows a schematic diagram of the continuous casting machine used in this work. The casting parameters for these membranes are not disclosed for reasons of commercial confidentiality, additionally they are not the main focus of this study.

After casting, the membranes were immersed into fresh water to remove residual solvents. The membranes were first immersed into a post processing solvent (e.g. methanol, isopropanol (IPA), methyl ethyl ketone (MEK)) to remove water and then immersed in a crosslinking solution (containing crosslinker in post processing solvent) for 24 hours at ambient temperature. The membranes were then washed with the post processing solvent to remove any residual crosslinker. The membranes were then immersed into a bath of solution containing the preserving agent in the post processing solvent, and subsequently air dried to remove the volatile solvent(s). This preservation/drying step was carried out on a portion of the membranes, with the remaining membranes stored in their post processing solvent(s) prior to testing. For non-crosslinked membranes, the preparation steps were the same, except that the crosslinking process step was not carried out.

Table 3.1 lists the formation parameters of the P84 membranes used in this study. Commercial PI OSN membrane, StarmemTM 122 (W.R. Grace) was also used. StarmemTM

122 is reported to be an integrally skinned asymmetric membrane made directly from P84 polymer and preserved with lube oil for it to be handled in a ‘dry state’.

Table 3.1: Formation parameters of the P84 membranes used in this study.

Membrane	Dope solution composition (wt%)			Post processing solvent	Crosslinker
	P84	DMF	Dioxane		
^a M1	18	20	60	Methanol	ODA
M2	24	19	57	^b IPA/water	-
^a M3	24	37	37	IPA	-
M4	24	76	0	IPA	-
^a M5	24	37	37	IPA/MEK	HDA

^a Containing 2 wt% of maleic acid.

^b Processing solvent is either one of the listed.

3.3.3 Preparation of air-dried water and solvent(s) wetted membranes

Water and solvent(s) wetted membranes subjected to air-drying were prepared by installing the wet membranes into crossflow filtration cells and purging air to the feed side at approximately 10 mbar gauge and ambient temperature for a minimum of 24 hours prior to testing. This methodology prevents the membrane from curling upon air-drying, where the membrane can crack and make it unsuitable for testing. To mimic the industrial production process, solvents in the membranes were exchanged by simply soaking the membrane in solvent for 1 hour before switching to the next solvent. For this to work, the sequential solvents have to be miscible. For example, membrane was solvent exchange from water to hexane, by first soaking the water wetted membrane in an IPA bath followed by toluene and then finally in a hexane bath. As for StarmemTM 122, preservative oil was removed by flushing with toluene at 5 bar until 100 mL of permeate were collected, where $< 0.1 \text{ g.L}^{-1}$ of dry weight was measured in the permeate.

3.3.4 Experimental apparatus and measurements

Two filtration apparatus were used, (i) *METcell* crossflow system (see Figure 3.8) and (ii) 5L crossflow system (see Figure 3.9). The *METcell* crossflow system allows membranes and test solutions to be rapidly swapped, while the 5L crossflow system is optimal for more rigorous testing of the behaviour of the membranes over extended periods.

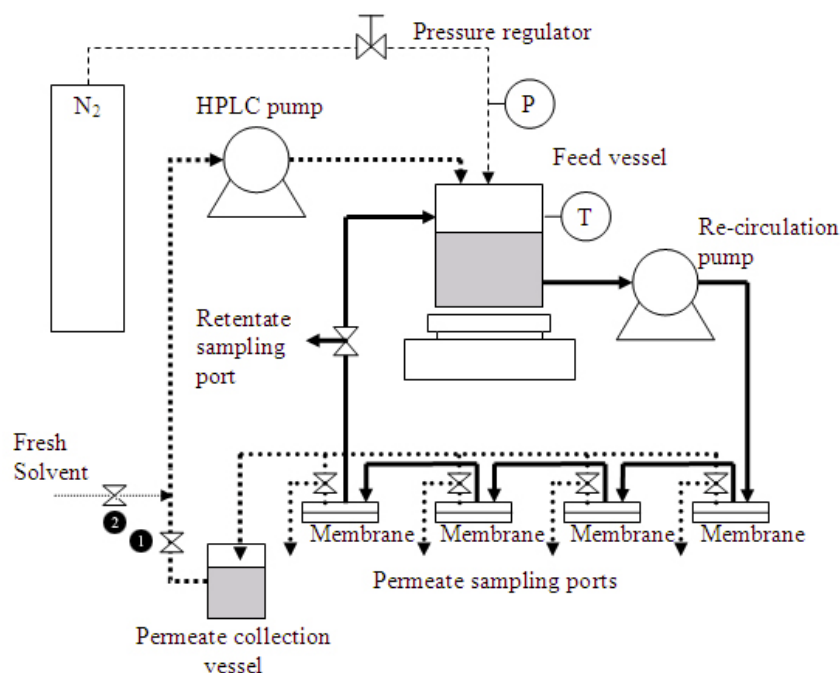


Figure 3.8: *METcell* crossflow system.

The *METcell* crossflow filtration apparatus consist of an 800 ml capacity feed vessel and a pumped recirculation loop through crossflow cells connected in series. N₂ from a gas cylinder was used as the driving force for the filtration, typically 30 bar filtration pressure was used. Mixing in the crossflow cells was provided by flow from the gear pump. The *METcell* crossflow apparatus can function in three filtration modes:

1. complete recycle of permeate for membrane screening (valve 1 opened, valve 2 closed),
2. volume reduction (valve 1 closed, valve 2 closed), and
3. diafiltration (valve 1 closed, valve 2 opened).

In the 5L crossflow system, the pressure was generated by liquid flow pumping against a back pressure regulator located downstream of a pressure gauge. The system consists of a 5L feed tank with the feed solution re-circulated at a flowrate of 60-80 L.h⁻¹ using a diaphragm pump (Hydra-Cell, Wanner International, UK) . The cumulative pressure drop across four crossflow cells was measured to be less than 0.5 bar, with a feed flow of 11,000 – 15,000 L.h⁻¹.m⁻². The solution temperature was kept constant at 30 °C using a heat exchanger.

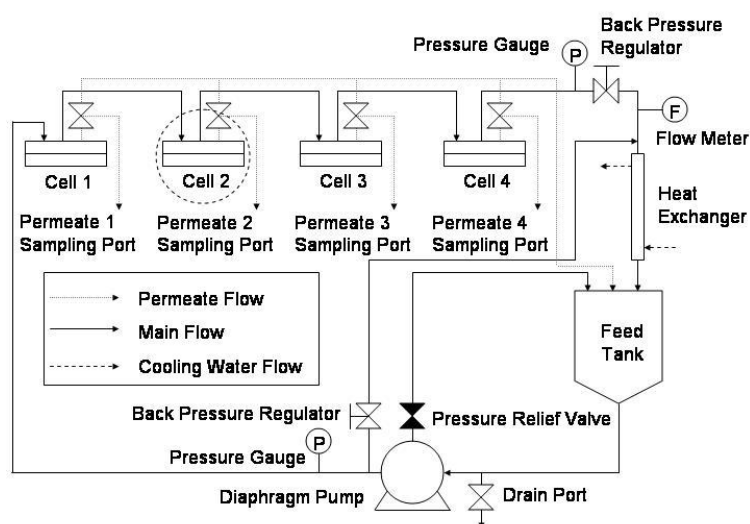


Figure 3.9: 5L crossflow system

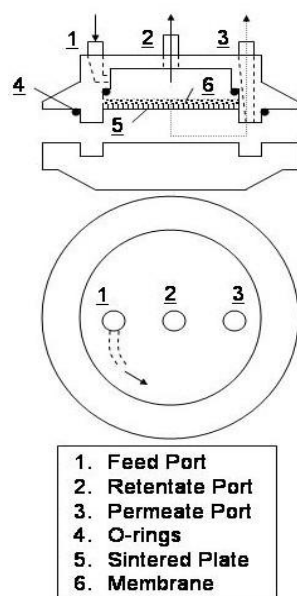


Figure 3.10: Schematic cross section and top view of a crossflow cell.

The schematic of a crossflow cell is illustrated in Figure 3.10. The feed stream is fed tangentially to the membrane surface at the outer diameter of the membrane disk and follows a spiral flow pattern to a discharge point at the centre of the filtration disc. This is a preferred method of operation to the often used dead-end filtration cell as it minimises the build up of material on the membrane surface and reduces the effects of concentration polarisation and fouling.

Prior to testing, pure filtration solvent was permeated through the membranes until 40 L.m^{-2} was collected from each disc. This is to remove the preserving agent or the storage solvent present in the membranes. During operation, permeate samples were collected from individual sampling ports and feed samples were taken from the feed tank once a steady flux measurement was recorded ($\pm 5\%$).

3.3.5 Analytical methods for membrane characterisation

Styrene oligomers in NF range

An Agilent 1100 HPLC system with a diode array detector operating in multiple single wavelength UV/Vis mode was used for analysis of the styrene oligomers. Separation of oligomers was achieved using a 4.6×250 mm TSKgel-ODS-80TS column with 5 μm bead size (purchased from Sigma-Aldrich, UK). The detailed analytical method used was published by See-Toh et al. [22]. Prior to analysing the samples, filtration solvents, toluene and acetone were evaporated from the sample and the solute was then re-dissolved in analytical grade DMF.

Alkanes

The alkanes were analysed using a gas chromatograph (GC) (6850 Series II, Agilent Technologies, UK) fitted with a Rtx-2887 100% dimethyl polysiloxane stationary phase column and a flame ionisation detector. The temperature programme selected was as previously published by Cherepitsa et al. [136] for petroleum fractions. The measurement error was less than 5 % for three independent measurements.

Styrene oligomers in UF range

These solutes were analysed using a Waters gel permeation chromatography (GPC) system fitted with a Waters 996 photodiode array detector. Separation of the styrene oligomers were achieved using Styragel HT-2 and HT-4 columns connected in series. A THF flowrate (mobile phase) of $0.7 \text{ ml} \cdot \text{min}^{-1}$ and fixed UV wavelength of 264 nm were used, with analysis temperature fixed at 40 °C. The analytical method used allows all solutes to be measured simultaneously to obtain the MWCO curves.

3.3.6 Dynamic vapour sorption (DVS)

The affinity of membranes with organic solvent and water were measured using a DVS Advantage 2 machine (Surface Measurement Systems Ltd., UK) controlled at the 95 % saturation point of the solvent under test. At least three measurements were taken for each sample with each solvent. The coefficient of variation was found to be between 2 – 5 %.

3.3.7 Porosity measurement

Bulk porosity (P_B) of a membrane can be defined by the following equation:

$$P_B = \frac{V_f}{V_T} \times 100\% = \frac{V_T - V_{P84}}{V_T} \times 100\% \quad (\text{Equation 3.4})$$

where V_f is the free volume in the membrane and V_T is the total volume of the membrane when wetted (when formed after phase inversion). V_T was measured based on liquid displacement theory - with the known density of P84 ($\rho = 1.34 \text{ g.cm}^3$) and mass of P84 in a dried membrane, V_f can be determined.

3.3.8 Contact angle

A drop shape analysis system, DSA100 (Kruss GmbH, Germany) integrated with DSA1 V1.9 software was used to measure the contact angle between select solvents (e.g. water, IPA and hexane) and P84 membranes.

3.3.9 Scanning electron microscopy (SEM)

Scanning electron micrographs were taken using a Leo 1525 field emission scanning electron microscope (FESEM). The membrane samples were first immersed in acetone to remove the preservatives used in this work (e.g. PEG400, α -methylstyrene dimer and undecanone), with the exception of mineral/lube oils which were removed by immersion in n-hexane. The

samples were subsequently immersed in liquid nitrogen, snapped , mounted onto the SEM stubs, and sputtered using an Emitech K550 gold sputter coater. SEM conditions used were 3 mm working distance and an Inlens detector with an excitation voltage of 5 kV.

3.4 Results and Discussion

3.4.1 Effect of air-drying of water and solvent(s) wetted membranes

First generation P84 membranes: Commercial and in-house

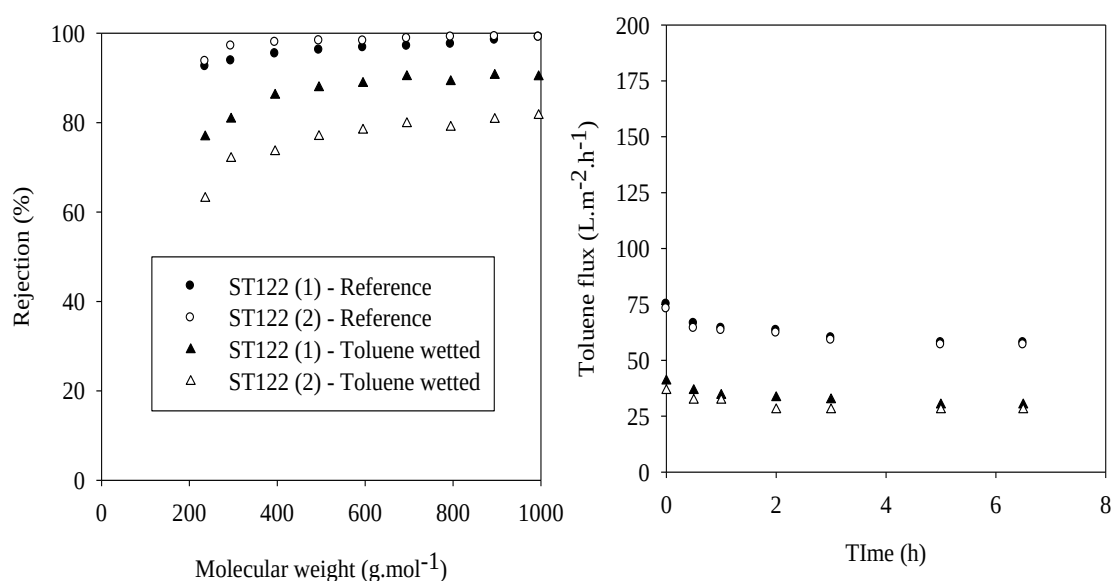


Figure 3.11: Comparison of (A) MWCO and (B) toluene flux of Starmem™ 122 membranes at 30 bar and 30 °C, before and after air-dried with toluene as wetting agent.

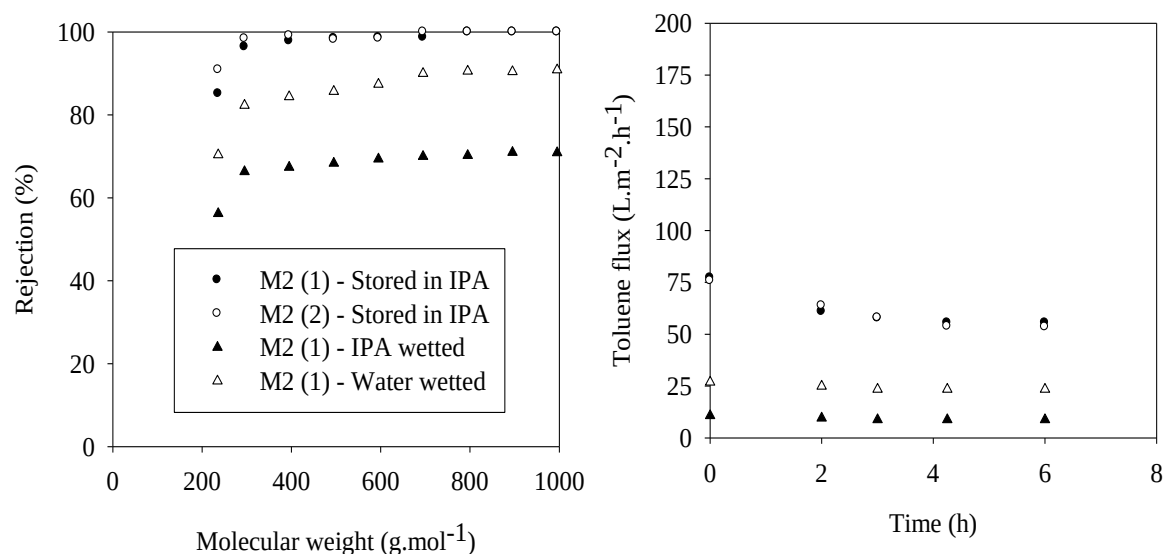


Figure 3.12: Comparison of (A) MWCO and (B) toluene flux of M2 membranes at 30 bar and 30 °C, before and after air-dried with water and IPA as wetting agents.

Figures 3.11 and 3.12 show the effect of direct air-drying of wetted StarmemTM 122 (ST122) and M2 membranes on the functional performance (MWCO and flux) of the membrane. The MWCO curves of ST122 were observed to shift downward with an average toluene flux drop of 49% when air-dried with toluene as the last solvent in contact. Consistent trends were also measured for M2 (a P84 membrane prepared in house) with an average toluene flux drop of 55 % when air-dried with IPA as wetting agent (see Figure 3.12). The worst effect was measured on the membrane performance of M2 when it is air-dried with water present in the membrane structure, giving a toluene flux decline of 83%. This may be explained by the high surface tension of water ($\gamma = 73 \text{ mN.m}^{-1}$) compared to IPA ($\gamma = 23 \text{ mN.m}^{-1}$). Given that the contact angle measured between water /M2 membrane and IPA/M2 membrane is similar ($\theta = 77^\circ$ and 72° for water and IPA respectively), the capillary force present in the water filled pores is 2.3 times the force present in the IPA filled pores (refer to equations 3.1 and 3.2). M2 was measured to have a tensile modulus (E) of 0.46 GPa. With the measured E value of M2, it was calculated that pores below 0.84 nm (refer to Figure 3.13) in the M2 membrane will

collapse with water as wetting agent upon air-drying. Concomitantly, with IPA as wetting agent, only pores below 0.26 nm of in the M2 membrane will collapse upon air-drying.

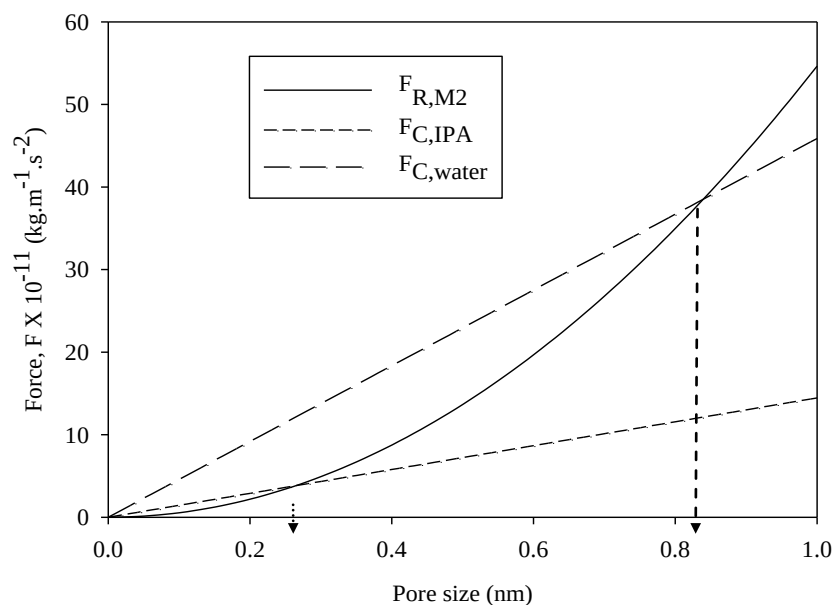


Figure 3.13: Relationship between F_R of M2 and F_c with IPA and water as wetting agent as a function of pore size.

Based on equations 3.1-3.2, the capillary forces present in liquid-filled pores are inversely proportional to the pore size. As demonstrated by See-Toh et al. [11], the mean pore size and standard deviation of pore size increases as the membrane become ‘looser’ with increasing DMF concentration (from M2 to M4, refer to Table 3.1) in P84/DMF/dioxane/water membrane systems prepared via phase inversion. Theoretically, at fixed F_R , the impact of air-drying on IPA wetted membranes would decrease from M2 to M4 due to the decrease in proportion of ‘smaller’ pores as illustrated in Figure 3.13. However, the E values of these membranes were measured to decrease from 0.46 GPa (M2), 0.45 GPa (M3) to 0.33 GPa (M4), since their casting solutions have different thermodynamic stability and dissimilar phase separation paths upon phase inversion. See-Toh et al. [11] had observed the migration of the cloud point curve at higher DMF concentration in P84/DMF/dioxane/water systems

towards the polymer/solvents axis. This observation corroborates the shifting from a delayed demixing (M2) towards an instantaneous mixing (M4), which may be responsible for the differences measured in tensile modulus. Figure 3.14 presents the relationship between F_R of M2, M3 and M4 and F_c with IPA as wetting agent as a function of pore size. Based on the calculated F_R profiles, IPA wetted pores of the same size (below 0.26 nm) in M2 and M3 will be affected upon air-drying, whereas pores below 0.40 nm in M4 will collapse upon air-drying.

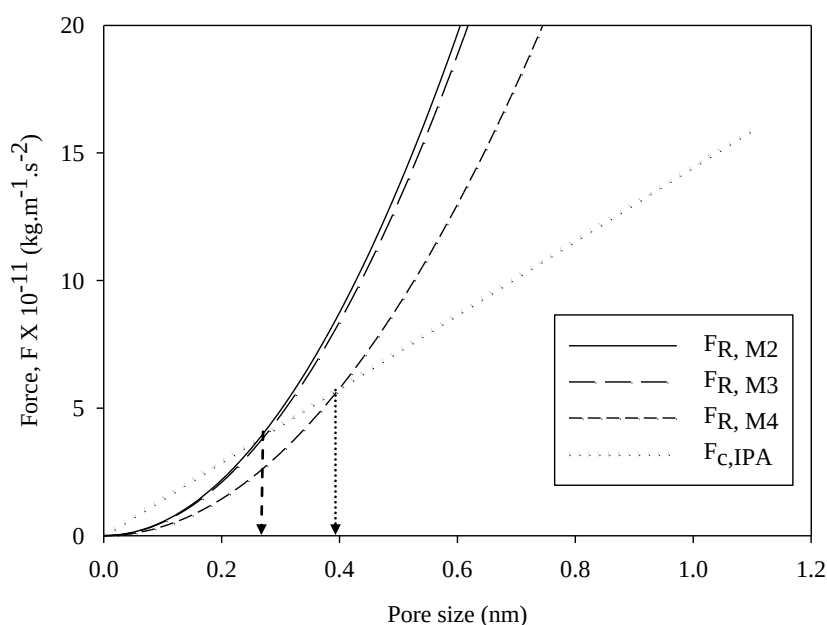


Figure 3.14: Relationship between F_R of M2, M3 and M4, and F_c with IPA as wetting agent as a function of pore size.

The effect of air-drying IPA wetted M3 and M4 membranes on their functional performance are presented in Figures 3.15 and 3.16 respectively. Interestingly, air-drying IPA-wetted M3 membranes provided the effect of lowering the MWCO, whilst simultaneously providing a drop in toluene flux. The same effect was also measured with the MWCO of M4. Surprisingly, a higher average toluene flux drop of 92% was also measured with M3, in comparison to M2 (52%) and M4 (31%) membranes. Similarly, both Staude et al. [137] and

Jeon et al. also observed a lowering of the MWCO and loss in solvent permeability when integrally skinned asymmetric UF polyamide and polyimide membranes respectively were subjected to direct air-drying after their preparation via phase inversion in water.

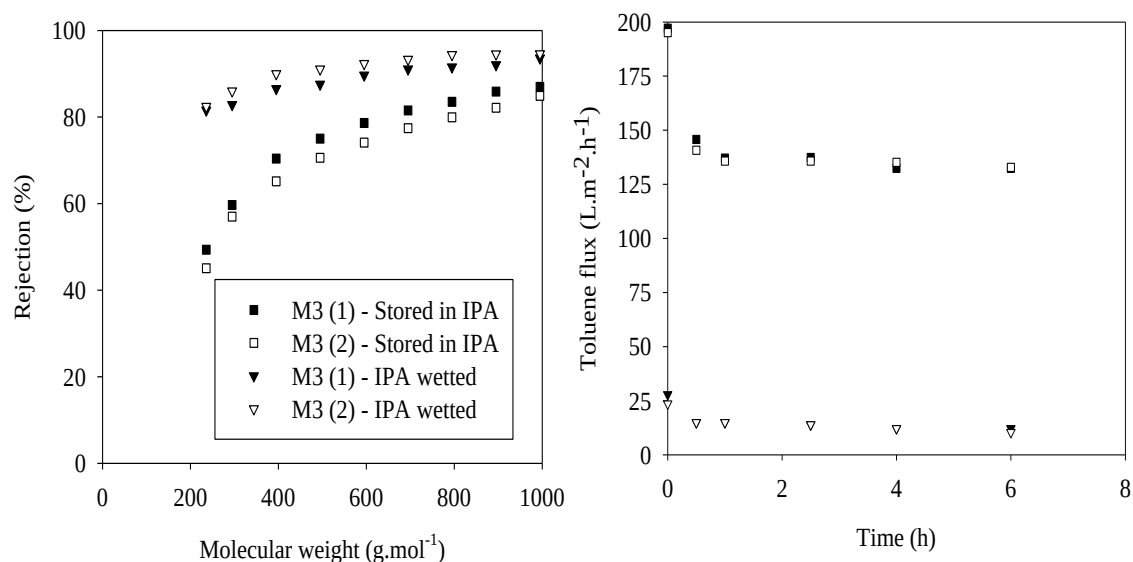


Figure 3.15: Comparison of (A) MWCO and (B) toluene flux of M3 membranes at 30 bar and 30 °C, before and after air-dried with IPA as wetting agent.

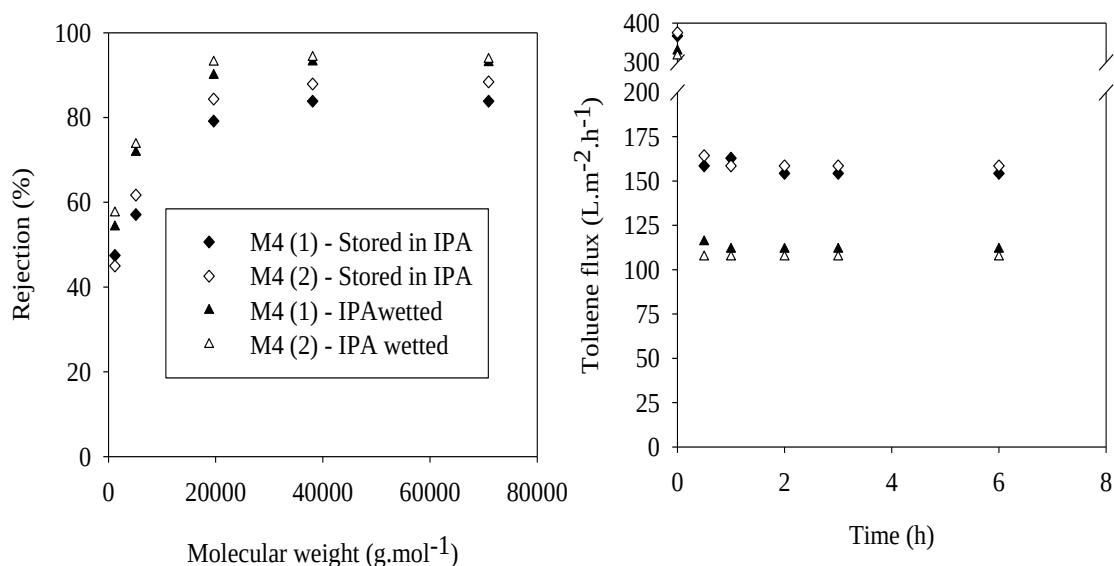


Figure 3.16: Comparison of (A) MWCO and (B) toluene flux of M4 membranes at 2 bar and 30 °C, before and after air-dried with IPA as wetting agent.

Shrinkage was observed on all membranes upon air-drying. In translating this observation into values, the porosity change during wet drying was measured. The porosity loss in each membrane (M2-M4) after being subjected to wet drying is presented in Table 3.2. The data values correlate well with the measured toluene flux loss upon wet drying. However, no correlation could be drawn between the bulk porosity loss and the membrane MWCO. Among all tested membranes, the M3 membrane (loose NF) was shown to have lost most of its bulk porosity. Assessing the SEM pictures in Figure 3.17, the most significant morphological difference observed between these membranes, was the presence of macrovoids in M4. This feature may account for the lower bulk porosity loss and toluene flux drop between M4 to M3, since the macrovoids may be the contributing factor to the high solvent permeability.

During the preparation of these SEM pictures, both wet dried and PEG 400 preserved membranes were analysed and both membranes were observed to exhibit a similar morphology with no visible differences. This observation is also in accordance with observations of Park et. al. [69], who reported negligible difference in structure of integrally skinned asymmetric membrane upon wet drying via SEM and AFM. Therefore, these results indicate that this technique is not suitable for relating the impact of air-drying of a wetted membrane to its performance and properties.

Table 3.2: Effect of wet drying on membrane porosity.

Membrane	^a Initial porosity (%)	Porosity loss upon wet drying (%)		
		Water	IPA	Hexane
M2	41 ± 2	39 ± 2	28 ± 3	-
M3	55 ± 6	-	42 ± 9	-
M4	70 ± 8	-	24 ± 6	-
M5	49 ± 4	-	25 ± 4	14 ± 2
M5	49 ± 4	-	^b 51 ± 4	-

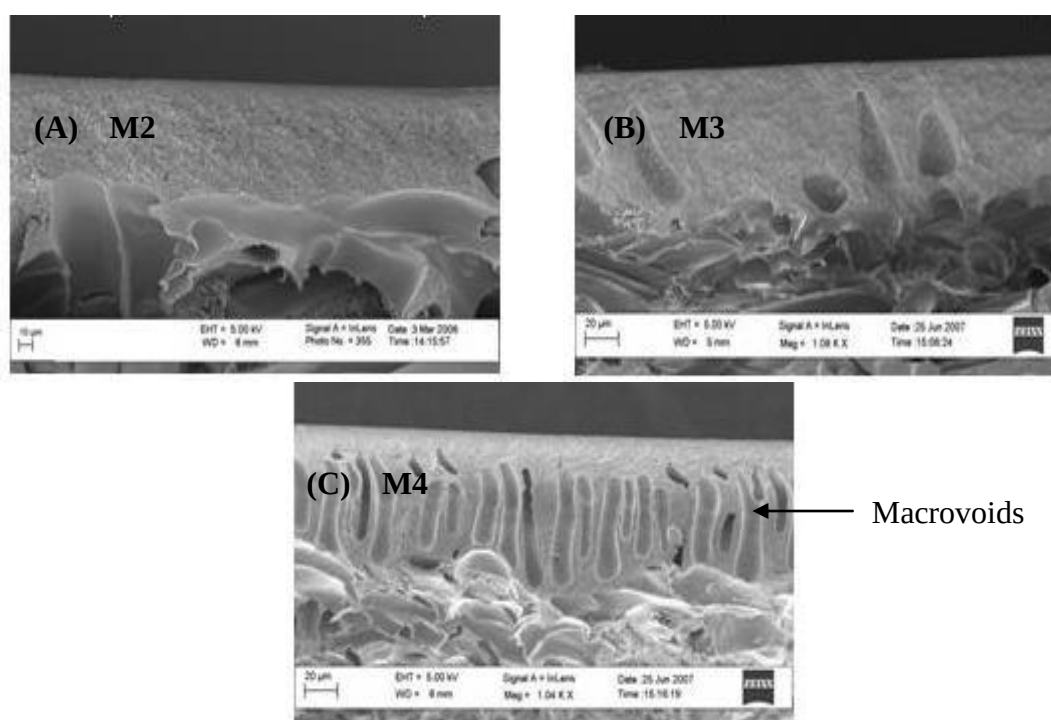
^a Membranes are stored in IPA.^b Thermally annealed at 75 °C for 19 hours.

Figure 3.17: Cross section SEM pictures (Magnification: 1,000X) of membrane M2, M3 and M4.

3.4.2 Pore size distribution based on solute rejection

Both the SD and PF models have been demonstrated to adequately describe mass transport in OSN. However in this chapter, the PF model is adopted as it is more useful in exploring the influence of air-drying of toluene/water/IPA/hexane wetted membranes on their separation performance.

Michaels [138] introduced the use of a two parameter log-normal distribution to relate solute rejection to solute diameter in the description of sieving characteristics of different UF membranes. A mean solute diameter ($\overline{d_s}$) and a solute standard deviation (σ_s) is used to describe the size of solutes rejected by the membranes. The rejection of different species (R_i) can be described by the error function as follow:

$$R = erf(z) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^z e^{-\frac{u^2}{2}} du \quad (\text{Equation 3.4})$$

where

$$z = \frac{\ln d_s - \ln \overline{d_s}}{\ln \sigma_s} \quad (\text{Equation 3.5})$$

Belfort et al. [139] further recommended that the mean pore diameter ($\overline{d_p}$) and standard deviation (σ_p) are equal to the corresponding values from the probability density function due to the skew of the probability density function (f_R), as presented by the following equation:

$$f(r) = \frac{1}{d_p \sqrt{2\pi b}} \exp \left[-\frac{\{\log(d_p / \overline{d_p}) + b/2\}^2}{2b} \right] \quad (\text{Equation 3.6})$$

where

$$b = \log \left[1 + \left(\frac{\sigma_p}{\overline{d_p}} \right)^2 \right] \quad (\text{Equation 3.7})$$

Most reported works describing pore size distribution in membranes are based on empirical fitting of experimental rejection data to the log normal distribution to obtain estimates of $\overline{d_p}$ and σ_p . Although this approach has been adopted widely [140,141], it lacks a physical basis.

Until recently, researchers have adopted hydrodynamic models of hindered solute transport in pores [142,143] to estimate $\overline{d_p}$ and σ_p . This approach has been successfully used for describing the behaviour of aqueous NF membranes [144] and OSN membranes [11]. As presented in Table 3.3, some of the tested membranes have $\sigma_s \gg \overline{d_s}$ due to these membranes offering > 80% rejection of the styrene oligomers used to characterise them. Therefore, prior to determining the pore size distribution of different types of membranes, rejection values between 50 and 90 % were obtained by using appropriate markers.

Hydrodynamic model

The hydrodynamic model used in this work is derived from the extended Nernst-Planck equation for transport of solutes inside the membrane [87,143,145]. The equation consists of flux terms due to diffusive, electric field gradient and convective driving forces:

$$j_i = -K_{i,d} D_{i,\infty} \frac{dc_i}{dx} - \frac{z_i c_i D_{i,p}}{RT} F \frac{d\psi}{dx} + K_{i,c} c_i V \quad (\text{Equation 3.8})$$

By ignoring the transport term due to electric field gradient for uncharged solutes (styrene oligomers and alkanes are uncharged [32]), equation 3.8 is simplified to:

$$j_i = -K_{i,d} D_{i,\infty} \frac{dc_i}{dx} + K_{i,c} c_i V \quad (\text{Equation 3.9})$$

where c_i is the solute concentration in the pore and x is the axial position within the pore. The solute diffusive and convective hindrance factors $K_{i,d}$ and $K_{i,c}$ are functions of the ratio between the solute and pore radius ($\lambda_i = d_s / d_p$). Assuming a parabolic fully developed solute flow within the pore, the hindrance factors may be expressed as:

$$K_{i,d} = 1.0 - 2.30\lambda_i + 1.154\lambda_i^2 + 0.224\lambda_i^3 \quad (\text{Equation 3.10})$$

$$K_{i,c} = (2 - \Phi_i)(1.0 + 0.054\lambda_i - 0.0988\lambda_i^2 + 0.441\lambda_i^3) \quad (\text{Equation 3.11})$$

where Φ_i (partition coefficient) is the ratio of the average intra-pore concentration to that of the bulk solution at equilibrium. When the interactions between the solute and pore wall are purely steric, this may be further approximated as follows:

$$\Phi_i = (1 - \lambda_i)^2 \quad (\text{Equation 3.12})$$

Neglecting the effect of concentration polarisation ($C_{m,i} = C_{i,f}$) and integrating equation 3.9 across the thickness of the membrane ($0 < x < \Delta x$) with the boundary conditions that $c_{i,x=0} = \Phi_i C_f$ and $c_{i,x=\Delta x} = \Phi_i C_p$ gives an expression for rejection as a function of pore size (d_p) as follows:

$$R_i = 1 - \frac{\Phi_i K_{i,c}}{1 - [1 - \Phi_i K_{i,c}] \exp(-P_{i,e})} \quad (\text{Equation 3.13})$$

where the Peclet number ($P_{i,e}$) is defined as follows:

$$P_{i,e} = \frac{K_{i,c}}{K_{i,d} D_{i,\infty}} \left(\frac{r_p^2 \Delta P}{8\mu} \right) \quad (\text{Equation 3.14})$$

and the diffusion coefficient of the solutes in the bulk solvent ($D_{i,\infty}$) was determined using the Wilke-Chang equation [146]:

$$D_{i,\infty} = 7.4 \times 10^{-8} (\phi \cdot M_{i,W})^{0.5} \frac{T}{\mu_o V_i^{0.6}} \quad (\text{Equation 3.15})$$

with the solute molar volume (V_i) at the boiling point determined using a group contribution method as presented by Geankopolis [147].

In cases where pore diameters are significantly smaller ($d_p \approx d_{\text{solvent}}$), pore viscosities are calculated to be significantly higher than the bulk values, thus necessitating a correction factor [143]. This is given by the following equation:

$$\frac{\mu}{\mu_o} = 1 + 18 \left(\frac{d_{\text{solvent}}}{d_p} \right) - 9 \left(\frac{d_{\text{solvent}}}{d_p} \right)^2 \quad (\text{Equation 3.16})$$

As the log-normal distribution is integrated from 0 to $+\infty$, large pores can have a significant effect on the pore-wise rejection. A truncated distribution was used to limit the ‘tail’ effects by normalising the probability density function f_R and integrating from 0 to $d_{\max}$ [142] (Equation 3.17), where values of $d_{\max}$ were kept at $d_{\max}=2\overline{d_p}$.

$$\frac{f_R}{f_R'} = \frac{1}{\int_0^{d_{\max}} f_R d(dp)} \quad (\text{Equation 3.17})$$

The calculated rejection, R_i^{cal} is obtained by integration of the pore-wise rejection [148]:

$$R_i^{\text{cal}} = \frac{\int_0^{d_{\max}} [f_R' d_p^4 R_i / \mu] d(dp)}{\int_0^{d_{\max}} [f_R' d_p^4 / \mu] d(dp)} \quad (\text{Equation 3.18})$$

Estimation of $\overline{d_p}$ and σ_p were obtained by fitting the calculated rejections for each solute R_i^{cal} to the experimentally determined values of R_i^{exp} for each membrane and solving equations 3.4, 3.13, 3.16 and 3.18 using gPROMs (PSE Ltd., UK.). The solute diameters ($d_{i,s}$) can be determined from the Stokes-Einstein equation [52]:

$$d_{i,s} = \frac{kT}{6\pi\mu D_{i,\infty}} \quad (\text{Equation 3.19})$$

The estimation of $\overline{d_p}$ and σ_p for membranes before and after being subjected to wet drying are presented in Table 3.3. Gibbins et al. calculated $\overline{d_p}$ of StarmemTM 122 membrane at approximately 0.6 nm using several different pore models. Here, the $\overline{d_p}$ for StarmemTM 122 and M2 stored in IPA (M2 has a similar MWCO curve to ST122) are estimated to be 0.77 and 0.63 nm respectively. Table 3.3 summarises the mean pore size and standard deviation for water and/or solvents wetted ST122, M2, M3, M4 and M5 membranes before and after being subjected to air-drying.

Table 3.3: Mean pore size and standard deviation for water and/or solvents (e.g. toluene and IPA) wetted ST122 , M2, M3, M4 and M5 membranes before and after being subjected to air-drying based on measured solute rejection data.

Entry	Membrane	Drying method	Solute type	Solvent tested	Pressure (bar)	Hydrodynamic model	
						Mean pore size, $\overline{d_p}$ (nm)	Standard deviation, σ_p
1	Starmem TM 122	Mineral oil	Alkanes	Toluene	30	0.77	0.45
2	Starmem TM 122	Air-drying, toluene wetted	Alkanes	Toluene	30	0.85	0.31
3	M2	Stored in IPA	Alkanes	Toluene	30	0.63	0.41
4	M2	Air-drying, IPA wetted	Alkanes	Toluene	30	0.81	0.27
5	M2	Air-drying, water wetted	Alkanes	Toluene	30	1.16	0.32
6	M3	Stored in IPA	Alkanes	Toluene	30	1.04	0.71
7	M3	Air-drying, IPA wetted	Alkanes	Toluene	30	0.92	0.32
8	M4	Stored in IPA	High MW polystyrene	Toluene	2	4.32	3.35
9	M4	Air-drying, IPA wetted	High MW polystyrene	Toluene	2	2.87	1.09
10	M5	Stored in IPA	Low MW polystyrene	Toluene	30	1.17	0.36
11	M5	Air-drying, IPA wetted	Low MW polystyrene	Toluene	30	1.09	0.32

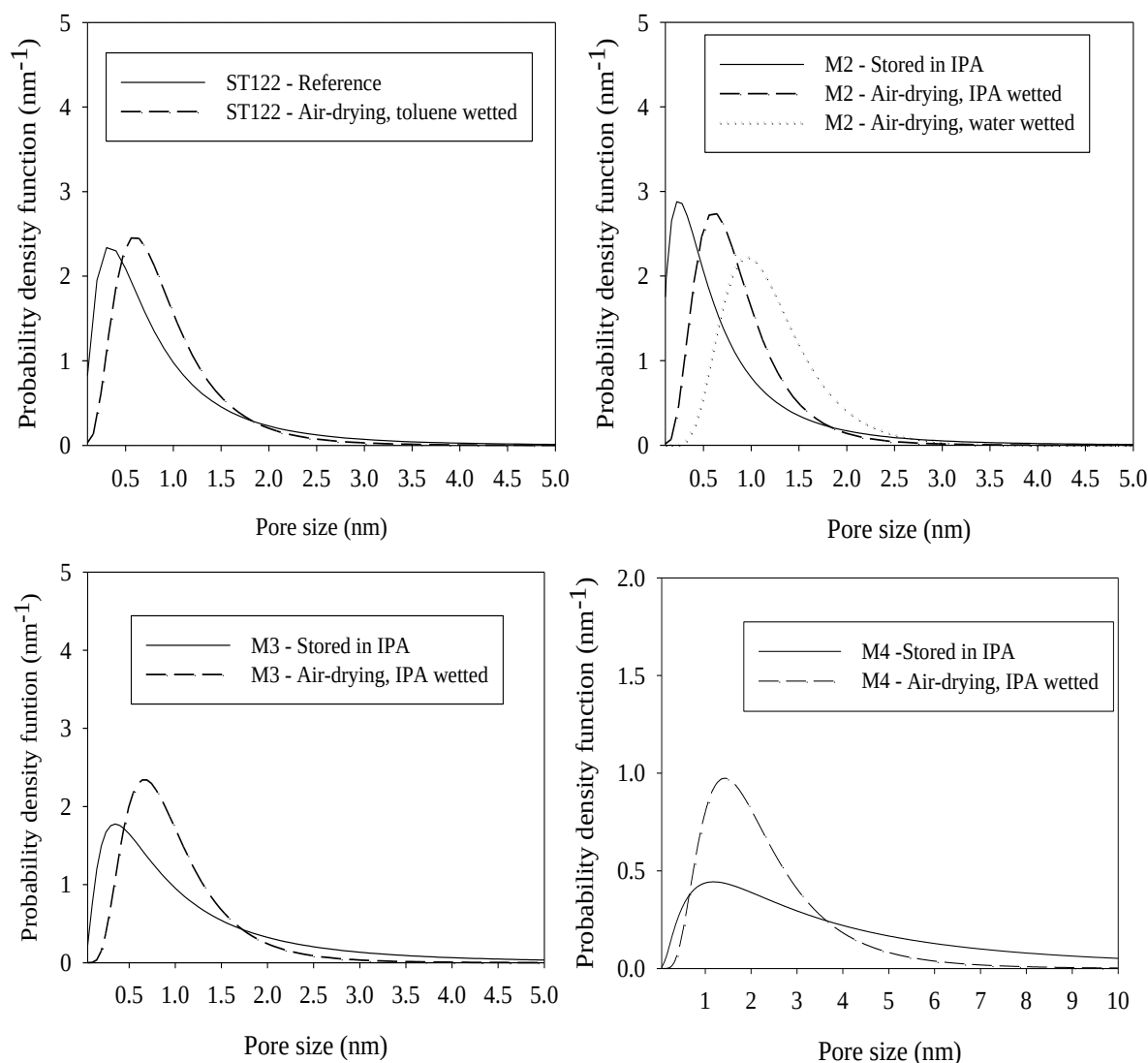


Figure 3.18: Probability density function curves for pore size of Starmem™ 122, M2, M3 and M4 membranes, before and after being subjected to air-drying with different wetting agents.

Figure 3.18 presents the probability density function curves for pore sizes of the Starmem™ 122, M2, M3 and M4 membranes before and after subjected to air-drying with different wetting agents. The figure shows that in general the pore size distribution shifts to the right when they are subjected to air-drying with toluene, water and IPA as wetting agents. These results are consistent with the theory derived earlier, where the smaller pores collapse during air drying. Interestingly however, the σ_p of IPA wetted M3 (loose NF) and M4 (UF) membranes also reduces significantly upon air-drying (i.e. the fraction of large pores

decreases), suggesting that the pore size distributions are subtly more narrow (see Figure 3.18). This loss of larger pores in the looser membranes explains the observed reverse behaviour of the MWCO curves measured for the tight NF (StarmemTM 122 and M2) membranes and the loose NF/UF membranes (M3 and M4) upon air-drying in section 3.4.1. Staude et al. [137] also reported similar observations of a positive shift in the MWCO curve of partially dried water wetted polysulfone UF membranes upon air-drying, by suggesting the loss of larger pores in the separating layer. However, the lack of information of how the pore size measurement and distribution was studied by Staude et al. [137] has led to the suggestion of loss of larger pores in the separating layer being disputed. Nevertheless, these observations (by Staude et al. [137] and in this work) do indicate that there is a reduction in the ratio of bigger pores to total number of pores in the separating layer. The limitations of the available technologies and techniques for selectively measuring the porosity of the selective top layer of the membrane does not currently allow a better insight to be made into the relationship between the observed change in pore size distribution of the top layer and the measured solvent flux drop.

3.4.3 Effect of crosslinking on the impact of air-drying on wetted membranes

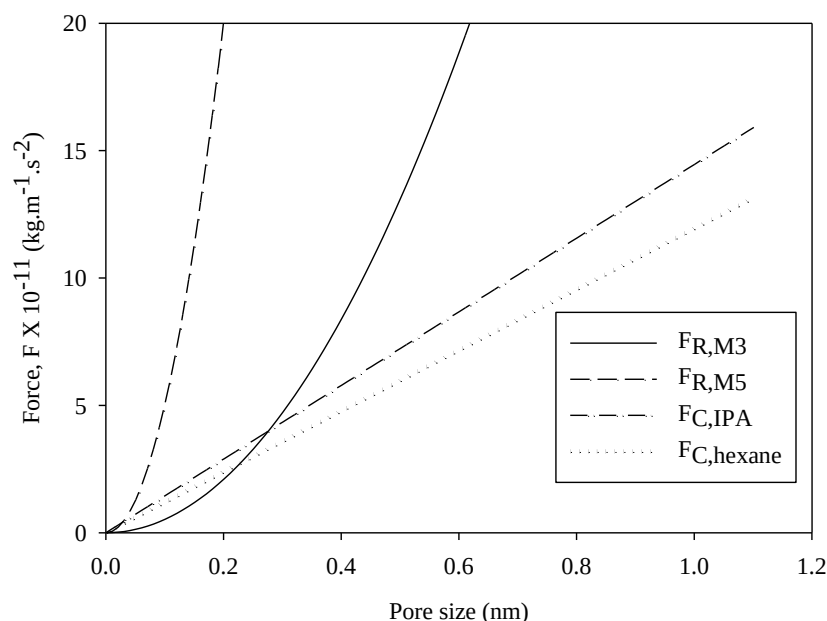


Figure 3.19: Relationship between F_R of M3 and M4, and F_c with IPA and hexane as wetting agents as a function of pore size.

In principal, crosslinking by introducing intermolecular bonds between the polymer chains may also be able to overcome the changes observed on water or IPA wetted membranes upon air-drying. For instance, a marked increase in the tensile modulus from 0.45 GPa (M3) to 4.21 GPa was measured for chemically crosslinked M5 membrane. Figure 3.19 presents the calculated relationship between the F_R of M3 and M5 and F_c with IPA and hexane as wetting agents, as a function of pore size. The profiles suggest that air-drying should have an insignificant ‘pore collapsing’ effect on IPA and hexane wetted M5, since $F_R \geq F_c$ for all pore sizes.

Figures 3.20 and 3.21 present the effect of air-drying on IPA and hexane wetted M5 membrane, based on their experimentally determined functional performance. Whilst Figure 3.22 shows the probability density function curves for the pore size distribution of M5 before and after being subjected to air-drying with IPA as the wetting agent. As predicted, no

changes in the MWCO were measured upon air-drying of IPA and hexane wetted M5. Similarly, the pore size distribution of the separating layer remained unchanged. However, a decrease in solvent flux (43% in DMF and 51% in toluene) was observed. This suggests that the fluxes of both the solute and solvent are reduced at the same rate, so that while the overall flux decreases the rejection remains constant. Concomitantly, an evident bulk porosity change upon air-drying of IPA and hexane wetted M5 was measured, but the porosity loss is relatively lower than M3 (see Table 3.2). This indicates that the separating layer of an IPA/hexane wetted M5 remain unaffected by air-drying due to the improved resistance of the closely packed polymer chains which are held together by the crosslinks. Whereas, the less densely packed sub-layer had more opportunity to rearrange to a thermodynamically favourable state and subsequently reduces both solute and solvent flux at the same rate.

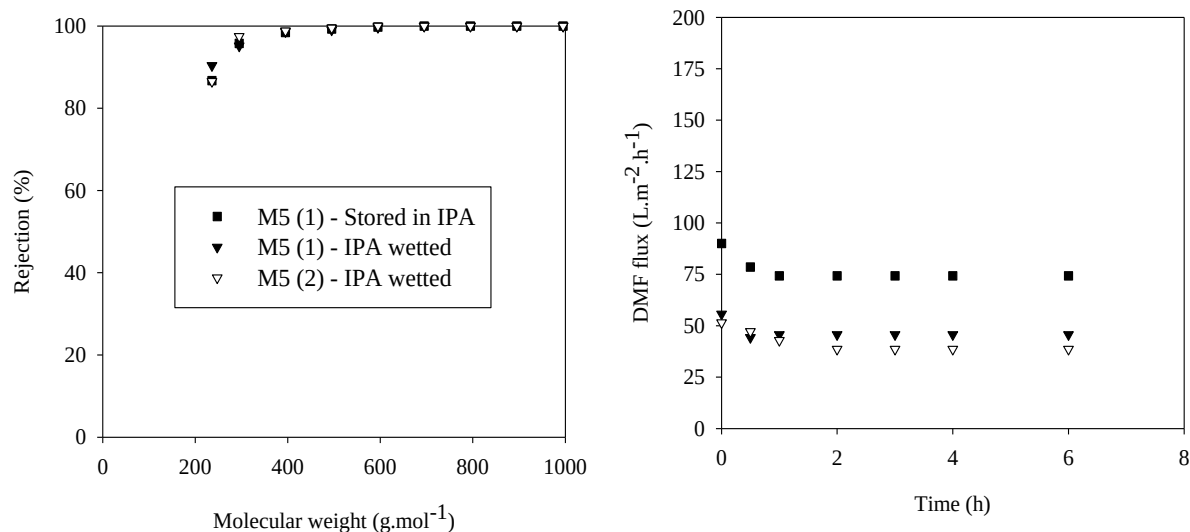


Figure 3.20: Comparison of (A) MWCO and (B) DMF flux of the M5 membrane at 30 bar and 30 °C, before and after air-drying with IPA as wetting agent.

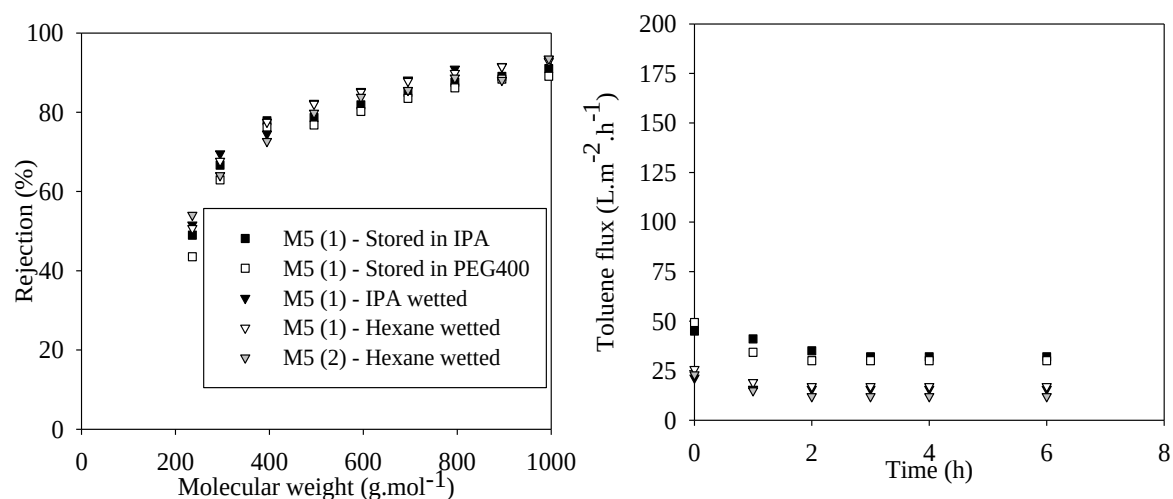


Figure 3.21: Comparison of (A) MWCO and (B) toluene flux of M5 membranes at 30 bar and 30 °C, before and after air-drying with IPA and hexane as wetting agent.

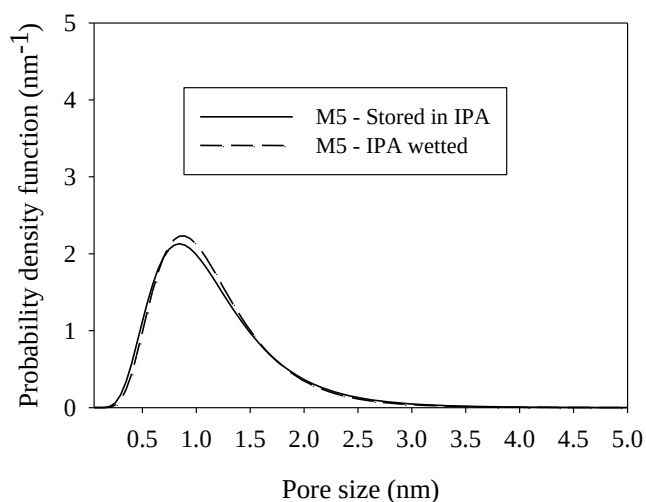


Figure 3.22: Probability density function curves for pore size of M5, before and after being subjected to air-drying with IPA as wetting agent.

3.4.4 Summary

Based on the results obtained in sections 3.4.1 to 3.4.3, it is postulated that two phenomena may occur during air-drying with water and solvents (e.g. toluene, IPA and hexane) wetted pores of integrally skinned asymmetric NF and UF membranes:

- (i) Collapse of smaller pores in the thin separating layer due to high capillary forces. This is dependent on three main factors, (a) pore size distribution of the membrane, (b)

strength of the capillary force (F_c) induced by the wetting agent, and (c) strength of the deformation force (F_R) induced by the membrane

- (ii) The rearrangement of polymer chains to a thermodynamically more stable state in the separating and sub-layer. This phenomenon is more pronounced for the M3 and M4 membranes due to the instantaneous demixing during the phase inversion process in membrane formation [11] (i.e. where the polymer structure is frozen in a thermodynamically unstable state with a high fraction of free volume [1]). The energy for the polymer chains to rearrange to a more stable state (i.e. lower free volume) is believed to be provided by the capillary force induced by the solvent in the pore. This is validated by the porosity loss measured upon air-drying (in Table 3.2) on the IPA/water wetted membranes, which is mainly contributed to by the relatively thick and porous sub-layer.

3.4.5 Preserving agent

Air-drying of water and solvents wetted membranes has been shown to impose a detrimental effect on membrane performance. Even introducing intermolecular bonding between the polymer chains via chemical crosslinking does not limit the degree of reorganisation of the polymer chains to their thermodynamically favoured structure. Furthermore, this technique also gives a rather brittle membrane without handling characteristics. Handling is a ‘must’ requirement for a production scale membrane. In this section, several preserving agents will be screened for their suitability to:

- (i) preserve the membrane performance formed after phase inversion, and
- (ii) provide good handling properties.

Material selection

A preserving agent must be readily absorbed into the membrane and also readily removed. In addition to this, a preserving agent must have low vapour pressure and un-reactive sites to facilitate long term storage. Several preserving agents have been reported in the literature and in data for commercial OSN membranes, including lube oil in StarmemTM membranes [13] and glycerol for RO cellulose acetate membranes [72]. Table 3.4 lists the types of preserving agents and their properties used in this study.

Table 3.4: Properties of preserving agents used in this study.

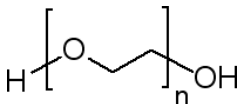
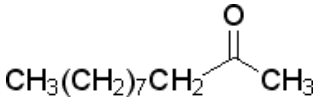
Preserving agent	Chemical structure	Molecular weight (g.mol ⁻¹)	Vapour pressure (mm Hg)
Mineral oil	Alkanes	Not known	< 0.5
PEG 400		380 - 420	Not known
Undecanone		170	< 1

Table 3.5: Effect of preserving agents on the physical property of M3 and M5 membranes.

Membrane	Preserving agent	Observation	^a Loading (g.m ⁻²)
M3 and M5	No preserving agent, in water or post processing solvent(s)	Membrane remains flat in solvent(s).	-
M3 and M5	No preserving agent, wet dried	Membrane is dried but curls into a roll towards surface.	-
M3	Mineral oil	Membrane is dried and remains flat.	50 ± 5
M5	Mineral oil	Membrane is dried and curls slightly towards surface.	32 ± 7
M3	PEG 400	Membrane is dried and remains flat.	49 ± 4
M5	PEG 400	Membrane is dried and remains flat.	52 ± 5
M5	Undecanone	Membrane is dried and remains flat.	54 ± 9

^a Membranes were impregnated with preserving agent by soaking in 40 vol% of preserving agent in solvent(s) for 24 hours. IPA and MEK were used for PEG400/undecanone and mineral oil respectively.

Table 3.5 shows the suitability of different preserving agents for M3 and M5 membranes. Both mineral oil and PEG 400 were observed to be good preserving agents for M3, allowing the membranes to be handled in a ‘dry’ state. For the M5 membrane, all three preserving agents allow a ‘dry’ membrane to be made, however some curling is observed for the mineral oil preserved membrane. The curling of M5 membrane preserved with mineral oil may be due to lower mineral oil loading in this membrane, believed to be due to the low affinity of M5 with hydrocarbons like hexane. Table 3.6 summarises the affinity of M3 and M4 membranes to MEK, isopropanol and hexane by measuring the mass gained at steady state. These solvents were chosen for the affinity measurements, as they contain similar chemical structure/functional groups to the preserving agents and thus were used as analogues of the preserving agents in the affinity measurements due to their volatility. Furthermore, to eliminate any effect of the MW of the compounds in the measurements [22,85], solvents with similar MW were used.

Table 3.6: Affinities of M3 and M5 membranes to different types of solvents, measured by DVS.

Solvent	Weight gained at steady state (%)	
	M3	M5 (After crosslinking)
Hexane	38	10
IPA	22	32
MEK	33	37

Effect on the functional performance

Figure 3.23 shows the effect of different preserving agents on the performance of M5 membranes. Of the different polar preserving agents (PEG 400 and undecanone) there was little difference between membranes preserved with them or stored in IPA, in terms of their MWCO curves and DMF flux. On the other hand, the MWCO of the M5 membrane impregnated with mineral oil shifted to higher MW and provided a lower DMF flux compared to the reference membrane stored in IPA. However, prewashing the M5 membrane impregnated with mineral oil with toluene provided MWCO curves that were consistent with the reference membrane, however the DMF flux remained unaltered at $25 - 27 \text{ L.m}^{-2}.\text{h}^{-1}$ (see Figure 3.24) versus the reference membrane flux of $65 \text{ L.m}^{-2}.\text{h}^{-1}$ (Figure 3.23B). These observations may be attributed to the limited solubility of mineral oil in DMF (measured solubility of mineral oil in DMF and toluene = 0.9 g.L^{-1} and $> 500 \text{ g.L}^{-1}$ respectively, and the solubility of PEG400/undecanone in DMF $> 500 \text{ g.L}^{-1}$), where mineral oil may still be present in the smaller pores during the testing. Due to the nature of the M5 membrane, mineral oil does not impregnate into the membrane well. This is likely to lead to collapse of pores in the sub-layer and may be difficult to flush the mineral oil from the membrane, leaving smaller pores blocked. This generates the observed negative impact on flux and rejection performance. These results demonstrate that proper washing of the membrane is essential to achieve full performance of the membranes.

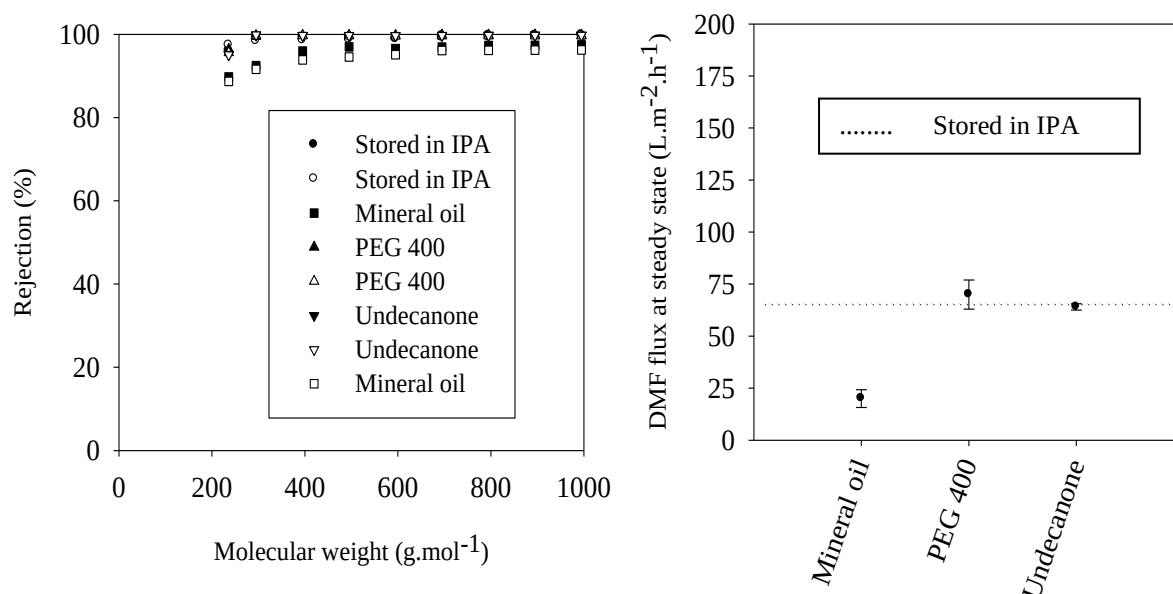


Figure 3.23: Comparison of (A) MWCO and (B) DMF flux (at steady state, filtration time at 24 hours) of M5 membranes impregnated with different types of preserving agents and pre-conditioned with DMF, at 30 bar and 30 °C.

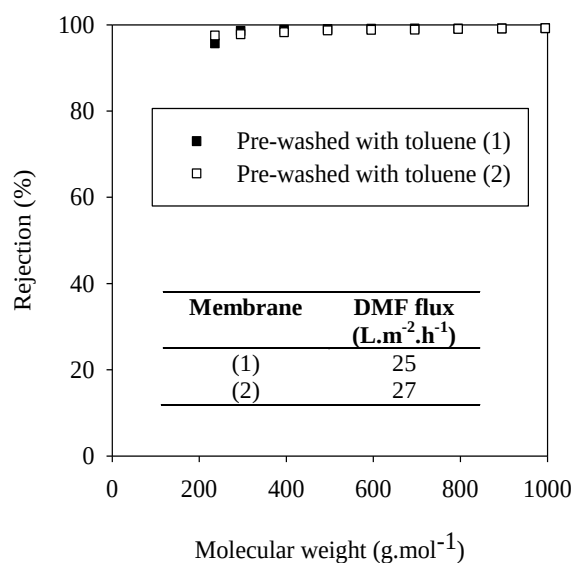


Figure 3.24: Comparison of (A) MWCO and (B) DMF flux (at steady state, filtration time at 24 hours) of M5 membranes impregnated with mineral oil and pre-conditioned with toluene, at 30 bar and 30 °C.

Kinetics

Both PEG 400 and undecanone were found to preserve the functional performance of M5 membranes, in terms of both MWCO and solvent flux. Based on the measured volume (60–

77 cm³.m⁻²) and porosity (45–53%) of the M5 membrane, and the instantaneous PEG 400 loading (13-18 cm³.m⁻²) into the non woven support, the minimum and maximum threshold of PEG 400 in M5 were calculated to be 45 and 66 g.m⁻² respectively. Figure 3.25 demonstrates the kinetics of PEG 400 impregnated into M5 as a function of time (t) and concentration of PEG 400 in the preserving solution (C_{PEG}). Figure 3.26 presents the performance of M5 at a range of PEG 400 loading, in comparison to membrane stored in IPA.

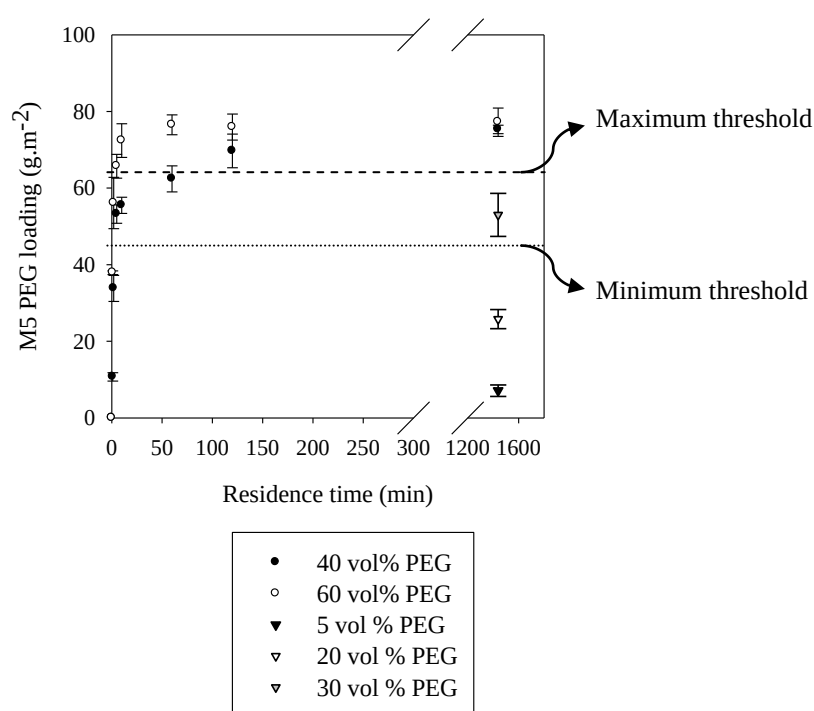


Figure 3.25: M5 PEG 400 loading as a function of (A) PEG 400 concentration in IPA and (B) time.

The quantity of PEG 400 impregnated into the M5 membrane can be controlled by the concentration of PEG 400 in the preserving solution and residence time. A minimum concentration of 30 vol% of PEG is required at a residence time of 24 hours to reach the threshold limits. Concomitantly, a minimum residence time of 5 and 2 minutes in 40 and 60 vol% of PEG would provide membranes with PEG loading within the threshold values. Figure 3.26 presents the MWCO curves and DMF flux of M5 membranes impregnated with

different PEG400 loading. The MWCO curves of M5 are independent from PEG loading. However, the flux profiles measured were closely related to PEG loading. Membranes with PEG loading (7 and 26 g.m^{-2}) below the threshold limits present a consistent DMF flux throughout the testing period up to 50 hours, but only measured approximately 67 - 74 % of the DMF flux of the control membrane (M5 stored in IPA) at steady state. Based on the study in section 3.4.1, the rearrangement of the polymer chains not filled with PEG 400 may contribute to the lower DMF flux. Advantageously, minimal compaction was measured with these membranes, 0% and 9% for membranes with PEG400 loading of 7 g.m^{-2} and 26 g.m^{-2} respectively. In comparison, membranes with PEG400 loading above the threshold measured more than 30% compaction. The flux profile of membrane with loading of 53 g.m^{-2} (within the threshold limit) follows the control membrane closely, whilst membrane with loading of 75 g.m^{-2} (above the threshold limit) has a much higher initial DMF flux and reached similar DMF flux to the control membrane at steady state. There is no clear reason behind this observation, however it is postulated that it may be due to the variation in membrane formation.

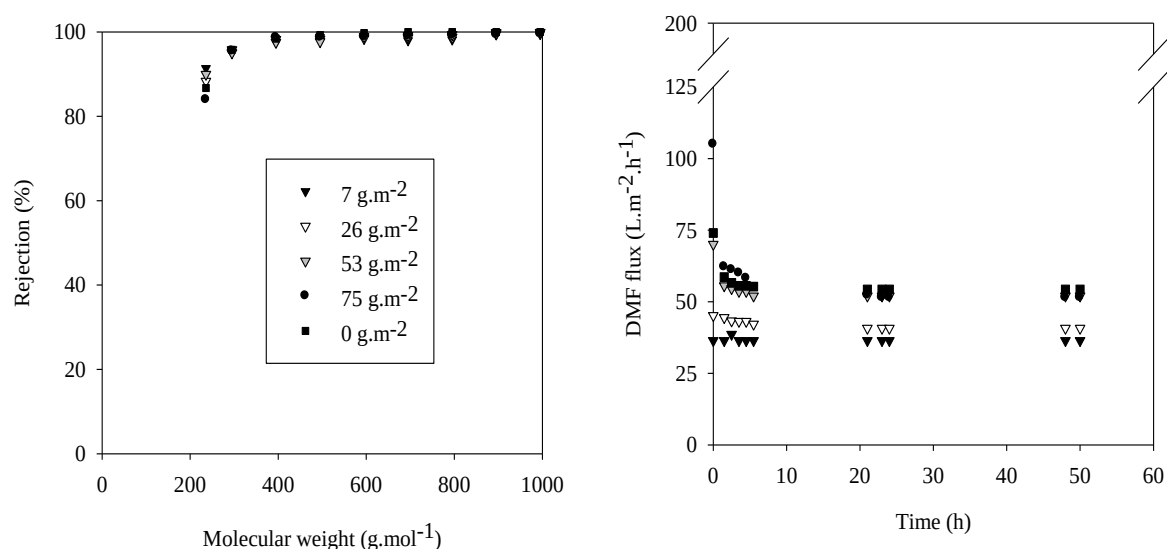


Figure 3.26: Comparison of (A) MWCO and (B) DMF flux of M5 membranes with a range of PEG 400 loading, at 30 bar and 30 °C. (Membrane with 0 g.m⁻² of PEG 400, was stored in IPA prior to testing.)

Table 3.7: Observation and handling properties of M5 membranes with different PEG 400 loading.

PEG loading (g.m ⁻²)	Observation	Handling properties
7	Pale surface and curling significantly towards surface.	Extremely difficult
26	Pale surface and curling slightly towards surface.	Difficult
53	Shinny surface and remains flat.	Good and flexible
75	Shinny surface and remains flat, a layer of PEG observed on the surface.	Good and flexible

Besides performance, the handling and storage properties of the membrane are equally important. Table 3.7 summarises the observations on handling properties of M5 membrane at different PEG 400 loadings. PEG loading within or above the threshold limits present membranes with good handling properties for remaining flat in the ‘dry’ state and being flexible (not brittle). PEG 400 is shown to be suitable for chemically crosslinked PI membranes, particularly due to the solubility of PEG 400 in most application solvents of relevance for this membrane [149] (e.g. polar solvents and polar aprotic solvents).

3.4.6 Effect of thermal annealing

Thermal annealing is often adapted to improve performance of PI gas separation [78,79] and pervaporation membranes [76,77] through densification of the membrane films to remove defects and suppress plasticisation. This usually results in increased selectivity at the expense of permeability. A decrease in solvent flux was also reported with OSN membranes made from P84 polyimide when annealed at 100-200 °C, whilst the MWCO curves remain largely unaltered [32]. In these cases, the observation has been attributed to the reorganisation of the polymer chains at elevated temperatures to thermodynamically favoured structures and the simultaneous densification of the membranes.

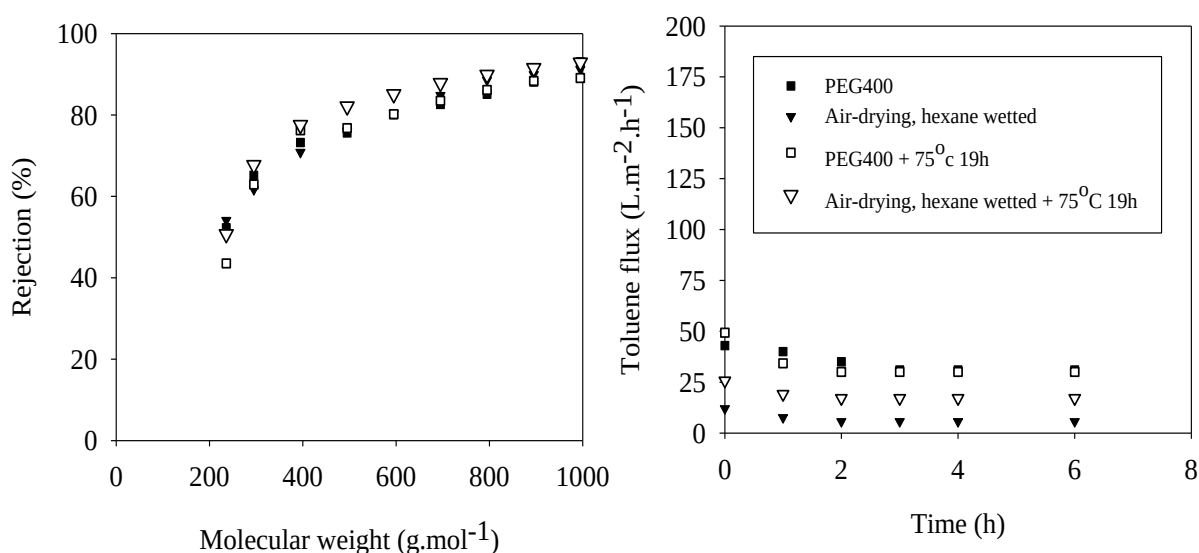


Figure 3.27: Effect of thermal annealing at 75 °C for 19 hours on the (A) MWCO and (B) toluene flux of M5 membranes preserved with PEG400 and undergone air-drying with hexane as wetting agent, at 30 bar and 30 °C.

Figure 3.27 shows the comparison of MWCO and toluene flux of M5 membranes that have undergone different drying procedures, (i) preserved with PEG400 and (ii) air-dried with hexane as the wetting agent, before and after annealing at 75°C for 19 hours. Membrane preserved with PEG 400 shows no performance changes after thermal annealing. Whereas,

the solvent flux of membrane that was air-dried with hexane as wetting agent decreased further, whilst retaining its MWCO curve. This suggest that the pore size distribution in the separating layer remain unaltered but the polymer chains had undergone further reorganisation to a more favourable state using the energy provided during thermal annealing. Ebert et al. [135] demonstrated using a porometer a change in the pore size distribution upon thermal annealing of a blend polyamide imide with titanium dioxide membrane (subjected to air-drying with water as the wetting agent) , where a loss of larger pores was measured with increasing temperature. Concomitantly, a drop in solvent permeability was measured [135]. In this work, the bulk porosity measurement of the membranes before and after thermal annealing also indicates the loss of pores (refer to Table 3.2) but there is inadequate data to identify which pore sizes are predominantly affected.

3.4.7 Performance between and within batches

A good product must also have low variations between and within batches. In a production plant, the consistency of a product is screened by testing random membrane sheets across several batches [123]. Figure 3.28 shows the position of samples taken for testing from a single batch of membrane to determine the batch variability (each batch is 70 m long). Table 3.8 lists the membrane types and batch analysed.

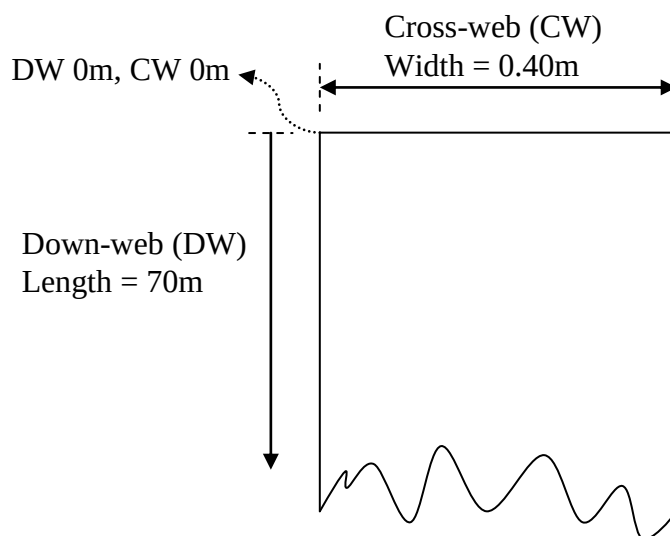


Figure 3.28: Schematic of samples taken from membrane sheet for testing.

Table 3.8: List of membrane type and their batch number, with the variability measured in solvent flux within and between batches.

Membrane type	Crosslinked (Y/N)	Preserving agent	Batch no.	^a Solvent flux ($\text{L.m}^{-2}.\text{h}^{-1}$)	
				Average flux	Standard deviation
M2	N	PEG 400	001	38	17
M5	Y	PEG 400	002	41	7
M5	Y	PEG 400	003	38	5

^a Toluene and acetone were used to characterise M3 and M5 membranes respectively. These solvents were selected based on the chemical stability of the membranes, where M3 is not stable in acetone.

Significant variation in both MWCO curves (Figure 3.29) and solvent flux (Table 3.8) were observed with the M2 membrane. This is often reported for gas separation polymeric membranes prepared via phase inversion, where a highly permeable layer (e.g. silicone rubber) coated on the surface is used to reduce the impact [150,151]. However, variations in MWCO (Figure 3.30) were reduced significantly for the chemically crosslinked P84 membranes (M5). All tested discs exhibited similar solvent flux, with a standard deviation of $5 - 7 \text{ L.m}^{-2}.\text{h}^{-1}$. Low variability was measured for M5 membrane performance between batches (refer to Figures 3.30 and 3.31). This result demonstrates that crosslinking not only

improves the chemical stability of these membranes in harsh solvent environments, but also reduces the impact of membrane production variation. Pinnau and Wind [152] have previously described how the exposure of polyetherimide membranes to organic solvents may enlarge or reduce the effective membrane pore size and result in changes to membrane rejection performance. In this instance, the chemical crosslinking may have reduced swelling of membranes in organic solvents, and effectively narrowed the distribution of pore sizes within the membrane batch, thus providing a more repeatable solvent flux.

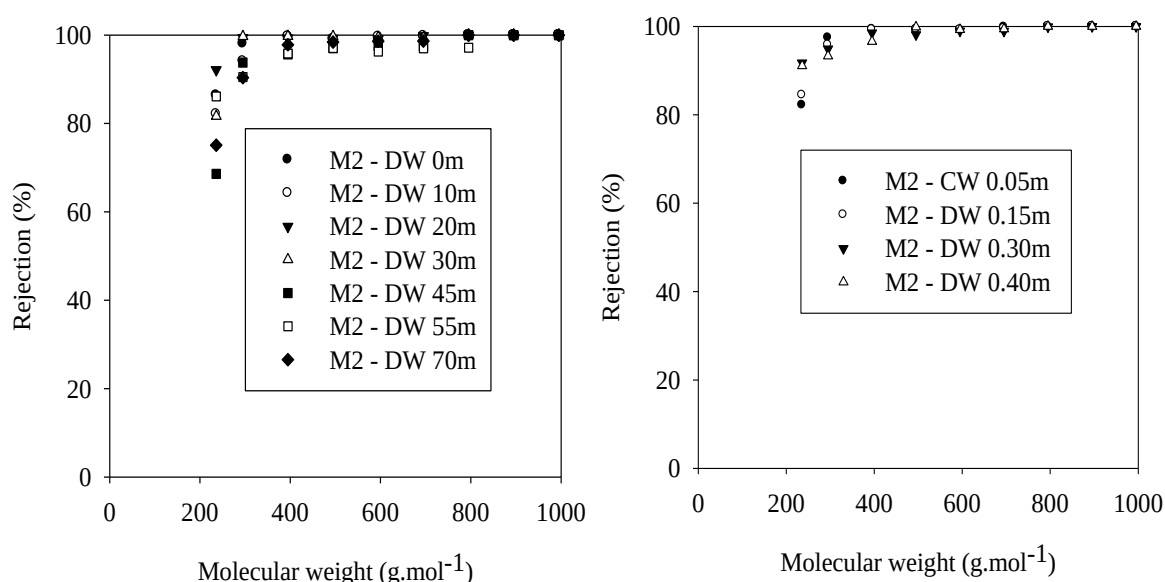


Figure 3.29: Performance of M2 membrane (Batch-001) in toluene. DW and CW membranes were sampled at CW 0.20m and DW 35m respectively.

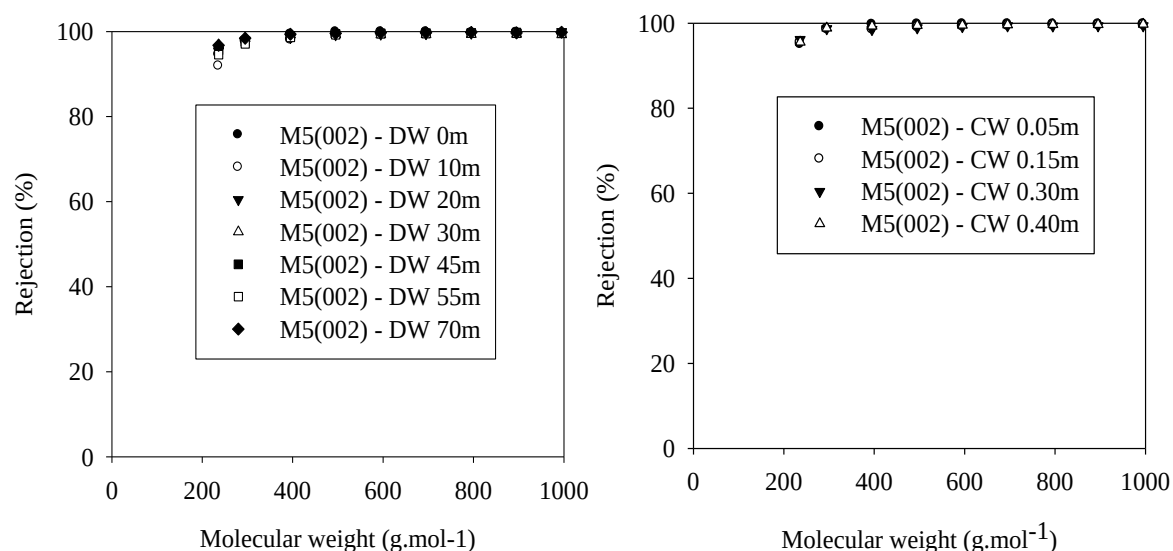


Figure 3.30: Performance of M5 membrane (Batch-002) in acetone. DW and CW membranes were sampled at CW 0.20m and DW 35m respectively.

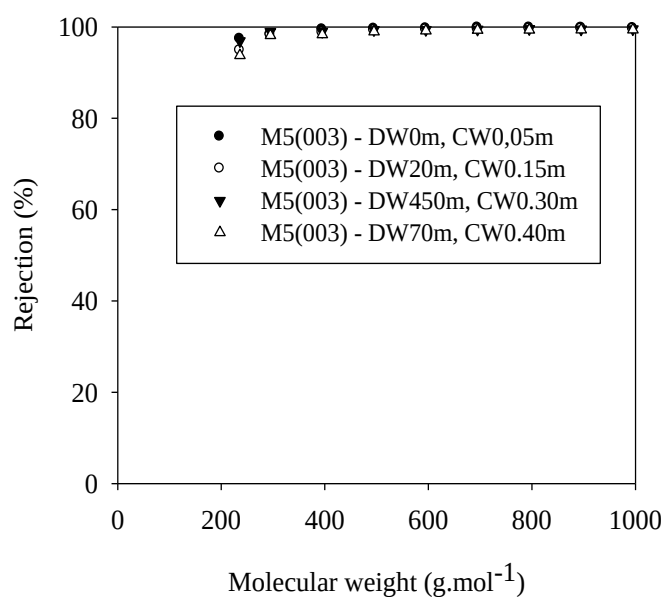


Figure 3.31: Performance of M5 membrane (Batch-003) in acetone.

3.5 Conclusion

In this chapter, the effects of air-drying of water and/or solvents wetted P84 and chemically crosslinked P84 OSN membranes on their functional properties were demonstrated. The following conclusions may be drawn from the presented results:

- Air-drying of water and/or solvents wetted membranes imposes detrimental effects on the solvent flux and porosity of both P84 and chemically crosslinked P84 OSN membranes.
- Changes in the MWCO curves upon air-drying of wetted membranes is dependent on intrinsic membrane parameters such as structure (e.g. morphology and porosity) and pore size distribution, as well as the capillary forces induced by the wetting agents.
- Upon air-drying, the MWCO curves of tight P84 NF membranes were observed to shift towards lower MWCO, whereas the MWCO curves of loose P84 NF and UF membranes were observed to shift towards higher MWCO.
- Through chemical crosslinking, the wetted membrane is less susceptible to air-drying, and the MWCO remains unaltered.
- It is difficult to ascertain the factors behind the observed behaviour for both P84 and chemically crosslinked P84 membranes using the currently available imaging technologies and techniques. The results imply that two phenomenon may be occurring during air-drying: (i) collapse of smaller pores in the separating layer and, (ii) the rearrangement of the unstable polymer chains in the separating layer and sub-layer to a thermodynamically favoured structure.
- The above summary suggests that care must be taken to preserve the membrane performance formed during phase inversion.
- Impregnating the membranes with the correct preserving agent provides a method for maintaining membrane performance. PEG 400 and undecanone were found to be suitable for crosslinked P84 membranes, whereas mineral oil was not appropriate for these membranes.

- Chemical properties (e.g. hydrophilicity, solubility) of the preserving agent and chemical interaction between the preserving agent and the membrane are factors that need to be considered for easy impregnation into and removal from the membrane.
- Improper removal of the preserving agent prior to testing will lead to undesirable membrane performance.
- The solvent flux across an air-dried wetted membrane was further reduced upon thermal annealing. There was no such effect for a membrane preserved with PEG400.
- The impact of variability in membrane performance can be adequately reduced through post formation chemical crosslinking. This is thought to be due to the ability of the chemically modified polymer to swell in organic solvents.

Chapter 4

Design of epoxy adhesive formulation for OSN

4.1 Abstract

This chapter address a key aspect in the scale up of the second generation PI membrane developed in chapter 3 to a spiral wound membrane module (see section 4.2), i.e. adhesives. Here, the effects of changing various formulation parameters in epoxy – amine adhesives on their stability in a range of organic solvents are reported. These include varying the type of epoxy resin, the resin functionality, type of amines used and their reactivity, the molar equivalence between reactive groups – epoxides and amines, and blending various types of fillers (nano sized and micro particulates) into the epoxy – amine adhesives. Of the various formulation parameters, the stability of the epoxy – amine adhesives seems to be most affected by the introduction of unreactive micro particulates (silica) into the system, which act as a filler to modify the free volume in the crosslinked matrix. Based on the knowledge gained from this work, the best epoxy – amine adhesive model formulated here showed good stability in all solvents tested including hexane, toluene, methanol, ethanol, acetone, THF, DMF, NMP, DCM and water for a period of over 140 days, whilst maintaining good adhesion and providing leak free seals. Furthermore, it is also suitable for use in regulated industries since $< 0.05\%$ extractables or leachables were measured with key industrial solvents, where all components are compliant to FDA 21 CFR.

4.2 Introduction

In practical applications, membranes are generally not used in their cast form; rather they are incorporated into membrane modules. The design of membrane modules is tailored to provide a relatively high surface area of membrane per unit volume of feed solution, to make a compact separation process. Common polymeric membrane module formats are plate-and-frame and spiral-wound for polymeric membranes cast in sheet format, and hollow fibre modules for polymeric membranes cast in tubular form [1,9,153]. Table 4.1 summarises the typical characteristics of the various membrane module designs. Hollow-fibre membranes are clearly superior in terms of packing density and do not require the use of backing material in membrane formation. However, they are highly susceptible to fouling, as well as physical deformation at high operating pressures (≥ 10 bar). Plate and frame designs are used in instances where fouling is critical, due to the ease of cleaning, but these units are expensive compared to alternatives and leaks through the gaskets required for each plate are a serious problem. At present the predominant design for most industrial applications is the spiral wound membrane module, because of their low cost and reasonable resistance to fouling.

Table 4.1: Typical characteristics of various membrane module designs (adapted from [1,9,153]).

Module design	Plate and frame	Spiral wound	Hollow-fibre
Packing density ($\text{m}^2 \cdot \text{m}^{-3}$)	30 to 500	200 to 800	500 to 9000
Resistance to fouling	Good	Moderate	Poor
Ease of cleaning	Good	Moderate	Poor
Relative cost	High	Low	Low

The schematic of a spiral wound module is shown in Figure 4.1. Multi envelope designs are usually employed to minimise the pressure drop encountered by the permeate fluid travelling towards the central pipe. In addition, the end of each module is fitted with an anti-telescoping device (ATD) which is designed to prevent the module leaves shifting under the pressure

required to force feed fluid through the module. Other aspects of a spiral wound module that are important are that they provide a means of (i) protecting the membrane from damage during transport and handling, and (ii) directing the process flow(s) over the membrane surfaces. To fulfil these requirements, a spiral wound module contains several components including the permeate spacer, feed spacer, end-cap (an ATD) and perforated tube (as depicted in Figure 4.1), which can be fabricated from different types of materials and must be attached together using adhesives. Ultrasonic welding can also be used to attach multiple permeate flow channels to a perforated tube [154]. However, the application of adhesives is still necessary to seal the membrane envelopes.

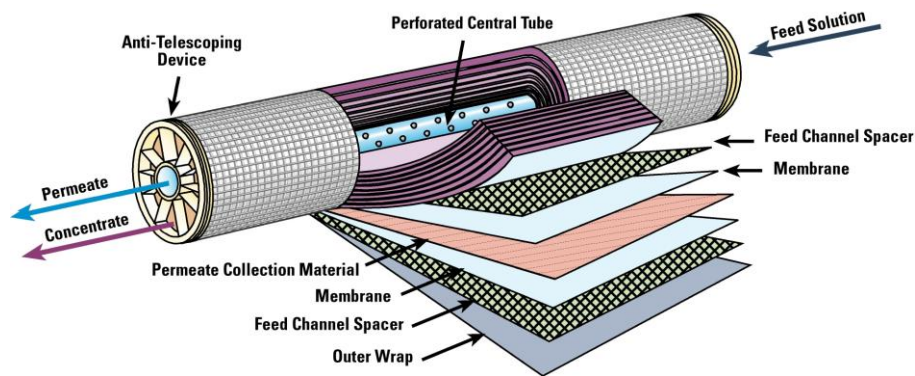


Figure 4.1: Schematic of the spiral wound module design (adapted from [153]).

A suitable adhesive for fabricating a spiral wound module for OSN has to provide a number of properties: (i) it must be resistant to the chemical environment in which it will be used [155]; (ii) it must be of a viscosity that allows it to be dispensed easily when forming glue lines during the fabrication process [156,157]; (iii) it must not swell to an extent that will damage the membrane module [155]; (iv) it must have a pot life (the time that it takes for the adhesive to cure sufficiently to be unworkable) greater than the time it takes to apply the glue lines and form the membrane module [156,157]; and (v) it must adhere to the components of

the membrane module [156,157]. Even though there are a wide variety of adhesives commercially available (e.g. epoxy adhesives, polyurethane adhesives, silicone adhesives, acrylic adhesives, etc.), very few provide the properties outlined above. Shuey et al. [156] claimed a silicone adhesive specifically formulated for spiral wound membrane modules for application in extraction solvent recovery processes that has excellent stability in some organic solvents especially NMP. King et al. [157] claimed an epoxy – polyamide system specially designed for spiral wound membrane modules for use in organic fluid mixture separations that has very good stability in a large range of organic solvents including methanol, DMF, acetone and dioxane when cured at low temperatures, even as low as 25 °C. However as demonstrated in Table 4.3, the chemical stability of the epoxy adhesive described by King et al. [157] in organic solvents can be further improved with a better curing agent. Table 4.2 summarises the typical characteristics of various type of adhesives. Among all types of adhesive, epoxy adhesives are superior in terms of both chemical and mechanical stability [158,159]. Epoxy adhesives also have high viscosities with controllable pot life, excellent adhesion to a wide range of materials and are relatively hazard free; thus making them prime candidates for use as precursors in the formulation of adhesives for nanofiltration applications in organic solvents.

Epoxy adhesives are thermosetting resins which solidify by polymerisation. There are two groups of epoxy adhesives, (i) two-part resin/curing agent systems which solidify by mixing with/without the acceleration of an external energy source, e.g. heat, dependent on the type of curing agent and (ii) one-part systems which require heat to initiate reaction via a latent catalyst, which are effective at temperatures above 100 °C and operate most effectively in the region 160 -200 °C [160]. The properties of epoxy adhesives are highly dependent on the type of curing agent [160-163] (i.e. amine, anhydride and etc) and the type of resin used

[160,163-165]. Table 4.3 lists the reported chemical resistance of common curing agents, together with their typical curing temperatures.

Table 4.2: Typical characteristics of synthetic adhesives (Adapted from [158,159]).

Type of adhesive	Chemical stability	Viscosity and pot life	Adhesion	Health and safety	Major benefits
Epoxy	Good, resistant to oils and water	High viscosity with variable pot life	Good	Relatively hazard free	Excellent mechanical strength, durable and versatile
Polyurethane	Poor	Short pot life	Excellent, but sensitive to humid environment	Toxic	Robust structural performance
Silicone	Very poor	Wide range of viscosities	Moderate	Toxic and present fire and health hazard	Simple to use and withstand extreme environmental stress
Acrylic	Moderate	Wide range of viscosities	Good	Some degree of precautions required	Good mechanical strength.

Table 4.3: Chemical resistance, typical curing temperatures and disadvantages of common epoxy curing agents (Adapted from [160]).

Curing agent	Chemical resistance	Room temperature hardening (Y/N)	Typical post curing temperatures (°C)	Disadvantages
Aliphatic amines	Moderate	Y	70 - 100	• Critical mix ratios • Exothermic reaction, runaway reactions (short pot life, ≤ 30 mins) • Rigid, poor peel and impact properties
Aromatic amines	Moderate	Y	70 - 200	• Rigid
Anhydride	Good	N	150 -200	• Long post curing, up to 4 hours
Dicyandiamide	Good	N	160 -200	• Long post curing, up to 4 hours
Polyamide	Low	Y	50 - 100	• High viscosity • Long curing time at room temperature • High formulation cost

As noted in chapter 3, the performance of P84 NF membranes is susceptible to heating at temperatures from 100 to 200 °C [32]. From Table 4.3, it is clear that epoxy curing agents capable of the highest chemical resistance require curing temperatures in the range that negatively affect P84 NF membranes, and thus in this work only epoxy systems based on aliphatic and aromatic amines are investigated since they can be post cured at temperatures ≤ 100 °C to achieve near 100% crosslinking [160]. In the making of a spiral wound membrane modules, room temperature hardening of the epoxy adhesive will be an advantage to provide a fabrication process with minimal hassle, minimal usage of materials to make the final wrap that holds the spiral wound membrane module together (especially for FDA compliant

environments), and to enable implementation of a quality control system before adhering the expensive ATD to the membrane module.

4.3 Curing mechanism of epoxy – amine adhesive system [160,163]

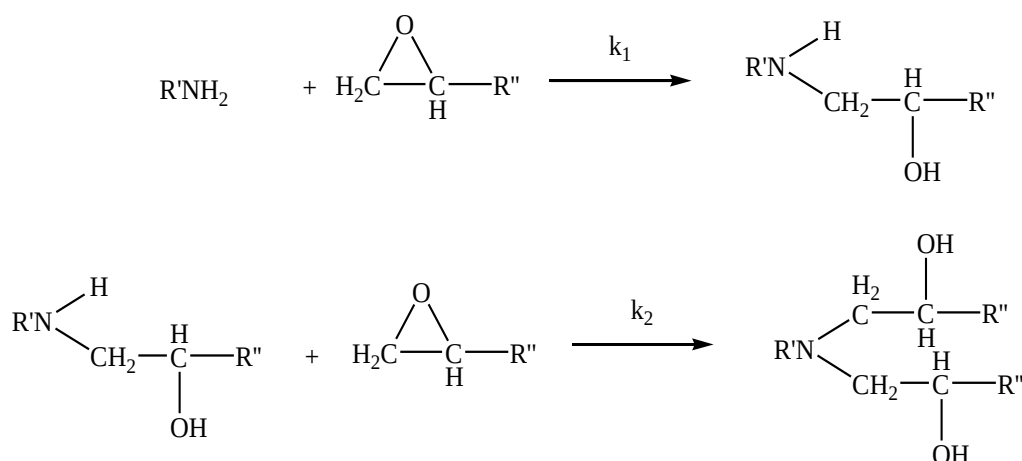


Figure 4.2: Addition of primary and secondary amine to epoxy ring present in a resin (reaction pathway 1).

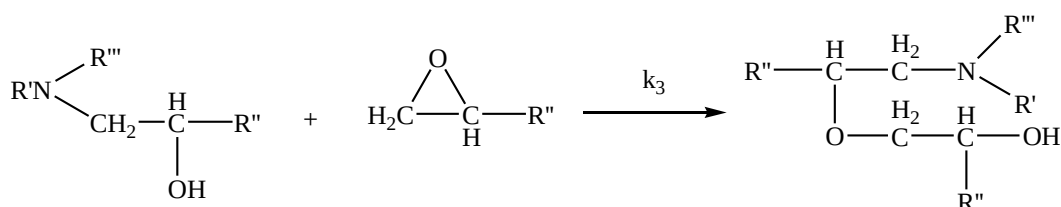


Figure 4.3: Addition of primary and secondary amine to epoxy ring present in a resin (reaction pathway 2).

The main crosslinking reaction pathway, in other words, the curing mechanism of epoxy – amine poly addition reaction (reaction pathway 1) is illustrated in Figure 4.2, where the primary and secondary amine adds to the epoxy ring, forming a tertiary amine. This reaction may also combine with a side reaction (reaction pathway 2) involving the addition of the formed secondary hydroxyl groups present in the tertiary amine molecules (from reaction pathway 1) to epoxy rings, which form an ether linkage between the epoxy groups. At room

temperature, the curing of epoxy – amine systems is dominated by reaction pathway 1 [160,163].

4.4 Overview and strategy in formulating epoxy adhesive resistant to organic solvents

Studies available in the literature are mainly focused on improving mechanical and thermal stability of epoxy systems. Limited studies on epoxy formulations focus on their stability in organic solvents. Atta et al. [166] had investigated the stability of Schiff base epoxy resin-amine systems in some solvents (water and MEK) by a perfunctory rub test through observation. However, many report hydrothermal effects [167-169] on epoxy adhesives and some are shown to degrade/plasticise in water or humid environments [170-173]. Based on these, it is postulated that the resistance of an epoxy-amine adhesive in organic solvents may depend on two main factors; (i) the epoxy-amine network structure (e.g. free volume [174]) and (ii) the functional groups in the network, determining epoxy system-solvent affinity.

Crosslink density is a common parameter used in epoxy adhesives to determine the rheological properties of the epoxy adhesive after cure, and it is defined as the number of effective crosslinks per unit volume [160]. Higher degrees of crosslinking usually indicate less free volume and segmental mobility remains available in the polymer [160,163]. Thus, solvent molecules are less able to penetrate through the crosslinked network. Crosslinking density of an epoxy-amine system could be controlled by the type (i.e. epoxy equivalent weight (EEW) and molecular weight – number of repeating units, n) and functionality of the epoxy resin [170]; and the reactivity of the amine curing agent [175,176]. Petrie et al. [160] have reported an increased crosslink density with a high functionality epoxy resin (e.g. epoxy novolac) by indirectly determining the thermal weight loss as less than 1 wt% at 160 - 210

°C, whereas a system formulated with a mono-functional epoxy resin lost almost 2 wt% at the same temperatures. However, increasing crosslinking density would also lead to an increased density of hydroxyl (-OH) groups in the crosslinked region, and may simultaneously increase the affinity between the crosslinked matrix and solvent molecules with hydrogen bonding abilities [166,173].

The uptake of liquid by epoxy adhesives can be determined using equation 4.1, defined by Fick's 1st law of diffusion [170]. Fick's 1st law of diffusion states that the flux (J_x), amount of liquid diffusing across a unit area in x-direction in a unit of time is proportional to the concentration gradient. As defined in equation 4.1, the diffusion of liquid into the epoxy matrix is controlled by the intrinsic coefficient of diffusion of the material (D) and the liquid pathway to the free volume (δx). Thus, by lowering D or increasing δx , the molecular transport of liquid into the epoxy network can be effectively reduced.

$$J_x = -D \frac{\delta C}{\delta x} \quad (\text{Equation 4.1})$$

Kahraman et al. [177] found that the addition of aluminium filler to an epoxy system decreases the total amount of water uptake at saturation. These particulate fillers are often inert and are used with epoxy resin systems to reduce cost, but they also have an added advantage of reducing shrinkage during cure, and maintaining the integrity of the adhesive bond [163].

In parallel, the chemical properties of the final epoxy matrix itself are equally important. For instance, a cured epoxy-amine network (as presented in Figures 4.2 and 4.3) contains sites such as hydroxyl groups available for hydrogen bonding with a polar molecule (e.g. water, alcohols). This is known to be the dominating factor in swelling and finally degrading the epoxy adhesives in humid environments [173]. Functional fillers such as fibrous silica

[160,178-181], precipitated calcium carbonate [160] and colloidal clay [160] are used by researchers to manipulate the functional groups in epoxy matrixes. The degree of chemical improvement provided by these fillers heavily depends on their properties; particle size, shape, surface chemistry and dispersion characteristics [160]. Some fumed silica (with siloxane groups on its surface) is known to provide superior moisture resistance in epoxy adhesives and coatings [178,179]. Similarly, this may improve the solvent resistance of epoxy adhesives, especially for polar solvents such as alcohols with high hydrogen bonding potential.

In this chapter, several formulation parameters of epoxy-amine adhesives are investigated for preparing their uses in OSN applications, ranging from apolar hydrocarbons (e.g heptane, toluene) through polar alcohols/ketones (e.g methanol, acetone) to polar aprotic solvents (e.g THF, DMF, NMP) and chlorinated solvents (e.g. DCM). The formulation parameters studied are focussed on:

- (i) increasing the crosslink density – by varying the type of epoxy resin, resin functionality, type of amines and their reactivity and the molar equivalence between reactive groups of epoxides and amines,
- (ii) lowering D and/or increasing δx of the crosslink network – by adding particulate fillers such as silica sand [173], and
- (iii) manipulating the functional groups present in the crosslink network – by blending various types of functional nano sized silica fillers into epoxy-amine systems.

Furthermore, their suitability to be used as an adhesive with the membranes developed in chapter 3 for making spiral wound membrane modules will be assessed using a technique developed in this work.

4.5 Experimental

4.5.1 Chemicals

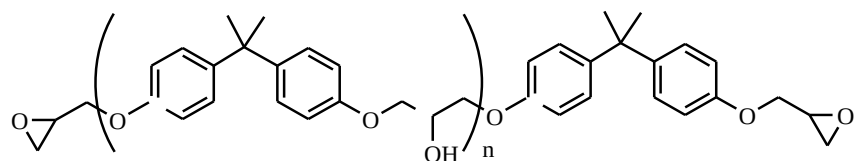
All solvents used in this work were purchased from Sigma-Aldrich. Four types of epoxy resin were used in this work. Table 4.4 lists the characteristics of the epoxy content of these resins. The general structures of these epoxy resins and their monomers are presented in Figure 4.4. Both Epikote 828 and 862 were purchased from Miller Stephenson, USA. Meanwhile, the multifunctional epoxy resin of D.E.N. 431 and 438 were kindly provided by Dow Chemical, EU.

Table 4.4: General characteristics of epoxy resins used (Adapted from [182,183]).

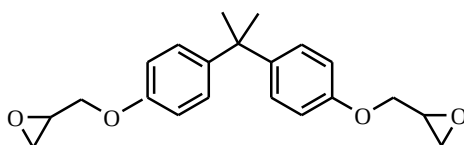
Commercial name	^a Type of epoxy resin	^b EEW (g.eq ⁻¹)	Viscosity at 25 °C (cP)	Monomer contents[184] (wt%)
<i>Bifunctional epoxy groups per base:</i>				
Epikote 828	DGEBA-R, n=0.1	185 – 192	11,000-15,000	85.3 of DGEBA
Epikote 862	DGEBF-R	165 - 173	2,500-4,500	74.4 and 1.9 of DGEBF and DGEBA
<i>Multifunctional epoxy groups per base:</i>				
D.E.N. 431	DGEBF(n)-R, n= 0.7	172 -179	1,000-1,700 (52 °C)	43.1 of DGEBF
D.E.N. 438	DGEBF(n)-R, n= 1.6	176 - 181	31,000-40,000 (52 °C)	23.0 of DGEBF

^a DGEBA-R and DGEBF-R are diglycidyl ether of bisphenol A and diglycidyl ether of bisphenol F epoxy resin respectively. Whereas, DGEBF(n)-R is multifunction diglycidyl ether of bisphenol F epoxy resin.

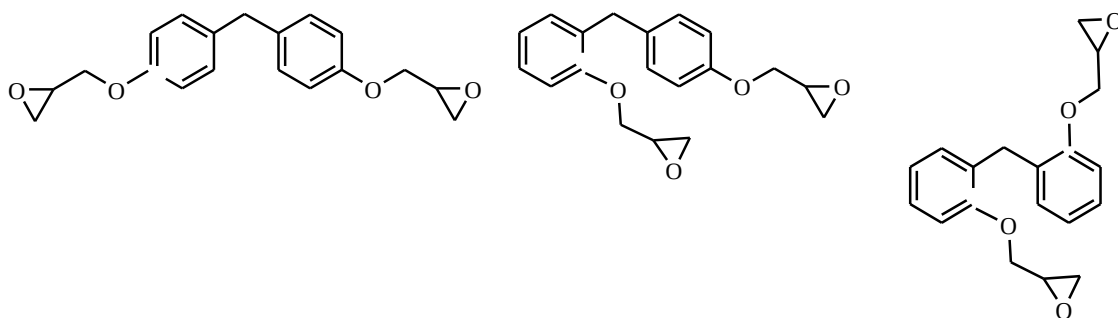
^b Epoxy equivalent weight (EEW) is defined as the weight of resin in grams that contains one equivalent of epoxy group.



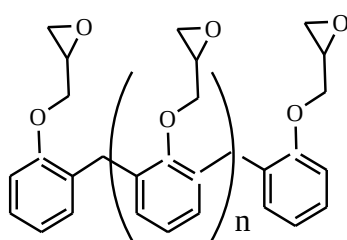
(a) DGEBA-R, diglycidyl ether of bisphenol A epoxy resin



(b) DGEBA-R, diglycidyl ether of bisphenol A epoxy monomer



(c) p,p'-DGEBF; o,p'-DGEBF and o,o'-DGEBF, diglycidyl ether of bisphenol F epoxy monomers



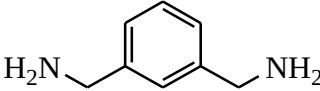
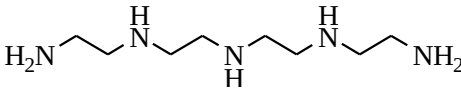
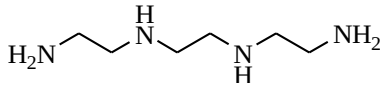
(d) DGEBF(n)-R, multifunctional diglycidyl ether of bisphenol F epoxy resin

Figure 4.4: The monomer and general structures of epoxy resins based on bisphenol A and bisphenol F [184].

The curing agents used in this work were aromatic amine – (i) *m*-xylylenediamine (XYL) - and aliphatic amines – (ii) tetraethylenepentamine (TEPA) and (iii) triethylenetetramine (TETA). Table 4.5 summarises the typical properties of the curing agents; giving the

chemical composition, chemical structure and amine equivalent weight. Amine equivalent weight (AEW) is defined as the ratio of molecular weight of the amine to the number of active hydrogen present. Epicure curing agents and xylylenediamine were purchased from Miller Stephenson (USA) and Sigma-Aldrich (UK) respectively.

Table 4.5: Properties of curing agents used (Adapted from [182]).

Commercial name	^a Chemical composition (wt%)	Chemical structure	AEW (g.mol ⁻¹ .eq ⁻¹)
-	Xylylenediamine, ≥ 99%		34.0
Epi-cure 3245	TEPA, ≤ 92% TETA, ≤ 5%		27.2
Epi-cure 3234	TETA, ≥ 99%		24.5

^a TEPA and TETA stands for tetraethylenepentamine and triethylenetetramine respectively.

Aerosil 200 VV Pharma, an amorphous colloidal silicon dioxide (≥ 99 wt% SiO₂) with an average particle size of 12 nm and a specific surface area of 200 ± 25 m².g⁻¹ was kindly provided by Degussa AG, Germany. Concomitantly, hydrophilic fumed silica – Cabosil M5 - and hydrophobic fumed silica – Cabosil TS720 - were kindly supplied by Cabot Corporation, EU. Cabosil TS720 is formed via chemical treatment of Cabosil M5, with a surface chemistry illustrated in Figure 4.5 [185]. The surface of Cabosil M5 undergoes reversible dehydration when heated to above 110 °C, as illustrated in Figure 4.6. The release of water at these conditions forms additional siloxane groups [185]. Surface hydroxyl groups removed from Cabosil M5 can be restored by exposure to humid air and/or by immersion into water. Micro particulate filler, silica sand (≥ 99 wt% SiO₂) - HPF6 - was kindly supplied by WBB Minerals, UK.

All chemicals and materials were used as supplied. Aerosil 200 VV Pharma, Cabosil M5 and Cabosil TS720 were dried at 100 °C under vacuum for at least 24 hours prior to use, unless stated.

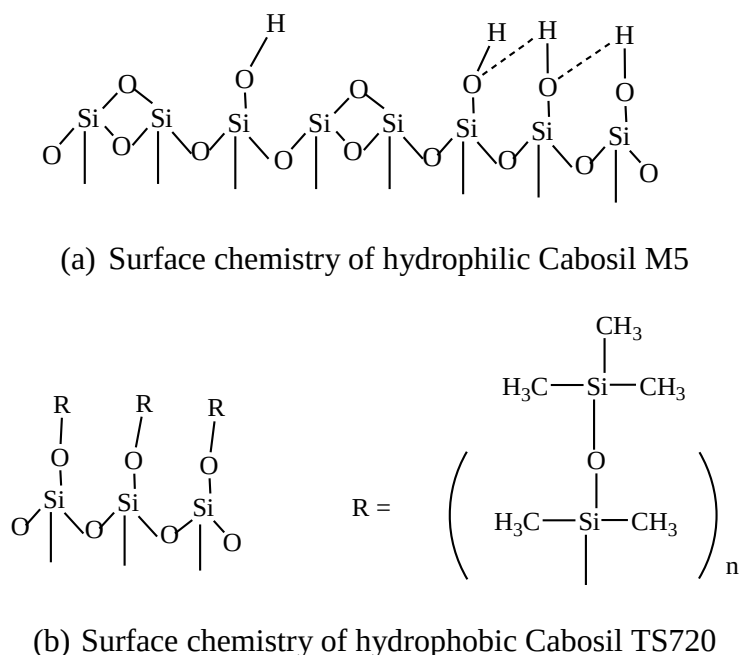


Figure 4.5: Surface chemistry of fumed silica: Cabosil M5 and Cabosil TS720 (Adapted from [185]).

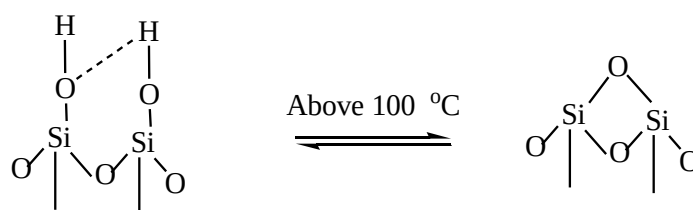


Figure 4.6: Reversible dehydration of Cabosil M5 fumed silica surface (Adapted from [185]).

4.5.2 Preparation of adhesive samples

Mixtures of epoxy resin and amine – curing agent were vigorously mixed using a motorised mixer until homogeneity was achieved. The mixtures were allowed to stand for 10 minutes to degas prior to the moulding procedure, and then post cured at 100 °C (2 hours) and 180 °C (2

hours) for aliphatic and aromatic amines respectively. The quantity of amine – curing agent added into the epoxy resin was calculated based on equation 4.2. For adhesive systems containing fillers, the epoxy resins and amine - curing agents were initially suspended with the fillers prior to mixing. Colloidal silicon dioxide (Aerosil 200 VV Pharma) and fumed silica (Cabosil M5 and TS720) were suspended into the amine – curing agent using a motorised mixer before placing into an ultrasonic bath for a further 2 hours to obtain a homogenous gel. Concomitantly, equivalent mass particulate fillers (HPF6, silica sand) were suspended into both epoxy resin and curing agent independently using a motorised mixer.

$$M_c = \left(\frac{AEW}{EEW} \right) \times \frac{M_e}{\text{Equivalent ratio of epoxide to active H}} \quad (\text{Equation 4.2})$$

Table 4.6 lists the epoxy-amine systems used in this work. Dosage of fillers (nano sized and micro particulates) was based on the total mass of all components used in each epoxy-amine systems.

Table 4.6: List of epoxy-amine systems used in this study.

Epoxy-amine system	Epoxy resin		Curing agent		Nano sized silica		Micro particulates	
	Commercial name	n	Type	Equimolar	Commercial name	Dosage	Commercial name	Dosage
A1	100 wt% E-828	2	TEPA	1.0	Nil	Nil	Nil	Nil
A2	100 wt% E-862	2	TEPA	1.0	Nil	Nil	Nil	Nil
A3	50wt% E-862 + 50wt% D-431	2.35	TEPA	1.0	Nil	Nil	Nil	Nil
A4	50wt% E-862+ 50wt% D-438	2.8	TEPA	1.0	Nil	Nil	Nil	Nil
A5	100 wt% E-828	2	TETA	1.0	Nil	Nil	Nil	Nil
A6	100 wt% E-828	2	XYL	1.0	Nil	Nil	Nil	Nil
A7	100 wt% E-828	2	TEPA	0.67	Nil	Nil	Nil	Nil
A8	100 wt% E-828	2	TEPA	1.25	Nil	Nil	Nil	Nil
A9	100 wt% E-828	2	TEPA	1.0	A-200 VV	5	Nil	Nil
A10	100 wt% E-828	2	TEPA	1.0	C-M5	5	Nil	Nil
A11	100 wt% E-828	2	TEPA	1.0	C-TS720	5	Nil	Nil
A12	100 wt% E-828	2	TEPA	1.0	Untreated C-M5	5	Nil	Nil
A13	100 wt% E-828	2	TEPA	1.0	Nil	Nil	HPF6	50
A14	50wt% E-862+ 50wt% D-438	2.8	TEPA	1.0	Nil	Nil	HPF6	25
A15	50wt% E-862+ 50wt% D-438	2.8	TEPA	1.0	Nil	Nil	HPF6	50
A16	50wt% E-862+ 50wt% D-438	2.8	TEPA	1.25	Nil	Nil	HPF6	50
A17	50wt% E-862+ 50wt% D-438	2.8	TEPA	1.25	A-200 VV	5	HPF6	50

4.5.3 Sorption test

The swelling and/or resistance of epoxy-amine systems in organic solvents was determined using a sorption test method. The samples were weighed on a balance with precision of 0.1 mg before and after being immersed into solvents at room temperature (20 to 25°C). The samples were periodically removed from the solvents and the external sample surface dried using tissue papers at room temperature before further the weight was measured. The solvent i mass uptake at time t , $M_{i,t}$ of the sample is defined as (Equation 4.3):

$$M_{i,t} = \frac{W_t - W_o}{W_o} \times 100\% \quad (\text{Equation 4.3})$$

Repeatability of the test with samples of different lengths (at a fixed diameter) was found to be within 0.01 to 0.04 wt%.

In the preliminary study, methanol was used as a solvent to investigate the effect of the formulation factors on the resistance of the epoxy-amine systems in organic solvents. Methanol was chosen as the primary test solvent due to its chemical properties; (i) hydrophilicity, (ii) low molecular weight, 32 g.mol⁻¹ and (iii) ability to bind with hydroxyl groups in the adhesive resin via hydrogen bonding.

4.5.4 Differential Scanning Calorimetry (DSC)

Calorimetric measurements were carried out using a DSC Q2000 machine integrated with TA Universal Analysis software (TA Instruments, UK) to measure the heat flow under non-isothermal conditions of samples with mass about 20 - 25 mg. Two scans from an equilibrated temperature of 20 °C to 200 °C at 2 °C.min⁻¹, 5 °C.min⁻¹ and 10 °C.min⁻¹ under nitrogen with an interim cool-down at 10 °C.min⁻¹ were performed on pre mixed epoxy resin – amine samples in closed aluminium pans. The heat of reaction (ΔH_T) of an epoxy resin – amine system was estimated by integrating the area under the exothermic curve obtained

from the first scan. Concomitantly, reported glass transitional temperature (T_g) of the fully cured epoxy – amine network was measured from the inflection point of the heat capacity curve on the second scan. T_g can be used as an indication of the degree of crosslinking in the epoxy resin – amine network [160,186,187].

4.5.5 Fourier Transform Infrared Spectroscopy (FT-IR)

The extent of cure in an epoxy resin – amine network was determined using a Perkin Elmer Spectrum 100 FT-IR spectrometer. Each sample was scanned from 4,000 to 400 cm^{-1} over 16 scans at a resolution of 4 cm^{-1} . In preparing FT-IR samples, 1 g of epoxy resin – amine mixture was dissolved into 5 ml of acetone and mixed thoroughly. The solution was then coated on 12 mm diameter $\times$ 1 mm thick potassium bromide (KBr) pellets to form a thin film of epoxy resin – amine sample. An approximately 10-15 micron thick film was formed after the evaporation of acetone at room temperature for 1 hour. The KBr samples were kept in desiccators at all times, before and after thin film sample preparation as well as after post curing at elevated temperatures. As the concentration of the absorbing species is linearly related to the area under the absorbance peak, the extent of cure (conversion of epoxy groups in the resin, α) can be calculated as:

$$\alpha = 1 - \left(\frac{A_{915,t}}{A_{915,o}} \right) \quad (\text{Equation 4.4})$$

where $A_{915,t}$ and $A_{915,o}$ are the area under the epoxy ring absorbance peak after curing at time, t s and before curing at time, 0 s.

FT-IR grade KBr purchased from Sigma-Aldrich was ground into a fine powder and dried at 200 °C under vacuum for at least 24 hours before being pressed into pellets.

4.5.6 Extractables

Soluble components of the post cured materials in a range of volatile organic solvents (toluene, methanol, acetone, THF and DCM) were extracted by Soxhlet extraction under reflux for 24 hours. Similarly, the solubility of components present in post cured samples in high boiling point organic solvents (e.g. DMF) was obtained at 80 °C for 24 hours, since an operating temperature of < 80 °C is generally employed in OSN.

4.5.7 Adhesion test

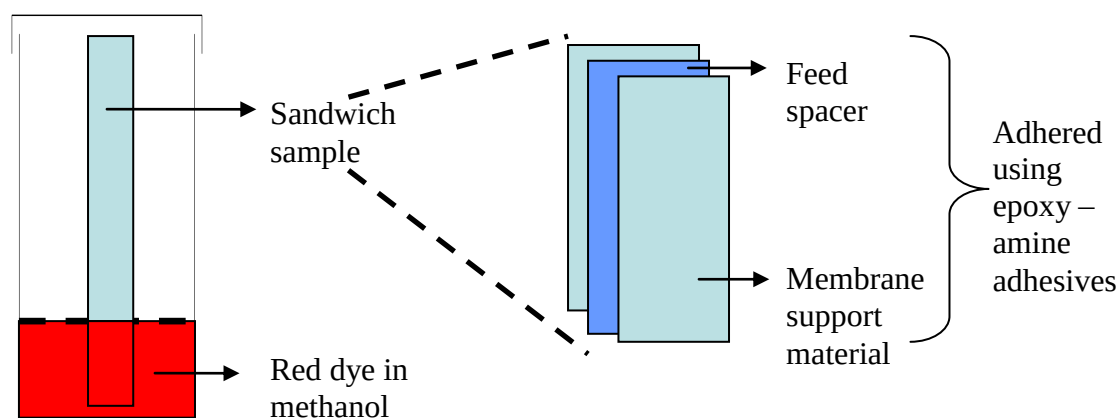


Figure 4.7: Schematic diagram of the capillary effect test designed to investigate adhesion between components in a spiral-wound membrane module with epoxy adhesives.

The adhesion ability of an epoxy resin – amine system for the components used in spiral wound membrane module fabrication was investigated using the capillary effect of methanol across a porous material. As illustrated in Figure 4.7, a test sample mimicking the configuration of materials in a spiral-wound membrane module, where a permeate spacer material was sandwiched between two strips of non woven material (used as a support to the OSN membrane developed in this work) glued together with an epoxy adhesive and placed into a methanol solution containing red dye. Test samples were post cured according to the schedule described in section 4.5.2. If poor adhesion is present in the test sample and/or loss

of adhesion occurred when that the sample swelled in organic solvents, then the red dye is expected to travel upwards in the test sample together with methanol due to the capillary effect. The picture in Figure 4.8 demonstrates the feasibility of this technique.

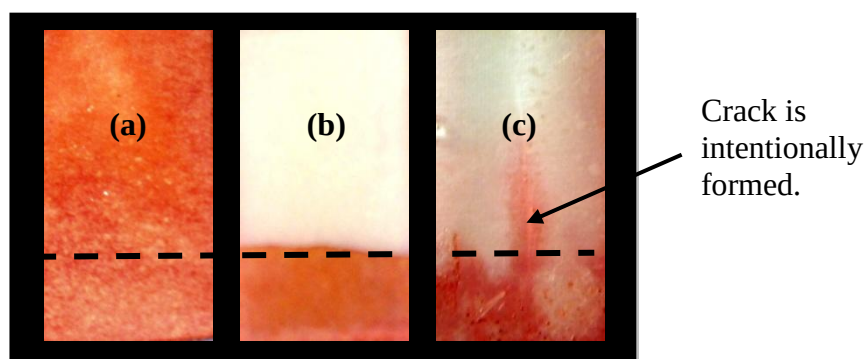


Figure 4.8: Picture of test samples introduced to the dye test described above; (a) non-woven, (b) non-woven and spacer adhered together with an epoxy adhesive and (c) sample b, where the sample was cracked intentionally to mimic adhesive failure.

4.6 Results and discussions

4.6.1 Effect of resin functionality and type

Figure 4.9 shows the effect of epoxy functionality and the type of epoxy resins on the glass transition temperature of cured samples, T_g , and methanol uptake of the cured samples after 21 days of immersion, M_{Me-OH} . The T_g of the DGEBF and DGEBF(n)-R (novolac) blends increased from 113 °C to 141 °C when the epoxy resin was changed from the di-functional (DGEBF) to multi-functional (DGEBF(n)-R). This is an expected result [170,187-189] as a higher crosslink density will be obtained from the multi-functional epoxy resin and this will concomitantly increase the T_g . Similarly, no reactivity enhancement was observed with increasing epoxy value, where 93 to 95 % of epoxides were converted in A2, A3 and A4. A denser crosslink network and/or lower free volume would lead to lower diffusivity of small molecules into the unoccupied volume and lower binding into the hydrogen bond sites in the network. The hypothesis agrees with the methanol absorption data shown in Figure 4.9.

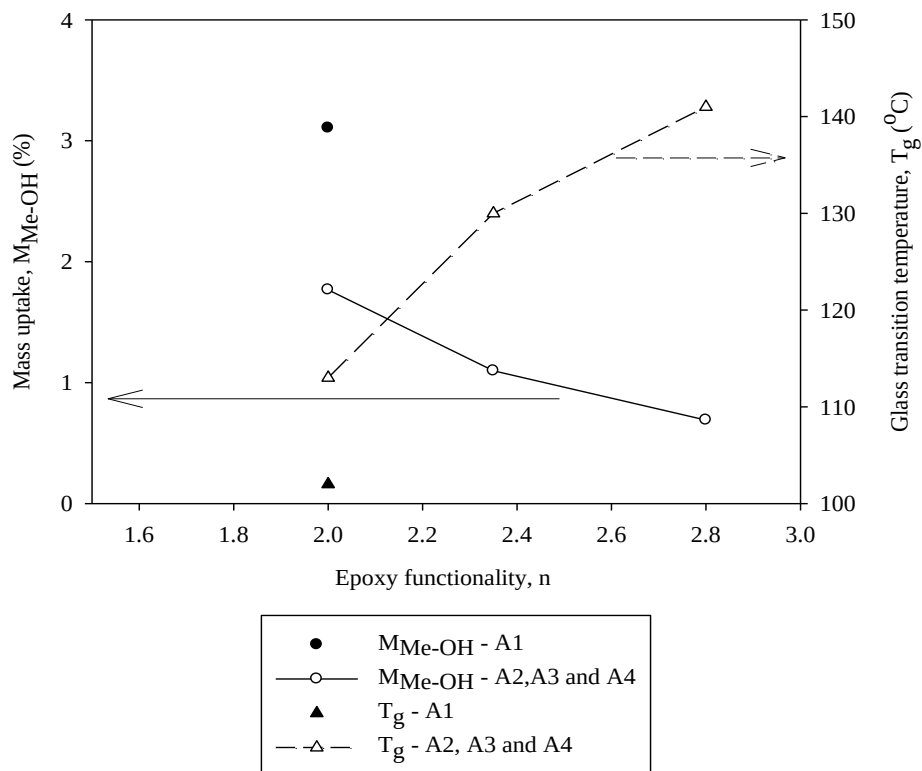


Figure 4.9: Effect of epoxy functionality and type on glass transitional temperature (T_g) of cured samples and mass uptake of cured samples in methanol (M_{Me-OH}). Measurements taken at time, $t = 21$ days.

Comparing bi-functional epoxy resins, DGEBA-R (A1) outperformed DGEBA-R (A1) by achieving higher T_g and lower M_{Me-OH} . For further understanding, the curing kinetics of these two resins were studied by a non-isothermal DSC method. The curing activation energies, E , calculated according to the method of Kissinger and Ozawa has been employed by several authors [189,190]. Kissinger's method [191] is based on the fact that the maximum heat temperature, T_p varies with the heating rate, β and that it assumes the maximum reaction rate, $d\alpha/dt$ occurs at T_p . Kissinger's equation can be expressed as the following:

$$E_k = -R \frac{d[\ln(\beta/T_p^2)]}{d(1/T_p)} \quad (\text{Equation 4.5})$$

where R is the ideal gas constant. Therefore, E_k can be obtained from the slope of a $\ln(\beta/T_p^2)$ vs $1/T_p$ plot. In Ozawa's method [192], it is assumed that the degree of conversion at T_p s at different heating rates is constant. Ozawa's equation gives:

$$E_o = \frac{-R}{1.052} \frac{d(\ln \beta)}{d(1/T_p)} \quad (\text{Equation 4.6})$$

where E_o can be obtained from the slope of a plot of $\ln \beta$ against $1/T_p$. The curing reaction order, n , was obtained by applying Crane's method [193] as described by the following equation:

$$\frac{d(\ln \beta)}{d(1/T_p)} = - \left[\frac{E_{a,K}}{nR} + 2T_p \right] \quad (\text{Equation 4.7})$$

where $E_{a,K}$ is activity energy calculated by Kissinger's method, and n is derived from the slope of $\ln \beta$ vs $1/T_p$ plot when $E_{a,K} \gg 2 T_p$. According to Kissinger's method, the frequency factor, A in the Arrhenius equation can be calculated from the following equation:

$$A = \frac{\beta E_{a,K} e^{(E_{a,K}/RT_p)}}{RT_p} \quad (\text{Equation 4.8})$$

The reaction rate constant, k at temperatures varying from 50 °C to 100 °C was deduced from the Arrhenius equation [190].

The E values calculated from Ozawa's method were slightly higher than that of Kissinger's method, but the trends of the E values determined by both methods are generally consistent. The E values of A1 are higher than A2. This may be attributed to the lower molecular mobility of the monomers and/or the partially formed network during the curing process of A1, which leads to a higher curing temperature (T_p) requirement. Due to the much higher initial viscosity of DGEBA-R (refer to Table 4.4) than DGEBA-R, the curing mechanism shifts to diffusion control with a slower rate of reaction at low temperatures ($T \leq 100$ °C) as

depicted by the k values in Table 4.7. As the curing temperature increases to above 140 °C, the relative rate of reaction, k_{A2}/k_{A1} reaches a constant ratio. The curing reaction is not only dependent on the molecular mobility, but also on the reactivity of the functional group, epoxides. The lower reactivity of A1 may be influenced by the ability of electron withdrawing groups, CH₃ in DGEBA-R (refer to Figure 4.4) to reduce the electron density cloud around the epoxides, which hinders the ring opening reaction of epoxy with amine and/or the epoxy polymerisation reaction. However, both systems follow the same order of reaction, n , 1.000 and 0.979 for A1 and A2 respectively.

Table 4.7: Curing kinetics parameters based on multi heating rates scan method for DGEBA system (A1) and DGEBF system (A2) with TEPA as curing agent.

Adhesive model	A1 - DGEBA	A2 - DGEBF
ΔH_T (J.epoxide ⁻¹), $\zeta = 100\%$	-95 ± 2	-96 ± 2
T_p (°C)	92.7, $\beta = 5\text{ °C.min}^{-1}$	86.2, $\beta = 5\text{ °C.min}^{-1}$
	102.4, $\beta = 10\text{ °C.min}^{-1}$	97.8, $\beta = 10\text{ °C.min}^{-1}$
	114.1, $\beta = 20\text{ °C.min}^{-1}$	107.7, $\beta = 20\text{ °C.min}^{-1}$
Kissinger's method, E_K (kJ.mol ⁻¹)	70	65
Ozawa's method, E_o (kJ.mol ⁻¹)	72	68
n	1.0	0.9
k	0.11 s ⁻¹ , $T = 50\text{ °C}$	0.16 (mol.m ⁻³) ^{0.1} .s ⁻¹ , $T = 50\text{ °C}$
	3.52 s ⁻¹ , $T = 100\text{ °C}$	4.11 (mol.m ⁻³) ^{0.1} .s ⁻¹ , $T = 100\text{ °C}$
	30.5 s ⁻¹ , $T = 140\text{ °C}$	31.7 (mol.m ⁻³) ^{0.1} .s ⁻¹ , $T = 140\text{ °C}$

In parallel, the reactivity of these systems, A1 and A2 were further studied when cured isothermally at 100 °C for 2 hours by determining (i) the conversion of epoxides, α and (ii) the extent of reaction, ξ . As predicted, a higher conversion of epoxides and extent of reaction were measured for DGEBF-R system (A2) as presented in Figure 4.10. However, small differences in α and ξ between the systems suggest the reactivity of DGEBF cannot be the only factor contributing to the 43 % improvement in methanol uptake. T_g is affected by

the backbone rigidity, molecular packing and crosslink density [160,189]. It is believed that the relative bulkiness of the CH_3 groups in DGEBA-R restrain the molecular packing between monomers as the polymer chains grow, leading to a less ordered matrix and hence lower T_g .

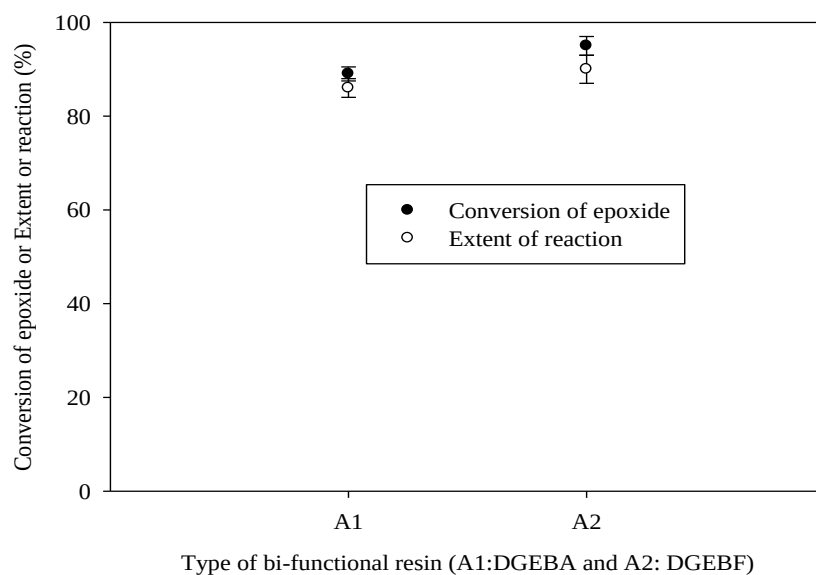


Figure 4.10: Conversion of epoxides, α and extent of reaction, ξ of bi-functional DGEBA (A1) and DBEGF (A2) resins with TEPA as curing agent when cured at 100 °C for 2 hours.

4.6.2 Effect of curing agent

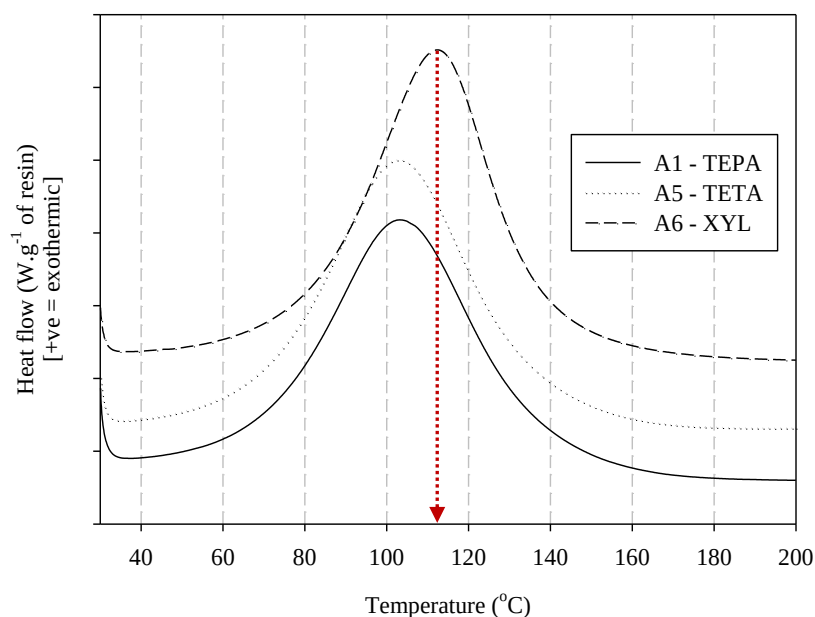


Figure 4.11: DSC thermograms of DGEBA-R systems with different curing agents A1: TEPA, A5: TETA and A6: XYL at stoichiometric quantity heated under non-isothermal conditions, from 30 °C to 200 °C at 10 °C.min⁻¹ (Positive heat flow indicates exothermic reaction in this case).

The curing of DGEBA-R with TEPA (A1), TETA (A5) and xylylenediamine (A6) as curing agents showed similar thermogram behaviour with an exothermic peak. The DSC thermograms of these systems are shown in Figure 4.11. It is observed that A6 peaks at a higher temperature, 113 °C, than that of A1 and A5, at 102 °C and 103 °C respectively. The measured exotherm derives from the curing reaction of epoxides with amines, indicating that the reactivity of DGEBA-R towards xylylenediamine, an aromatic amine is lower than TEPA and TEPA (aliphatic amines) at temperatures ≤ 100 °C, but improves as the temperature increases. However, as presented in Tables 4.7 and 4.8, the activation energy (E) of all three systems obtained based on Kissinger's and Ozawa's methodologies (A1, A5 and A6) are comparable, with a difference of ≤ 1 kJ.mol⁻¹. This is in agreement with the hypothesis that the epoxy resin is responsible for the activation energy.

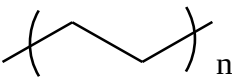
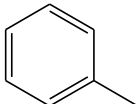
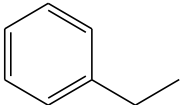
Table 4.8: Curing kinetics parameters based on the multi heating rates scan method for DGEBA systems with TETA (A5) and xylylenediamine (A6) as curing agents.

Adhesive model	A5 - TETA	A6 - Xylylenediamine
ΔH_T (J.epoxide ⁻¹), $\zeta = 100\%$	-94 ± 2	-104 ± 1
T_p (°C)	94.1, $\beta = 5\text{ }^\circ\text{C.min}^{-1}$	100.1, $\beta = 5\text{ }^\circ\text{C.min}^{-1}$
	103.4, $\beta = 10\text{ }^\circ\text{C.min}^{-1}$	113.2, $\beta = 10\text{ }^\circ\text{C.min}^{-1}$
	115.7, $\beta = 20\text{ }^\circ\text{C.min}^{-1}$	122.0, $\beta = 20\text{ }^\circ\text{C.min}^{-1}$
Kissinger's method, E_K (kJ.mol ⁻¹)	70	69
Ozawa's method, E_o (kJ.mol ⁻¹)	72	72
n	1.0	1.0
k		0.06 s^{-1} , $T = 50\text{ }^\circ\text{C}$
	0.09 s^{-1} , $T = 50\text{ }^\circ\text{C}$	1.96 s^{-1} , $T = 100\text{ }^\circ\text{C}$
	2.88 s^{-1} , $T = 100\text{ }^\circ\text{C}$	16.92 s^{-1} , $T = 100\text{ }^\circ\text{C}$
	25.3 s^{-1} , $T = 140\text{ }^\circ\text{C}$	27.21 s^{-1} , $T = 150\text{ }^\circ\text{C}$
		99.79 s^{-1} , $T = 180\text{ }^\circ\text{C}$

The rate of reaction, k calculated for A1 (in Table 4.7), A5 and A6 (in Table 4.8) at temperatures from 50 °C up to 180 °C is expressed as a ranking (based on the reactivity of the curing agents) in the order TEPA > TETA > xylylenediamine. This agrees well with the classification of reactivity based on the pK_a values of aliphatic and aromatic amines (e.g. aniline and methylaniline [194]) presented in Table 4.9. Due to the ability of the aromatic ring to delocalise the lone pair of electrons on the nitrogen into the ring, xylylenediamine, a sterically hindered amine is not as reactive as TEPA and TETA at low temperatures. Atta et al. [195] had reported similar observations with aromatic *p*-phenylenediamine and aliphatic pentaethylenehexamine. Concomitantly, TEPA is relatively more reactive than TETA. This may be due to the higher number of active equivalent weight of hydrogen in TEPA. Similarly to the DSC thermogram of A6 shown in Figure 4.11, the rate of reaction, k of A6 reached an appreciable rate of 27.21 s^{-1} and 99.79 s^{-1} at elevated temperatures 150 °C and 180 °C respectively. More interestingly, the total heat of reaction of A6 (in Table 4.9) was measured to be the largest among all three systems (A1 in Table 4.8 and A5 in Table 4.9) when the

reactions reached completion ($\xi = 100\%$). Therefore, appropriate temperatures for each types of amines must be employed for curing to achieve as close to 100% completion as possible.

Table 4.9: pK_a values of aliphatic and aromatic amines (Adapted from [194])

R	R-NH₂	R₂-NH	R₃-N
	10.7	11.0	10.3
	4.6	N/A	N/A
	4.9	N/A	N/A

A1, A5 and A6 were cured isothermally at temperatures ranging from 100 °C to 180 °C for 2 hours. Figure 4.12 presents the methanol mass uptake (M_{Me-OH}) and the conversion of epoxides (α) of A1, A5 and A6 systems after isothermal curing at temperatures ranging from 100 °C to 180 °C for 2 hours. The chemical stability of A1, A5 and A6 in Figure 4.12 are in agreement with the kinetic results. Cured DGEBA-R with TEPA and xylylenediamine possessed the best chemical stability in methanol ($M_{Me-OH} = 3.1\%$) and had the highest conversion of epoxides ($\alpha = 89\%$ for TEPA and 96 % for xylylenediamine) at 100 °C and 180 °C respectively. The reason for a higher conversion of epoxides in A6, but similar chemical stability to A1, is associated with the combined effect of higher crosslinking density [195] and availability of more free volume in the A6 cured network [167]. T_g measurements show a higher measured T_g for A6 (118 °C) compared to A1 (102 °C), which probably arises from the stiff and bulky phenyl ring that would restrain the internal rotations and thermal motion of the polymer segments. On the other hand, the observed conversion of epoxides with TEPA decreases with temperature, and this could have resulted from the autocatalytic

behaviour of TEPA. In this condition, the reduced nucleophilicity of the sluggish secondary amine groups of TEPA could be sterically hindered from reacting with epoxide groups.

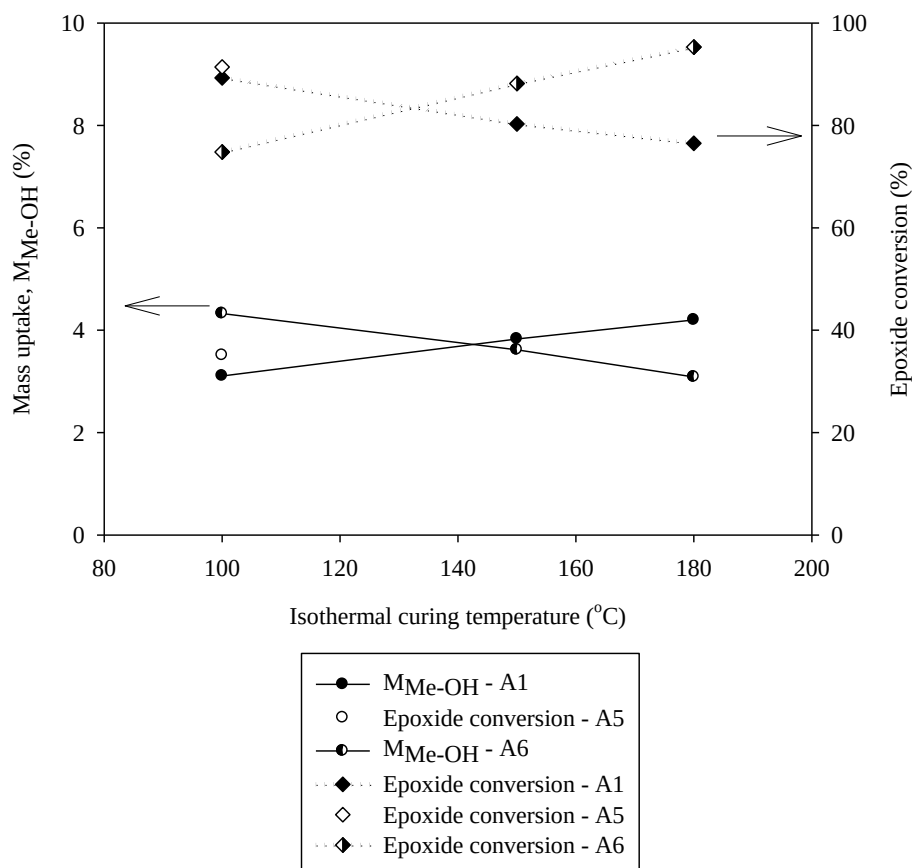


Figure 4.12: The methanol mass uptake and epoxide conversion of A1, A5 and A6 cured at temperatures ranging from 100 °C to 180 °C for 2 hours. Measurements taken at time, $t = 21$ days.

4.6.3 Effect of equimolar quantities of active groups

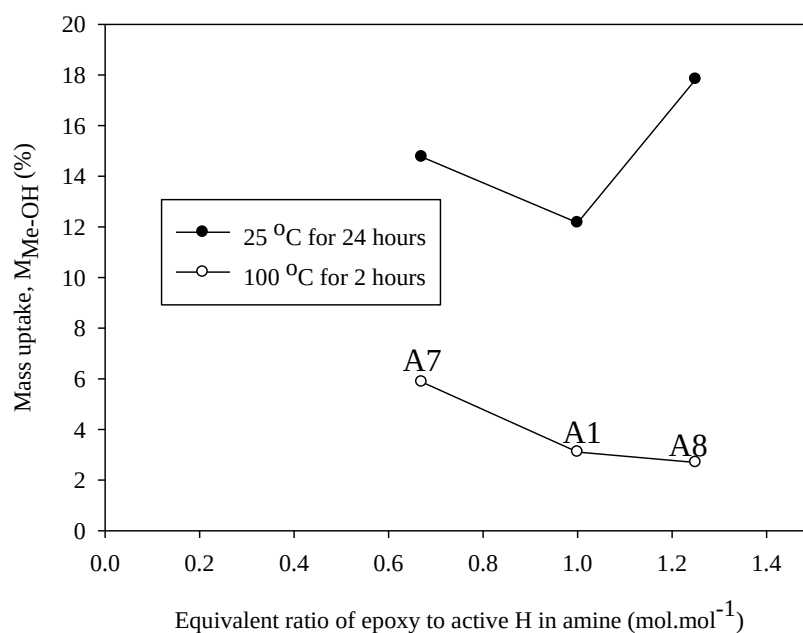


Figure 4.13: Effect of equimolar quantities of active groups (epoxides to amine) to the chemical stability, M_{Me-OH} of DGEBA-R with TEPA. Measurements taken at time, $t = 21$ days.

Table 4.10: Total heat of reaction (ΔH_T) when DGEBA-R is reacted with different quantities of TEPA and their total epoxides conversion (α) after curing at 100 °C for 2 hours.

Adhesive model	A7	A1	A8
Equivalent ratio of epoxy to active H in amine (mol.mol ⁻¹)	0.67	1.00	1.25
^a ΔH_T (J.epoxide ⁻¹), $\zeta = 100\%$	-106 ± 2	-95 ± 2	-87 ± 3
α (%), cured @ 100 °C for 2 hours	85 ± 1	89 ± 1	91 ± 2
T_g (°C), cured @ 100 °C for 2 hours	89 ± 1	104 ± 1	113 ± 2

The effect of equimolar quantities of active groups (epoxides to active H in amine) on the chemical stability, measured by the methanol mass uptake (M_{Me-OH}) of DGEBA-R and TEPA respectively as epoxy resin and curing agent is summarised in Figure 4.13. Overall, the chemical stability of the system follows a different trend when cured at 25 °C for 24 hours and 100 °C for 2 hours. At 25 °C, both non-stoichiometric systems (A7 and A8) suffered from reduced chemical stability. A slight improvement in chemical stability was observed when the system deficient in active H to epoxides (A8 system) was cured at 100 °C for 2

hours. These behaviours may be attributed to the different reaction pathway of each system at specific curing conditions. Shechter et al. [176] have demonstrated that etherification between hydroxyl groups formed with epoxides is plausible at elevated temperatures (>50 °C), when epoxides are in excess. Therefore, with similar epoxides conversion, the outstanding improvement in T_g noted for A8 compared to A1 (in Table 4.10) may be caused by the three dimensional network of A8.

Although the reactivity with TEPA increases with the moles of TEPA present in the system (in Table 4.10), the chemical stability of A7 is weakest. This may be attributed to the trapped and sluggish secondary amine groups formed during the reaction [196], which further hinders the reaction between the active amine H and epoxide. It may also be due to early termination [197] of the crosslinking reaction, leading to pendant amines trapped in the network which increase the number of available H bonding sites.

4.6.4 Effect of functional nanometric particles - silica

Apart from the structure, the influence of strongly polar hydroxyl groups present in the crosslinked amine-cured epoxies were studied using different types of nanometric silica containing different functional groups. Figure 4.14 presents the effect of different functional groups on the M_{Me-OH} by comparing the addition of 5 wt% of treated (120 °C at vacuum) and untreated nanometric silica to the DGEBA-R and TEPA epoxy system. The results are presented based on the relative mass uptake of the filled systems compared to the unfilled system (A1) as expressed by the following equation:

$$\text{Relative mass uptake(\%)} = \left(\frac{M_{Me-OH, unfilled} - M_{Me-OH, filled}}{M_{Me-OH, unfilled}} \right) \times 100\%$$

(Equation 4.9)

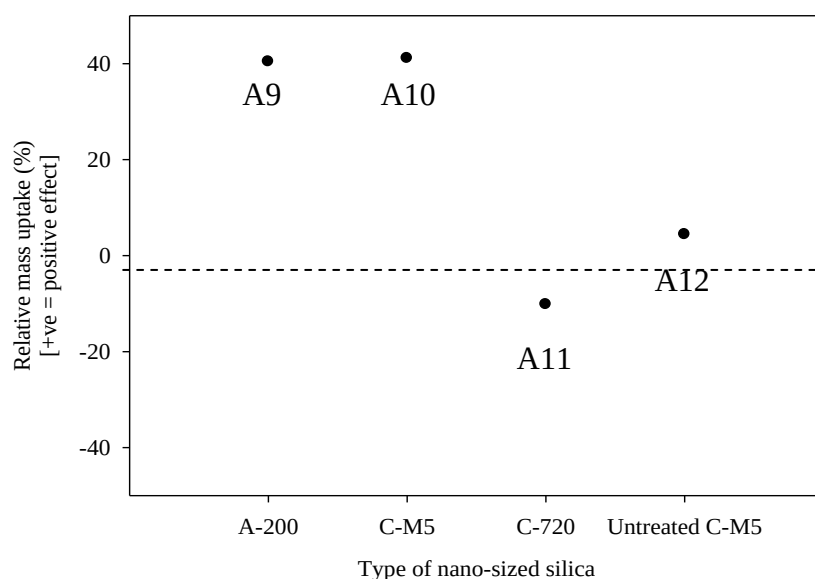


Figure 4.14: Effect of 5 wt% treated and untreated nano-sized silicas (A-100, C-M5 and C-720) on the methanol mass uptake (M_{Me-OH}) of DGEBA-R-TEPA system. Measurements taken at time, $t = 21$ days.

The untreated hydrophilic nanometric silica – Cabosil M5 (A12) imposed a slight improvement in methanol mass uptake of the DGEBA-R-TEPA system (A1), $\approx 5\%$. This result fits well with the observations of Benard et al. [178,198] through ^1H and ^{13}C NMR analysis, where the authors found fixation of hydroxyl functions on the DGEBA-R-amine network to silanol functions (Si-OH) at the surface of untreated silica by hydrogen bonds. Interestingly, a significant improvement, 44 % was observed for the DGEBA-R-TEPA system when it is filled with heat treated Cabosil M5 (A10), which is rich with siloxane groups (Si-O-Si) in comparison to untreated Cabosil M5 (A12). Similarly, colloidal silica – Aerosil 200 (A9) entailed a similar impact on the DGEBA-R-TEPA system when immersed in methanol. On the other hand, hydrophobic nanometric silica, Cabosil-TS720 (C-720) had the opposite effect on the DGEBA-TEPA system. This suggests that the hydroxyl groups formed during the epoxy-amine reaction strongly favour their absorption to the oxygenated siloxane functions (Si-O-Si) on the surface of the heat-treated M5 silica. Overall, these results suggest that the bulky hydrophobic group on the surface of Cabosil TS720 (Figure 4.5) and

the adjacent hydroxyl groups on the surface of untreated Cabosil M5 effectively shield the interaction between the siloxane groups (Si-O-Si) on the surface of these silicas with the hydroxyl groups formed during the reaction between epoxide and amines.

Table 4.11: Curing kinetics parameters based on multi heating rates scan method for DGEBA-TEPA systems filled with nanometric silica, Cabosil M5 (A10) and Cabosil T720 (A11).

Adhesive model	A10 – Cabosil M5	A11 – Cabosil TS720
ΔH_T (J.epoxide ⁻¹), $\zeta = 100$ %	-88 ± 1	-84 ± 2
T_p (°C)	88.5, $\beta = 5$ °C.min ⁻¹	89.6, $\beta = 5$ °C.min ⁻¹
	98.3, $\beta = 10$ °C.min ⁻¹	101.4, $\beta = 10$ °C.min ⁻¹
	106.1, $\beta = 20$ °C.min ⁻¹	107.3, $\beta = 20$ °C.min ⁻¹
Kissinger's method, E_K (kJ.mol ⁻¹)	80	83
Ozawa's method, E_o (kJ.mol ⁻¹)	82	85
n	1.2	1.2
k	$0.09 (\text{mol.m}^{-3})^{-0.2} .\text{s}^{-1}$,	$0.08 (\text{mol.m}^{-3})^{-0.2} .\text{s}^{-1}$,
	T = 50 °C	T = 50 °C
	$5.15 (\text{mol.m}^{-3})^{-0.2} .\text{s}^{-1}$,	$4.94 (\text{mol.m}^{-3})^{-0.2} .\text{s}^{-1}$,
	T = 100 °C	T = 100 °C
α (%), cured @ 100 °C for 2 hours	82 ± 1	79 ± 1

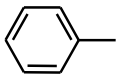
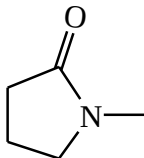
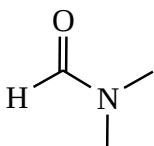
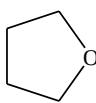
The kinetic study of both heat treated hydrophilic (Cabosil M5) and hydrophobic (Cabosil TS720) silica is presented in Table 4.11. Addition of nanometric silicas comprised of hydrophilic and hydrophobic functions led to an increase in the activation energy (E_k), consequently lowering the conversion of epoxides (α). In both situations, the nanometric silicas also improve the rate of reaction (k) relative to the unfilled system (A1 – refer to Table 4.7 and 4.10). Overall, the kinetic results obtained fit well with the observations reported by Benard et al. [198]. According to Benard et al. [178,198], in the presence of hydrophilic nanometric silica (e.g. treated Cabosil M5 and Aerosil 200), the reactivity of primary amines to form a secondary amine structure is enhanced by the hydrogen bonds with oxygenated functions on the surface of the silica whilst improving the nucleophilic character of the

primary amine function and therefore improving the reactivity with epoxides. However, the predominance of the secondary amine structure weakens the reactivity of the epoxides due to steric hindrance and weaker mobility of the bulky chain of the epoxy-amine-silica chain. Likewise, the presence of bulky hydrophobic groups on the surface of Cabosil TS720 (in Figure 4.5) sterically hinders the reactivity of active amine groups with the epoxides, leading to reduced crosslinking and results in a less dense network. It should be noted that the network structure of crosslinked epoxy resin is not homogenous, but is a mix of highly crosslinked micro-gel particles (or micelles) embedded in a less highly crosslinked matrix [167,169]. Because of their higher density, the micelles are less easily penetrated by molecules than the surrounding matrix.

Table 4.12 summarises the chemical stability of both unfilled (A1) and filled (A10) DGEBA-R-TEPA systems in a range of organic solvents of different polarities and hydrogen bonding abilities; methanol, acetone, toluene, *N*-methyl-2-pyrrolidone and *N,N*-dimethylformamide (DMF). The degree of mass uptake of organic solvents by the epoxy-amine matrix is found to be a function of (i) the polarity of the solvent and (ii) the availability of active sites for hydrogen bonding (as bound molecules) in the epoxy – amine network. Based on the above observations, a filled matrix with hydrophilic silica (i.e. Cabosil M5) is expected to have higher free volume and fewer available hydrogen bonding sites than an unfilled matrix. This would suggest that for apolar solvents there should be minimal impact of introducing a filler on the mass uptake of the amine-epoxy resin as there is no hydrogen bonding and the inherent interaction between the apolar molecule and highly polar epoxy – amine network is low – this is verified by the toluene data in Table 4.12. In the case of NMP, which is a polar solvent but of relatively low hydrogen bonding potential, there is an overall increase in mass uptake due to the increase in free volume of the matrix which dominates over the reduction in hydrogen

bonding sites. Furthermore, solvents such as DMF and acetone with a higher polarity factor compared to their hydrogen bonding ability also impose a negative effect on mass uptake. Whereas, an opposite effect was observed with THF, which has a higher hydrogen bonding ability than polarity factor. However, in the case of methanol, which readily forms hydrogen bonds and is highly polar, the most positive impact was observed as the reduction in hydrogen bonding sites dominates the increase in free volume. This data in Table 4.12 thus confirms the epoxy-amine structures for both filled and unfilled materials hypothesised in this work.

Table 4.12: Chemical stability of unfilled and filled DGEBA-TEPA systems in a range of organic solvents.

Solvent	Structure	Hansen solubility parameters [199] (MPa ^{0.5})			Mass uptake (%)		ΔM_{Me-OH} (%)
		δ_p	δ_H	δ_H/δ_p	A1 - Unfilled	A10 - Filled	
Toluene		1.4	2.0	1.4	0.2	0.2	0
NMP		12.3	7.2	0.6	1.4	1.9	-0.5
DMF		13.7	11.3	0.8	2.3	2.7	-0.4
THF		5.7	8.0	1.4	1.3	1.1	0.2
Methanol	CH ₃ -OH	12.3	22.3	1.8	3.1	1.8	1.3
Acetone		10.4	7.0	0.7	1.6	1.8	-0.2

4.6.5 Effect of micro silica filler

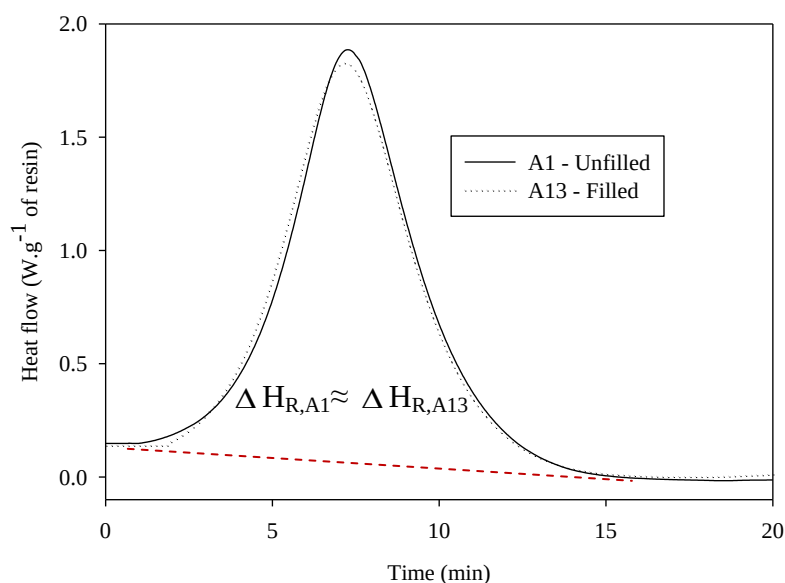


Figure 4.15: DSC thermograms of DGEBA-TEPA systems filled and unfilled with 100 % of micro particles – silica sand, heated under non-isothermal conditions, from 30 °C to 200 °C at 10 °C.min⁻¹ (Positive heat flow indicates exothermic reaction in this case).

In this section, the influence of ‘unoccupied volume’ on the chemical stability of epoxy-amine system was studied by filling the unoccupied volume with micro particle - silica (HPF6). The thermograms of both unfilled (A1) and filled with 50 wt% of HPF6 (A13) systems presented in Figure 4.15, showed that the presence of HPF6 particles has minimal impact on the reactivity of DGEBA-R with TEPA. Consequently, 90 ± 1 % of epoxides conversion was measured in both the A1 (unfilled) and A14 (filled) systems. The relative methanol mass uptake of the filled matrices of DGEBA-R with TEPA and a mix of DGEBF-R/DGEBF(n)-R with TEPA to the unfilled matrices were assessed and presented in Figure 4.16. For the DGEBA-R-TEPA system (A1), the methanol mass uptake was reduced by 90 % when the matrix was filled with 50 wt% of HPF6 (A13). Similarly for the DGEBF-R/DGEBF(n)-R-TEPA system (A4), a similar outcome was observed with the methanol mass uptake reducing from 79 – 83 % with increasing weight percentage of HPF6 from 25–50 wt% (A14 and A15 respectively) in the system. This data shows a higher impact of the

presence of silica micro particles on methanol uptake for DGEBA-R-TEPA, which indicates that there is more unoccupied volume present in DGEBA-R-TEPA than DGEBF-R/DGEBF(n)-R-TEPA matrixes due to the less packed/irregular of DGEBA-R-TEPA structure as discussed in section 4.6.1.

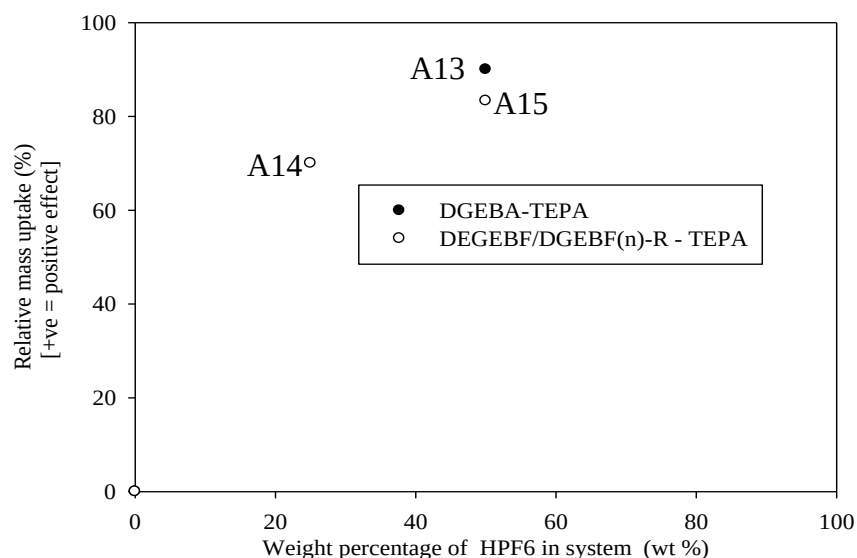


Figure 4.16: Effect of micro particles – silica (HPF6) on the methanol mass uptake (M_{Me-OH}) of DGEBA-R-TEPA (A1) and DGEBF-R/DGEBF(n)-R-TEPA (A4) systems. Measurements taken at time, $t = 21$ days.

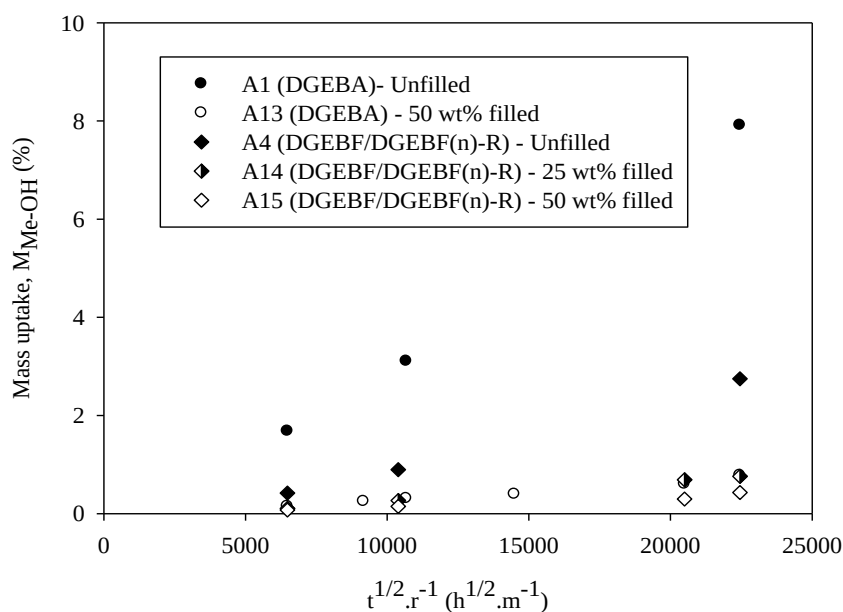


Figure 4.17: Kinetics of methanol uptake by A1, A13, A4, A14 and A15 at 20 – 25 °C.

Typical isothermal methanol absorption curves of A1, A13, A4, A14 and A15 are shown in Figure 4.17. In a previous study by Karad et al. [170], the isotherms of the same epoxy resins were observed to continue to absorb water (molecule with strong hydrogen bonding ability) without reaching equilibrium. This behaviour is believed to be attributed to the kinetically slow molecular reorganisation of the cured network at temperatures below 50 °C, where the bound methanol molecules are immobilised and unbound molecules contained in the network's free volume are relatively free to travel through the free volume voids [170]. This non-steady state diffusion can be modelled using Fick's Second Law [200], and the diffusion coefficient, D , can be expressed by the following equation provided that the source concentration is constant and the geometry is cylindrical:

$$D = \frac{\pi}{64} \left(\frac{s}{M_{\infty}} \right)^2 \quad (\text{Equation 4.10})$$

where s is the initial slope of the plot $M_{\text{Me-OH}}$ against $t^{0.5} \cdot r^{-1}$, t is time, r is the sample radius and M_{∞} is the mass uptake at equilibrium. The absorption plots for all samples were non-Fickian since a non-equilibrium mass uptake was reached. For calculating the diffusion coefficient, the methanol mass uptake achieved after 85 days of immersion was used to provide an effective value of M_{∞} . Table 4.13 provides the apparent isothermal diffusion coefficients of these unfilled and filled DGEBA-R-TEPA and DGEBF-R/DGEBF(n)-R-TEPA blends. As seen in Table 4.13, the diffusion coefficients appeared to increase with;

- i) the decrease in the functionality of the resin (Refer to Section 4.6.1)
- ii) and the increase of HPF6 content (silica micro particulate) in the system.

Table 4.13: Diffusion coefficient, D of unfilled and filled epoxy systems with unreactive micro particulates – silica (HPF6).

Adhesive system	Diffusion coefficient, $D \text{ (m}^2\text{.h}^{-1}) \times 10^{-11}$		
	Unfilled	Filled	
	0 wt% HPF6	25 wt% HPF6	50 wt% HPF6
DGEBA-R-TEPA	7.06 (± 0.10)	N/A	7.26
DGEBF-R/DGEBF(n)-R-TEPA	6.50 (± 0.03)	7.61	10.65

The error bars include the uncertainty associated with taking the value of M at $t = 85$ days as M_{∞} for the purpose of the calculations. As reflected in the values of D , the micro particulate silica extends the pathway along which methanol must diffuse into the crosslinked network, but also reduces the available sites (i.e. free volume) for methanol to cluster as shown by the sharp depression in M_{∞} when the systems were filled with HPF6. This unexpected behaviour of higher D of the filled network may be due to the increased polarity of the crosslinked network attributed to the silica particulates (Si-OH). Similarly, Kahraman et al. [177] also demonstrated that the addition of aluminium powder into epoxy adhesive specimens has no significant effect on moisture diffusivity (D) (most likely due to no interaction between the water and aluminium), and the addition of aluminium filler into the epoxy simultaneously decreases the total amount of water intake at saturation (M_{∞}).

4.6.6 Summary

The results from Sections 4.6.1 to 4.6.5 show that within the formulation parameter space explored in this work, the various components that constitute an epoxy – amine adhesive formulation such as the base epoxy resin, amine curing agent and silica fillers (nano-sized and micro particulate) are capable of generating appreciable changes in the mass uptake of methanol. These parameters effectively change the degree of crosslinking, the molecular packing of the structure (free volume), polarity and the availability of hydrogen bonding sites in the cured network. The greatest change in the mass uptake of methanol was observed when

the epoxy – amine matrix is filled with silica micro particulates and suggests that the free volume present in the network is important in determining the methanol mass uptake at equilibrium.

Also, the mass uptake of a solvent by a cured epoxy-amine network depends on the polarity and hydrogen bonding ability of the solvent. This finding was for instance verified when the Hildebrand δ_p (polarity) and δ_H (hydrogen bonding) coefficients of the tested solvents were applied for correlating mass uptake of different epoxy – amine matrixes. The reduction in active hydrogen bonding sites is highly favourable for minimising mass uptake for polar solvents with high hydrogen bonding ability (e.g. methanol), and also polar solvents with higher hydrogen bonding ability to polarity factor, $\delta_H/\delta_p > 1$ (e.g. THF). On the other hand, the packing structure and crosslink density, which influence the availability of free volume in the cured network, is the key to low mass uptake of polar solvents with low hydrogen bonding ability (e.g. NMP) and polar solvents with lower hydrogen bonding ability to polarity factor, $\delta_H/\delta_p < 1$ (e.g. DMF, acetone). A cured epoxy – amine network is highly polar, due to the by-product, OH groups and C-O-C bonds present in the resins used in this work [173]. Therefore, the reduction in active hydrogen bonding sites and changes in the molecular packing of the cured network has minimal impact on the chemical stability in apolar solvents (e.g. toluene).

4.6.7 Stability in different solvents over extended periods

The mass uptake of a range of organic solvents by A13, A16 and A17 (formulated based on the results obtained from sections 4.6.1 to 4.6.4) over an extended period of 140 days is presented in Table 4.14. As expected, both A16 and A17 had the least mass uptake of a series of organic solvents ranging from apolar solvents (i.e. hexane and toluene) through polar

solvents (e.g. methanol, ethanol, water and acetone) to polar aprotics (e.g. THF, NMP and DMF) and chlorinated (e.g. dichloromethane (DCM)). Apart from DCM, less than 1 % mass uptake was measured for both A16 and A17 after immersion in all solvents over a period of 140 days. A highly packed structure with more active hydrogen bonding sites as in A16 is preferable for reduced mass uptake of DCM. Based on the findings of Marchetto et al. [201], this may be attributed to the lower content of pendant secondary amines in the crosslinked matrix of A16. Marchetto et al. [201] reported that DCM significantly swells an amine deprotonated resin and swelling (average volume of solvent absorbed by the resin) increases with the content of amine groups in the resin. It is postulated that the electrophilic nature of DCM (with AN of 20.4 and DN of 1.0 [202]) makes DCM a very strong electron acceptor and this allows a reasonable degree of adduct formation with electron donors - amine groups on the resin backbone. Similar trends were also reported in DMF with the increasing content of amine groups in the resin, and this correlates well with the results presented in Table 4.12.

Glass transition temperature (T_g) is used in the literature [168,173,203] to describe the effect of water absorption on the properties of epoxy adhesives. Table 4.14 presents the depression in glass transition temperature of the epoxy – amine samples after soaking in solvents over a period of 140 days. As seen, A13 suffered the largest depression in glass transition temperature after contact with methanol (with 2.15 % mass uptake), whereas insignificant changes in glass transition temperature were measured for acetone, toluene, THF and DMF (all with < 1 % mass uptake). Insignificant changes in glass transition temperature were also measured for A16 after soaking in methanol and DMF (with < 1 % mass uptake). Astonishingly, with a mass uptake of approximately 2 %, minimal reduction in glass transition temperature was measured for A16 in DCM. During the measurement of glass transition temperature with DSC, the sample specimens undergo thermal stress, which may

release the solvent molecules from the epoxy – amine matrix and lead to a minimal observed reduction in glass transition temperature. However, Gonon et al. [173] showed that absorbed water molecules cannot be totally removed by thermal annealing from epoxy – amine samples, even after prolonged drying for 100 hours at 240 °C. Zhou and Lucas [203] reported that the molecules bound to the epoxy matrix are responsible for the reduction in the glass transition temperature, which also leads to swelling of the network and finally the chemical failure of the adhesive. It is hypothesised that the significant reduction in glass transition temperature for the A13 sample in methanol is due to the strong hydrogen bonding of methanol molecules to the sample matrix, as reflected by the glass transition temperature loss in both wet and dried samples. Inversely, the minimal impact on the glass transition temperature for DCM adsorption to A16 can be due to the reversible interaction between the DCM molecules and the amine groups in the resin backbone. This implies that obtaining glass transition temperature via thermal cycling is not an ideal measurement to indicate the chemical stability of an epoxy – amine adhesive in solvents, especially for molecules which are weakly bound to the matrix.

Table 4.14: Mass uptake and depression in glass transition temperature of A13, A16 and A17 when immersed in a range of organic solvents over a period of 140 days.

Solvent, <i>i</i>	Mass uptake, M_i , $t = 140$ days			Depression in glass transition temperature, $\Delta T_{g, i, t = 140 \text{ days}}$	
	(%)			(°C)	
	A13	A16	A17	A13	A16
Methanol	2.15	0.32	0.27	23 ± 3 (^a 28 ± 1)	2 ± 1
Ethanol	-	0.10	0.06	-	-
Acetone	0.87	0.30	0.35	0	-
Hexane	-	0.02	0.02	-	-
Toluene	0.63	0.11	0.11	0	-
THF	0.74	0.21	0.18	0	-
DMF	0.69	0.19	0.77	2 ± 0	0
NMP	0.50	0.13	0.45	-	-
DCM	-	1.99	2.99	-	1 ± 0
Water	-	0.81	0.68	-	-

^a Samples were dried in vacuum condition at 65 °C, boiling point of methanol is 64.7 °C.

Further testing on the chemical integrity of A13 and A16 in aggressive solvents such as methanol, DMF, THF and DCM was performed using the adhesion technique described in Section 4.5.7. All test samples were soaked in solvents over a period of 140 days. Good adhesion with no leaks was observed for all samples as shown in Figure 4.17. This suggests that even with a significant mass uptake of 2.15 % and a loss in glass transition temperature of A13 in methanol, a good adhesion between the spacers and non-woven sandwich was maintained.



Figure 4.17: Typical picture of a sample subjected to adhesion test after being soaked in methanol, toluene, acetone, DMF and DCM for over 140 days.

4.6.8 Compatibility in regulated environments

Table 4.15: Extractables extracted from A13 and A16 epoxy – amine adhesives with a range of organic solvents at 80 °C (DMF) and at their boiling points (others).

Solvent	Boiling point (°C)	Extractables, g of dry mass. g of sample ⁻¹ (%)		
		Wash 1		Wash 2
		A13	A16	A13
Methanol	64.7	0.07 ± 0.05	0.04 ± 0.05	-
Acetone	56.5	0.38 ± 0.04	0.07 ± 0.04	0.31 ± 0.04
Toluene	110.6	0.05 ± 0.05	0.05 ± 0.05	-
THF	66.0	0.04 ± 0.05	0.02 ± 0.05	-
DMF	153.0	^a 0.41 ± 0.06	^a 0.06 ± 0.06	0.28 ± 0.06
DCM	40.0	-	^a 0.55 ± 0.10	-

The characterisation and control of extractables and leachables from all process components involved in the manufacturing of any pharmaceutical compound is a formidable task for the pharmaceutical industry. Here, the degradation and transformation products that result from the active chemistry that occurs when epoxy – amine adhesives were in contact with aggressive solvents under extreme conditions were studied. Table 4.15 presents a summary of

the extractables extracted from A13 and A16 with a range of organic solvents under the harshest conditions. Apart from A13 with acetone and DMF, the extractables measured for all solvent / epoxy-amine systems were within the measurement error. The amount of materials extracted from A13 with acetone and DMF were found to continue in consecutive washes, with less than 0.5 % measured in each washes (respective to mass of sample), which is below the acceptable limits [204,205].

4.7 Conclusion

In this chapter, the relationship between the various formulation parameters that affect the stability of epoxy – amine adhesives in organic solvents was demonstrated. The following conclusions may be drawn from the presented results:

- The chemical stability of an adhesive in organic solvent can be deduced from sorption (mass uptake) and adhesion tests. The glass transition temperature is not an ideal analytical method to indicate the state (swelling and/or plasticisation) of the adhesive after exposure to solvents. Care must be taken especially for unbound/weakly bound solvents.
- The solvent molecules can exist in the crosslinked epoxy – amine media in two states: unbound, or bound to the polymer matrix. Unbound molecules are contained in the matrix's free volume and are relatively free to travel through the free volume voids, whereas the bound molecules are immobilised through interaction with the polymer backbone. Whether a particular solvent is bound or unbound to the epoxy-amine media is dependent on several factors: i) packing structure of the crosslinked epoxy – amine matrix, ii) functional groups (i.e. –OH, primary/secondary/tertiary amines, etc.) available in the matrix and iii) the type of solvent.

- Of the various formulation parameters, the stability of the epoxy – amine adhesives seems to be most affected by the introduction of unreactive micro particulates (e.g. silica) into the system, which act as a filler to reduce the free volume in the crosslinked matrix.
- Other formulation parameters; epoxy resin type and functionality, amine type and their reactivity, and the molar equivalent between reactive groups (epoxides and amines) are equally important in controlling the packing structure of the crosslinked epoxy – amine matrix and the extent of reaction between epoxy – amine and epoxy – epoxy moieties.
- Epoxy – amine adhesives are most stable in apolar solvents (i.e. low mass uptake) because of the polarity of the crosslinked matrix due to the presence of OH groups and C-O-C bonds in the polymer backbone.
- Conversely, epoxy – amine adhesives are susceptible to polar solvents. Epoxy – amine adhesives with limited hydroxyl sites, which simultaneously reduces the crosslinking density, showed enhanced stability in solvents with $\delta_H > \delta_P$ (e.g. methanol, ethanol, water and THF), but demonstrated reduced stability in solvents with $\delta_H < \delta_P$ (e.g. DMF, NMP and acetone) and chlorinated solvents (e.g. DCM). The latter was caused by the unfavourable increase in free volume, which can readily accommodate polar molecules. In addition, a higher content of unreacted amines in the matrix also contributes to reduced stability in DCM.
- The optimised formulation of an epoxy – amine adhesive (A16) provides good stability in a very broad range of solvents including hexane, toluene, methanol, ethanol, acetone, THF, DMF, NMP, DCM and water, whilst retaining adhesion after exposure to these solvents for a period of over 140 days. It can be concluded that A16 is suitable for making spiral-wound membrane modules for applications in these solvents.

- Epoxy – amine adhesives present the worst stability in solvents with (i) low molecular weight and (ii) the ability to chemically bind to the crosslinked network. This includes solvents such as methanol and DCM.

Chapter 5

Optimisation of epoxy adhesive for PI OSN membranes

5.1 Abstract

In chapter 4, several formulation parameters influencing the stability of epoxy – amine adhesives were studied and A16 was identified as the best adhesive for use in spiral wound membrane modules for OSN. Elevated temperature post curing at 100 °C for 2 hours plays a vital role in providing the observed good chemical and mechanical properties of the A16 adhesive. However, it is known that exposure to temperatures above 100 °C has a detrimental effect on the performance of P84 OSN membranes [32]. This chapter reports the effects of traditional thermal and a novel microwave curing technique on the chemical stability of epoxy adhesive as well as functional membrane performance (both P84 and chemically crosslink P84 with aliphatic diamine) by varying the temperature/power and exposure time. To achieve the optimal curing conditions, a trade-off needs to be reached between preventing the loss of membrane performance whilst ensuring that the epoxy is sufficiently cured to provide good chemical stability. Extended testing periods in DMF and THF show that the membrane modules cured following the proposed temperature curing technique are stable, i.e. good adhesion was maintained so the modules were leak free, and demonstrated no significant differences in membrane performance compared to flat sheets.

5.2 Introduction

Curing conditions are highly important in obtaining a stable adhesive and also for maintaining membrane performance in the spiral wound membrane modules. The curing

conditions for the epoxy – amine adhesive plays a vital role in determining the chemical and mechanical properties of the final network [160,206,207]. Perrin et al. [207] studied the influence of curing cycle on the water transport in a DGEBA-R/DGEBF-R system with various types of aliphatic amines and found that the curing cycle is critical in obtaining an optimal system for applications in humid environments. The best adhesive (A16) developed in chapter 4 is cured thermally at 100 °C for 2 hours to give good stability in organic solvents, however P84 (PI) based OSN membrane are reported to show a detrimental effect on solvent permeability when annealed above 100 °C, but without a negative effect on the MWCO [32].

One possible approach in addressing this issue is to consider an alternative curing technique, such as using microwave energy to replace conventional thermal energy. Microwave curing is attractive due to the selective nature of its heating, where only materials that have available polarisable electrons (e.g. epoxy groups) and flexible backbones allow molecular rotation and are consequently heated. Successful microwave-assisted synthesis of polyimide [208,209] and poly(amide-imide) [210] polymers, with a polar organic medium used as a primary microwave absorber have been reported. This suggests that these polymers are inert to the microwave electromagnetic energy and thus the performance of PI membranes prepared by phase inversion technique may not be affected by microwave radiation. Additionally, this technique is also reported to provide superior properties (e.g. improved glass transitional temperature [211-213] and tensile strength [211,214]) of epoxy composites, compared to those which are thermally cured. This is mainly associated with the rapidity and uniformity of the microwave-assisted curing mechanism, where fewer surface irregularities are observed than thermally cured epoxy materials. Furthermore, microwave curing provides a definite

acceleration in the cure process compared to conventional thermal curing, which is reasoned to be due to faster heat dissipation within the network [215,216].

Chapter 4 describes an investigation into the key parameters in formulating epoxy – amine adhesives for application in OSN. This chapter extends this investigation to microwave curing of the epoxy adhesive developed in chapter 4, as well as optimising the conventional thermal curing cycle. The primary objective of this work is to locate an optimum curing schedule that:

- (i) provides excellent chemical stability of epoxy adhesives from chapter 4 in all types of organic solvents, and
- (ii) imposes minimum impact on the performance of P84 OSN membranes (P84 and P84 chemically crosslinked with diamines) exposed to the curing process.

Finally, adaptation of the curing technique and cycle developed in this chapter to industrial application is demonstrated.

5.3 Experimental

5.3.1 Chemicals

The chemicals used for preparing membranes and adhesives in this chapter are described in chapters 3 and 4 respectively.

5.3.2 Preparation of membrane

Table 5.1: Membrane preparation parameters.

Membrane	Polymer	Polymer concentration (wt%) (DMF:Dioxane)	Crosslinked with HDA (Y/N)	Preserving agent
M6	P84	18 (1:3)	Y	PEG 400
M7	P84	18 (1:3)	Y	^a PMP
M8	Torlon 4000T-HV	22 (1:1)	N	Mineral oil

^a PMP = α -methylstyrene dimer

Membranes were prepared as described in chapter 3. A summary of the membranes used in this chapter is given in Table 5.1. Commercially available polyimide membranes, StarmemTM 122 (P84) and StarmemTM 240 (Matrimid 5218), were also used. These membranes were filled with mineral oil as a preserving agent.

5.3.3 Preparation of adhesive samples

A13 and A16 as described in chapter 4 were used. Both formulations are known to provide good chemical stability in many organic solvents as presented in chapter 4. A13 was shown to be stable in all organic solvents used except methanol and dichloromethane (DCM), whilst A16 is stable in all organic solvents tested. All samples were post cured thermally and with microwave energy before characterisation. Microwave cures were conducted in a MARS microwave generator at a frequency of 2.45 GHz, CEM Corporation, USA.

5.3.4 Spiral-wound module fabrication

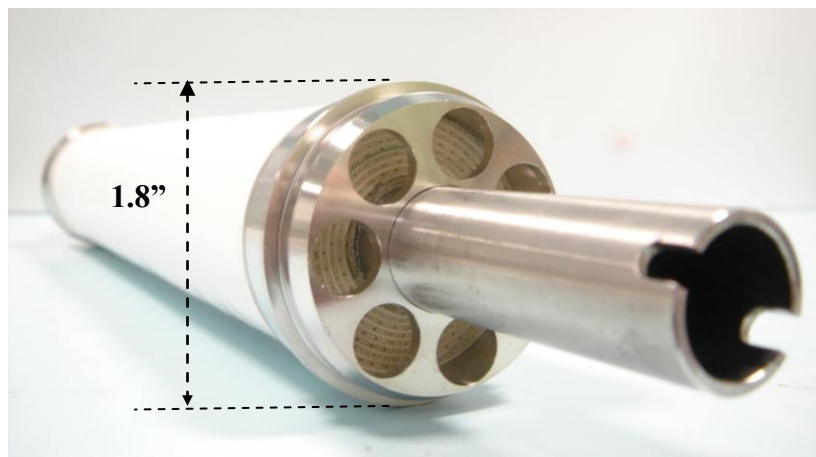


Figure 5.1: Picture of a 1.8" × 12" spiral-wound membrane module. Typical membrane area is 0.3 m².

The membrane leaf and spacers were cut to the desired length and wound round a perforated stainless steel pipe using a rolling machine (Spiral Assembly Systems, USA). Epoxy adhesive (A13) was used to seal the membrane envelope and to secure the membrane leaf to the permeate tube. Epoxy adhesive was coated on the outer layer of the module providing a casing to protect the membrane from mechanical stress during handling and transportation. Stainless steel anti-telescoping end caps were then affixed and the module was then post cured to produce the final membrane module. The membrane module produced has a diameter of 1.8" and is 12" long (total length = permeate tube length) providing a membrane area of approximately 0.3 m².

5.3.5 Nanofiltration experiments

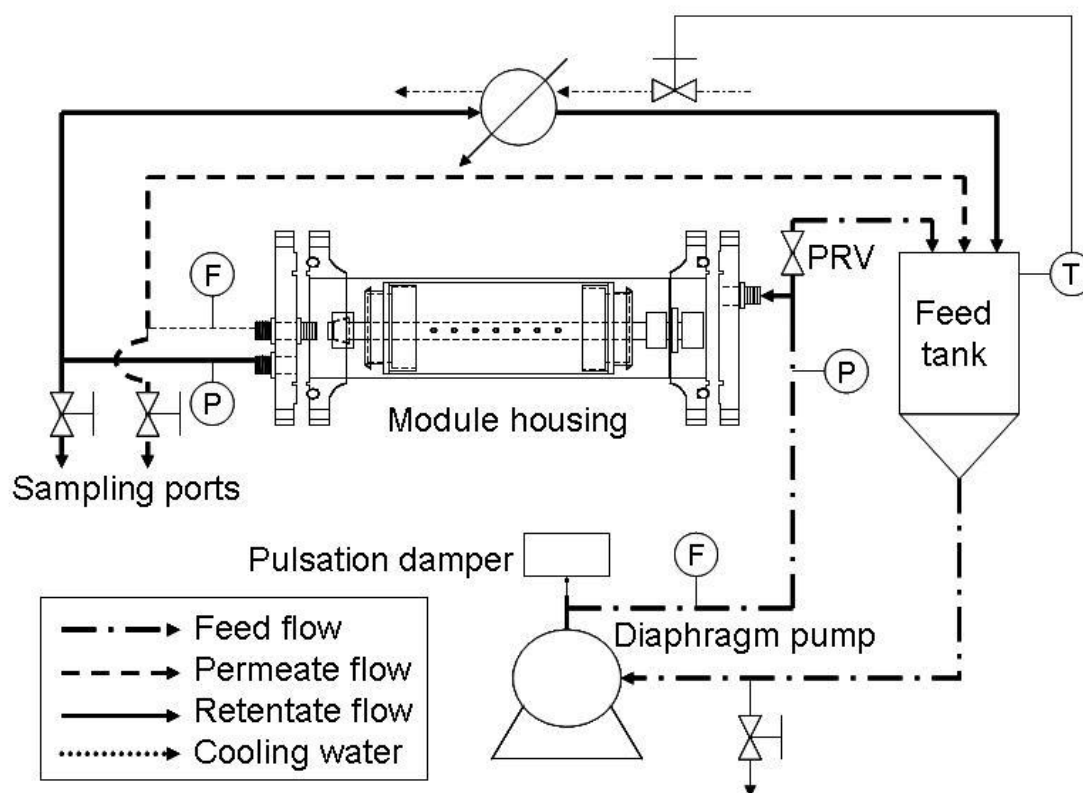


Figure 5.2: Schematic of apparatus used for testing spiral-wound module.

Flat sheet membranes were tested in the *METcell* crossflow system according to the procedures outlined in chapter 3. All tests were carried out using styrene oligomers to determine the MWCO as described in chapter 3. A schematic of the apparatus used to test membrane modules is shown in Figure 5.2. A single test element was loaded into the housing and sealed. Fresh solvent was charged into a 5 L feed tank and re-circulated at a flow rate of 100 L h^{-1} using a diaphragm pump (G03-E Hydra-Cell, Wanner International, UK). Pressure was generated using a back pressure regulator located downstream of a pressure gauge. The pressure drop across the module was measured to be less than 1 bar. The re-circulating fluid was kept at 30°C by a heat exchanger. During start-up, the conditioning agent was removed by passing solvent through the module at low pressure (2 to 5 bar) and discarding the initial

permeate until 40 L.m⁻² were collected. During operation, permeate and retentate samples were collected from individual sampling ports.

5.3.6 Scanning electron microscopy (SEM)

The details for preparing SEM samples and equipment are described in chapter 3.

5.3.7 Thermal gravimetric analysis (TGA)

Thermogravimetric analysis was performed using a TGA Q500 (TA Instruments, UK) machine integrated with TA Universal Analysis software.

5.3.8 Dielectric constant

The dielectric constant of liquid samples was measured using a 870 liquid D.E. meter from Brookhaven Instruments Corporation (UK) at ambient temperature.

5.3.9 Sorption test

The extent of swelling and the chemical stability of the final cured epoxy - amine (adhesives) networks in organic solvents was determined using the sorption test described in chapter 4.

5.3.10 Differential scanning calorimetry (DSC)

The extent of reaction, ξ , during (i) isothermal thermal curing and (ii) by gradient heating thermal curing were determined using DSC. Gradient curing was carried out as described in chapter 4. During isothermal curing, the calorimetry chamber temperature was set to a fixed temperature for a fixed duration to measure the heat of reaction (ΔH_R) under pre-determined conditions. This was followed by an interim cool-down at 10 °C.min⁻¹ to 20 °C and a gradient heating from an equilibrated temperature of 25 °C to 200 °C at 10 °C.min⁻¹ to determine the glass transition temperature of the cured adhesive network.

Based on the currently available instruments, it is not possible to directly measure the heat of reaction released during microwave curing. Therefore, the extent of reaction of microwave cured samples was determined by applying two scans from an equilibrated temperature of 20 °C to 200 °C at 10 °C.min⁻¹ on the post-cured samples. If the reaction is incomplete, the remaining heat of reaction, ΔH_r can be determined during the first scan. By assuming the chemistry of thermal and microwave curing follow the same mechanism, the extent of reaction of microwave samples were calculated based on equation 5.1, where the total heat of reactions (ΔH_T) were obtained during temperature gradient curing.

$$\cdot \xi = \left(\frac{\Delta H_T - \Delta H_R}{\Delta H_T} \right) \times 100\% \quad (\text{Equation 5.1})$$

The inflection point of the heat capacity curve on the first and second scans determine the glass transition temperature, T_g of the adhesive network after microwave curing and when complete reaction is achieved.

5.3.11 Fourier transform infrared spectroscopy (FT-IR)

The conversion of epoxides during the curing of an epoxy resin – amine sample was measured using FT-IR, as described in chapter 4.

5.3.12 Microwave energy absorbance

The ability of compounds to absorb microwave energy was determined by measuring the temperature change of the compound when subjected to microwave radiation at 1200 W for 5 minutes. The sample temperature was monitored by an infra-red thermometer, capable of measuring temperatures in the range -35 °C to 500 °C with a 0.1 °C sensitivity. By assuming

no energy loss and that all absorbed energy is converted to thermal energy, the energy absorbed, $E_{a,i}$ by compound i is defined as;

$$E_{a,i} = m_i C_{p,i} \Delta T_i \quad (\text{Equation 5.2})$$

However, compounds such as 1,6-hexanediamine (HDA), polyimide P84 and HDA-crosslinked P84 are solid state materials at room temperature. Once P84 is crosslinked with HDA as described in chapter 3, the material is not totally soluble in any organic solvent and not soluble in acids or bases without some chemical modification. To determine the microwave energy absorbance of solid materials, 30 wt% of these compounds were suspended (for polymers) or dissolved (for HDA) in toluene, an inert solvent to microwave radiation. The temperature change contributed by compound i (due to absorption of microwave energy) was determined by the following equation defined based on the energy balance of a closed system.

$$\Delta T_i = \frac{M_T \Delta T (0.7 C_{p,\text{toluene}} + 0.3 C_{p,i}) - M_{\text{toluene}} C_{p,\text{toluene}} \Delta T_{\text{toluene}}}{M_i C_{p,i}} \quad (\text{Equation 5.3})$$

5.4 Results and discussion

5.4.1 Thermal vs microwave cure

Thermal curing: Epoxy activation temperature

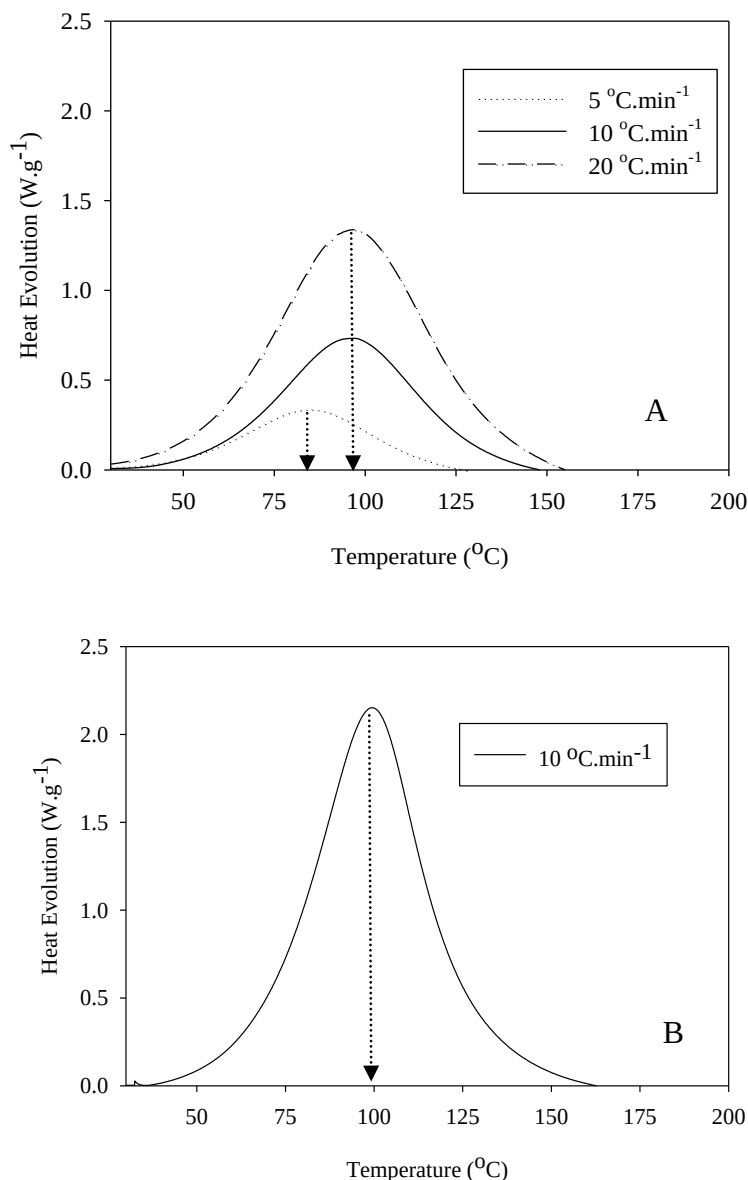


Figure 5.3: Heat evolution of cure of epoxy – amine adhesives (A) A13 and (B) A16 when subjected to gradient thermal heating from 30 °C to 200 °C.

The reactive nature of the TEPA curing agent used in both A13 and A16 epoxy – amine adhesive systems allows the systems to cure from room temperature up to 100 °C [160]. The thermal scan plots of the A13 and A16 systems are shown in Figure 5.3(A) and (B) respectively. The curing reaction of A13 and A16 began at room temperature, $\approx 20 - 25$ °C

with the reaction peaks at 85 °C to 100 °C dependent on the heating rate provided to the adhesive systems. However, due to the increasing temperature during the thermal scan, the cure reaction appeared to be lagging behind the scan rate of the DSC. Taking this into account when determining the optimal curing temperature, an interval of 10 °C below the temperature of maximum heat evolution (maximum cure rate) at the lowest heating rate, 5 °C.min⁻¹, was used to determine the optimal temperature [216]. Intuitively, the optimal curing temperatures of systems with TEPA as curing agent are expected to be in the range 75 °C to 100 °C.

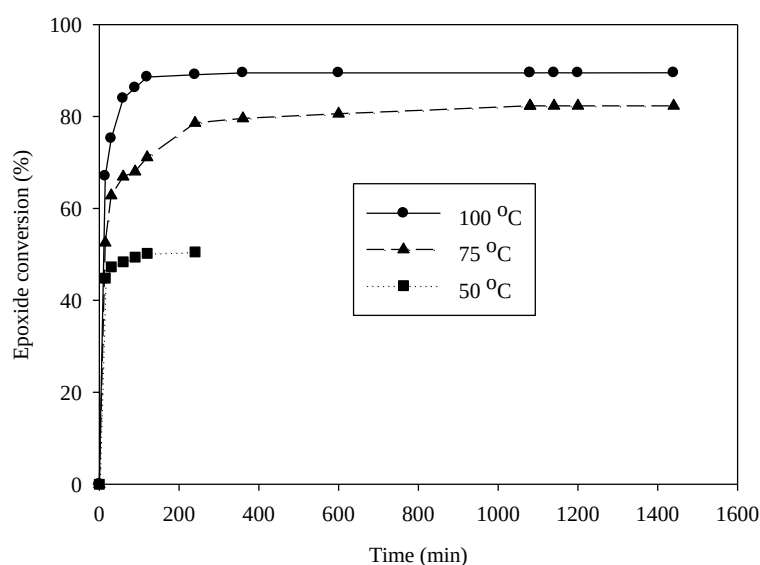


Figure 5.4: Epoxide conversion of the A13 adhesive system when cured isothermally at temperatures in the range 50 °C to 100 °C.

The epoxide conversion of A13 systems cured isothermally at 50 °C, 75 °C and 100 °C are presented in Figure 5.4. The results clearly confirm a minimum temperature of 75 °C is required to fully activate the reactions between the epoxy – amine and/or epoxy – epoxy groups in order to achieve a high degree of reaction. A maximum 89 ± 2 % and 82 ± 1 % of epoxides in A13 are converted at 100 °C and 75 °C in minimum curing times of 2 hours and 18 – 19 hours respectively. On the other hand, at 50 °C, the extent of cure is well below the target with maximum of ≈ 50 % epoxides reacted.

Table 5.2: The final properties (α and T_g) of A13 systems cured at various curing conditions.

Entry	Curing cycle	Curing time (min)	ζ (%)	α (%)	T_g (°C)
1	25 °C to 200 °C at 5 °C.min ⁻¹	35	100	≥ 98.0	114 ± 2
2	25 °C to 100 °C at 5 °C.min ⁻¹	15	82 ± 2	85 ± 2	109 ± 1
3	Isothermal at 75 °C	30	70 ± 3	69 ± 1	83 ± 1
4	Isothermal at 100 °C	30	58 ± 1	79 ± 1	78 ± 2
5	Isothermal at 75 °C	1140	^a N/A	82 ± 1	98 ± 1
6	Isothermal at 100 °C	120	^a N/A	89 ± 1	105 ± 2
7	600 W, 2.45 Hz	30	^b N/A	88 ± 1	107 ± 11
8	1200 W, 2.45 Hz	15	^b N/A	87 ± 1	103 ± 12

N/A = Not applicable

^a No heat flow was measured after 30 minutes of curing. This is suspected to be due to the small heat flow released by the system, below the limitation of the equipment.

^b No heat flow was measured during the first scan. But an improvement in T_g (about 8 -10 °C) was measured when the cured samples were subjected to a second thermal scan from 25 to 200 °C at 10 °C.min⁻¹.

The rate of reaction is governed by the slope of the epoxide conversion versus time curve (in Figure 5.4), $\frac{d\alpha}{dt}$. As demonstrated in Figure 5.4, the initial curing rate of A13 cured isothermally at 100 °C is significantly higher than the system cured at 75 °C. Interestingly, during the first 30 minutes of curing, the extent of reaction of the system cured at 75 °C (entry 3, in Table 5.2) is measured to be higher than the system cured at 100 °C (entry 4, in Table 5.2). This has also resulted in a better T_g , which is an indication of the chemical stability of A13 as suggested by the results in chapter 4. Simultaneously, the T_g of A13 cured at 100 °C for 2 hours is measured to be higher than the A13 system cured at 75 °C for 19 hours (entries 5 and 6, in Table 5.2).

These results suggest that the reaction pathways of curing at 75 °C and 100 °C may be different. The assumption used during determination of the extent of cure by DSC is that all

reactions involving an epoxide are exothermic, which may or may not be the case. Under isothermal curing, the following are postulated to occur:

- (i) At 100 °C, the rapid crosslinking creates a rigid molecular network which traps unreacted functional groups within the network and subsequently forms shorter epoxy – amine polymer chains. The higher conversion of epoxides (i.e. due to steric hindrance limiting the quantity of available primary amines) induces etherification reactions of epoxy with hydroxyl groups generated in the epoxy - amine reactions [176], which add a branch point to the epoxy-amine polymer chains to form a three dimension network structure that causes a significant increase in the crosslink density (reaction pathway 2, see section 4.3), as well as reducing the moles of hydroxyl groups per moles of epoxides reacted.
- (ii) At 75 °C, slow crosslinking following reaction pathway 1 (refer to section 4.3), involving epoxy reacting with primary amines and secondary amines to form long crosslinked polymer chains is followed. It is possible that the larger secondary amine group may be hindered physically or otherwise in mobility due to steric hindrances [216] and becomes significantly less reactive. Hence, etherification (reaction pathway 2, see Section 4.3) is also limited [176].

Novel curing methodologies

Since lower temperature curing (e.g. at 75 °C) favours the formation of long polymer chains and high temperature curing (e.g. at 100 °C) improves the reactivity of primary and secondary amines with epoxy and etherification forms a highly crosslinked three dimensional network, it is thought curing at a temperature gradient from room temperature up to 100 °C (entry 2, in Table 5.3) would provide a network compromising both structures. Through gradient curing, the final adhesive structure achieved a T_g of 109 °C, similar to the system

cured at 100 °C for 2 hours (entry 6, in Table 5.3). However, this may not be a direct indication of the chemical stability in organic solvents due the different reaction pathway resulting in the presence of different functional groups in the final network. This is discussed in the following section. But, the main advantage of this curing methodology the observation that the reaction rate is greatly enhanced, reducing the curing time from 2 hours to only 15 minutes. This is indicated by the extents of cure, ξ , and epoxide conversions (entries 2 and 6, in Table 5.3) achieved in the curing methodologies.

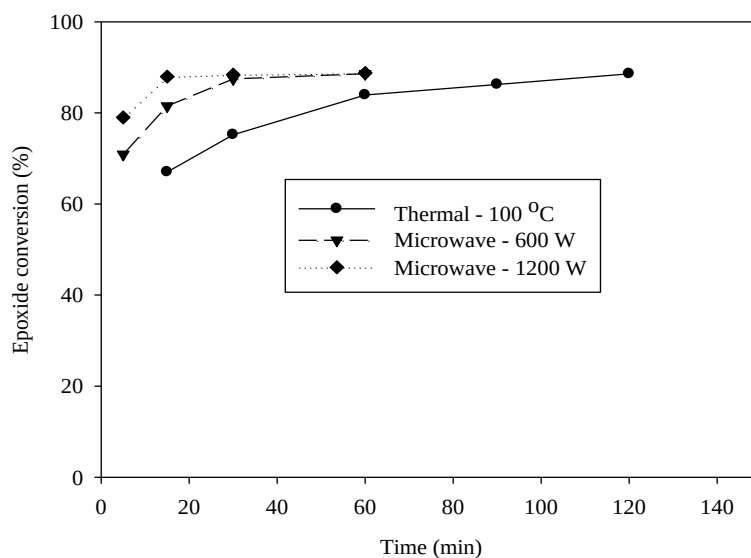


Figure 5.5: Epoxide conversion of A13 adhesive system cured at different power levels of microwave radiation.

Figure 5.5 shows the effect of different power levels of microwave radiation on the reactivity of epoxides in A13. As the microwave power increases, the rate of the epoxide converted rose significantly and results in a greatly reduced cure time. With a total time of 30 minutes at 600 W and 15 minutes at 1200W, maximums of 88 % and 87 % of epoxides are reacted respectively. In comparison, under isothermal curing at 100 °C, only 75 % of epoxides are reacted in 30 minutes and this technique requires a minimum curing time of 2 hours to achieve complete cure. This trend is consistent with that demonstrated by several authors

[216-218] with different amine curing agents. This behaviour may be due to the reactive polar groups (i.e. epoxides) being selectively activated by microwave radiation, whereas under isothermal curing, heat is transferred by conduction to excite the entire epoxy resin molecule before the epoxides (end groups) can react. As the power increases, the incident radiation is subsequently higher and increases the reaction rate. In addition, under microwave radiation, the ability of secondary amines to absorb microwave radiation appreciably causes the more ready formation of ether bonds [216]. Comparatively, there is rate enhancement of more than 800 % at 1200 W and 400 % at 600 W, whilst achieving comparable T_g values of 103 °C and 107 °C (Entries 7 and 8, in Table 5.2) respectively compared to a T_g of 105 °C for isothermal curing at 100 °C for 2 hours.

However, non uniformity in curing has also been observed for microwave radiation. This is indicated by the large T_g variation (11 - 12 °C) for both microwave samples (entries 7 and 8, in Table 5.2). It has recently been demonstrated that discontinuous radiation of microwaves can improve the T_g distribution without compromising reaction rates and the final mechanical and chemical properties [219]. Similar observations of T_g variation suppression from 12 °C to 4 °C was measured for A13 systems, whilst providing comparable average T_g of 103 °C and 105 °C when cured under continuous and discontinuous (pulsed) mode respectively. The discontinuous process was found to be more efficient than the continuous radiation process, and may be associated with the activation of step – growth polymerisation [219,220]. Rao et al. [219] studied the uniformity of continuous and discontinuous curing through a thermal imaging technique and found hot spots in the epoxy – triethylenetetra amine system under continuous microwave radiation. This was thought to be due to thermal runaway and non-uniform microwave field typically prevalent in domestic microwave ovens. Figures 5.6 (a)

and (b) depict the respective continuous and pulsed microwave cure schedules evolved for A13 systems at 1200 W with a total exposure time of 15 minutes.

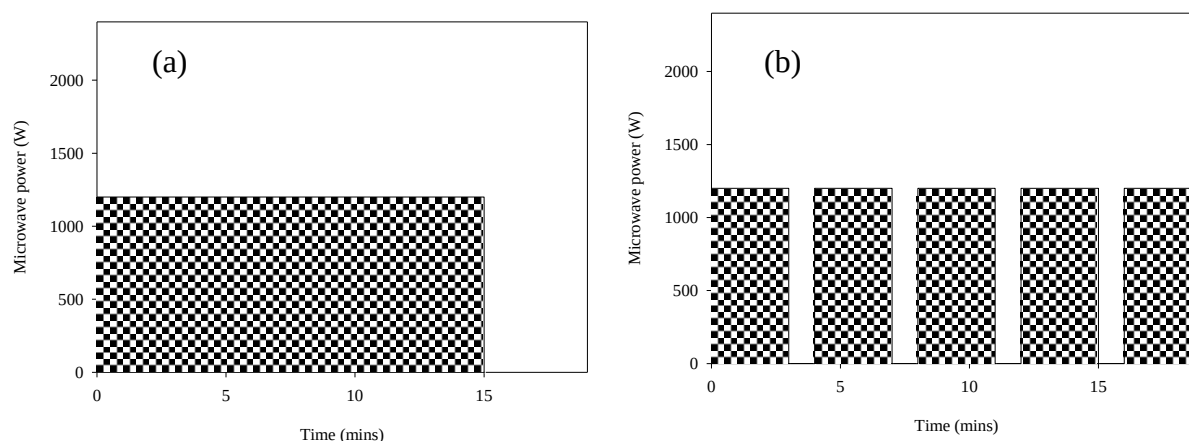


Figure 5.6: Microwave cure schedule for epoxy – TEPA systems; (a) continuous mode and (b) pulsed mode.

Table 5.3: Optimal curing conditions for epoxy – TEPA systems using thermal and microwave energy.

Curing schedule	Energy source	Mode	Curing condition
S1	Thermal	Isothermal	100 °C for 2 hours
S2	Thermal	Isothermal	75 °C for 19 hours
S3	Thermal	Gradient	5 °C.min ⁻¹ , from 30 °C to 100 °C
S4	Microwave	Discontinuous	600 W for 0.5 hours (exposure time)
S5	Microwave	Discontinuous	1200 W for 0.25 hours (exposure time)

Based on the results presented earlier, Table 5.3 lists the optimal curing conditions for epoxy – TEPA systems using both thermal (S1, S2 and S3) and microwave energy at 2.45 Hz (S4, S5 and S6). The chemical stability of A13 and A16 cured under these curing conditions will be studied and discussed in the following section.

5.4.2 Epoxy chemical stability

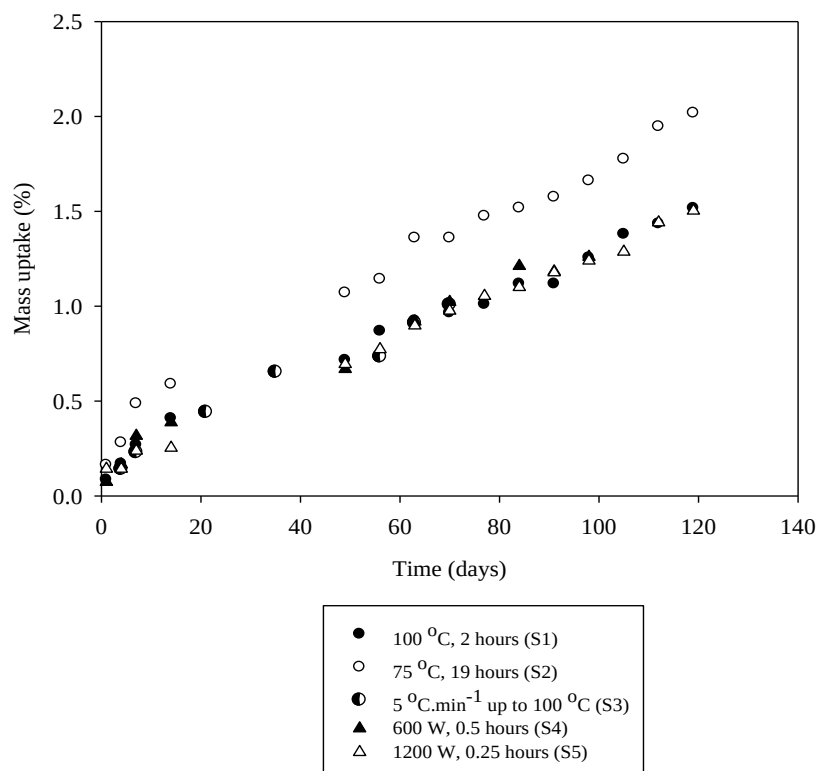


Figure 5.7: Stability of A13 in methanol when subjected to different curing conditions.

Figure 5.7 shows the mass change over time of A13 cured at various thermal and microwave energy curing conditions when stored in methanol. The results generally corroborate the measured glass transition temperature of A13 (T_g) (in Table 5.2) obtained at the various curing conditions. As expected, curing condition S2 (see Table 5.3) has significantly more mass uptake of methanol over time than the other curing conditions. This may be attributed to two effects: (i) the lower crosslinking density of the resultant cured adhesive, as reflected by the lower T_g and the higher initial diffusion coefficient of methanol (D), where D was calculated to be $5.9 \times 10^{-11} \text{ m}^2 \cdot \text{s}^{-1}$ for S2 and approximately $2.1\text{--}2.3 \times 10^{-12} \text{ m}^2 \cdot \text{s}^{-1}$ for S1, S3, S4 and S5 (taking M at $t = 119$ days as M_∞ for the purpose of the calculations); and (ii) the presence of more hydroxyl groups in its structure and the ability of hydroxyl groups to hydrogen bond to methanol. It is reasonable to note that density of hydroxyl groups ($-\text{OH}$) in the matrix increases with crosslinking density [173]. Therefore, these results show further

evidence for the curing mechanism suggested for thermal curing at 75 °C and 100 °C in the previous sections.

Table 5.4: Chemical stability of A16 cured isothermally and by microwave radiation in organic solvents. The mass uptakes were measured after over 140 days of immersion.

Solvent	Mass uptake after immersion in solvents for 140 days (%)				
	S1	S2	S3	S4	S5
Methanol	0.32	0.55	0.33	0.38	0.33
Acetone	0.30	0.33	-	-	0.27
Toluene	0.11	0.12	-	-	0.11
THF	0.21	0.83	-	-	0.24
DMF	0.19	0.78	0.22	0.27	0.21
DCM	1.99	*23.06	2.73	2.44	1.88

*Failure mode: Ductile. Measurement was taken after 70 days of immersion.

Sorption tests were also carried out in various organic solvents on the A16 formulation cured at various curing conditions. Table 5.4 shows the percentage weight gain of A16 cured under various conditions. Less than 3 % mass uptake was measured in all tested solvents at equilibrium for all curing conditions, except for S2 cured material when exposed to DCM. The sample cured under S2 conditions was observed to fail in DCM and become ductile due to the significant swelling of the network (with mass uptake of 23 %). All other curing conditions, isothermal curing conditions – 100 °C for 2 hours (S1), gradient curing conditions – 5 °C.min⁻¹ up to 100 °C (S3) and microwave curing conditions - 600 W for 0.5 hours and 1200 W for 0.25 hours (S4 and S5 respectively) showed significantly reduced degree of swelling in DCM relative to the S2 curing conditions. This is due to the higher crosslinking density provided by these curing conditions.

Through various levels of optimisation, it is concluded that S2 is the minimum curing conditions required to cure A16 and provide good chemical stability across a broad range of

organic solvents, apart from chlorinated solvents (i.e. DCM). However, for chlorinated solvent environments, it is necessary to cure A16 under more intensive curing conditions using either thermal energy (S1 and S3) or microwave energy (S4 and S5), to maximise the lifetime of the A16 adhesive.

5.4.3 Material selection

Table 5.5: Dielectric properties of various preserving agents at 2.45 GHz, together with their measured temperature change (ΔT) when subjected to microwave radiation at 1200 W for 1 minute.

Preserving agents	Dielectric constant, ϵ' @ 20 °C	Dielectric constant, ϵ' [221] @ 20 °C	Dielectric loss tangent, $\tan \delta$ [221]	ΔT (°C)
Mineral oil	0.2 ± 0.1	2.7	0.0001	0.5 ± 0.2
PEG 400	12.2 ± 0.5	12.0	1	78.2 ± 1.0
PMP	1.9 ± 0.1	2.5 – 2.6	0.0003	0.9 ± 0.3
Undecanone	10.1 ± 0.5	-	-	55.7 ± 2.3
Dimethylsuccinate	5.5 ± 0.1	-	0.02	49.3 ± 1.8
Water (Reference)	76.0 ± 0.3	76.7 - 78.2	0.157	75.1 ± 1.4

While the final properties of the cured epoxy adhesive are critical, the materials present in the whole spiral wound membrane module (e.g. membrane polymer, preserving agent, spacers, non woven and centre tube) also require consideration for the microwave radiation based curing process. The choices of preserving agents used for making P84 membrane modules cured via microwave radiation are determined by measuring the dielectric constant (ϵ') of the materials, and by obtaining the dielectric loss tangent of the materials ($\tan \delta$) from literature [221]. ϵ' and $\tan \delta$ provide a measure of polarity and the ability of the materials to polarise in response to the electromagnetic field at a fixed frequency. Mathematically, the power absorbed (P) by a material in an electromagnetic field can be expressed as follows:

$$P = 2\pi f \epsilon'' E^2 \tan \delta \quad (\text{Equation 5.4})$$

where f = frequency of the electromagnetic radiation, ε^0 = permittivity of free space (8.86×10^{-14} Farads.cm⁻¹), E = electric field strength, ε' = dielectric constant of material and $\tan \delta$ = dielectric loss tangent of material. The product of ε' and $\tan \delta$ is designated as ε'' , the dielectric loss factor.

From equation 5.4, at a constant frequency and fixed electric field strength, the absorbed power can be controlled by modifying the dielectric properties of the material. For example, materials which have high dielectric loss values, such as PEG 400 ($\varepsilon'' = 12.2$) and water ($\varepsilon'' = 11.9$) are expected to absorb microwave radiation readily. On the other hand, mineral oil ($\varepsilon'' \rightarrow 0$) and α -methylstyrene dimer (PMP) ($\varepsilon'' = 0.00057$) have low dielectric loss factors and are essentially transparent to microwaves. This fact is clear from the data in Table 5.5, which represents a summary of dielectric properties of the preserving agents and their temperature gained when subjected to microwave radiation at 1200W for 1 minute. Of all the preserving agents, mineral oil and PMP are predicted to be the most transparent to microwave radiation at 2.45 GHz with the smallest product of ε' and $\tan \delta$, which was confirmed by ≤ 1.0 °C temperature gain measured when these materials were subjected to microwave radiation at 1200 W for 1 minute.

5.4.4 Impact of curing on membrane performance

Analytical study

The thermal stability of the P84 and crosslinked P84 membranes was investigated by thermal gravimetric analysis (TGA), dynamic scanning calorimetry (DSC) and FT-IR spectroscopy. Figure 5.8 shows a plot of weight change and the derivative of weight change of both P84 and crosslinked P84 membranes against temperature. To eliminate any interference from other materials, both membranes were prepared without non woven support material and were air-dried with IPA as wetting agent prior to analysis. To ensure residual solvents (e.g.

DMF, dioxane and water) were fully removed, the membranes were flushed at 5 bar until 40 L.m⁻² of permeate were collected.

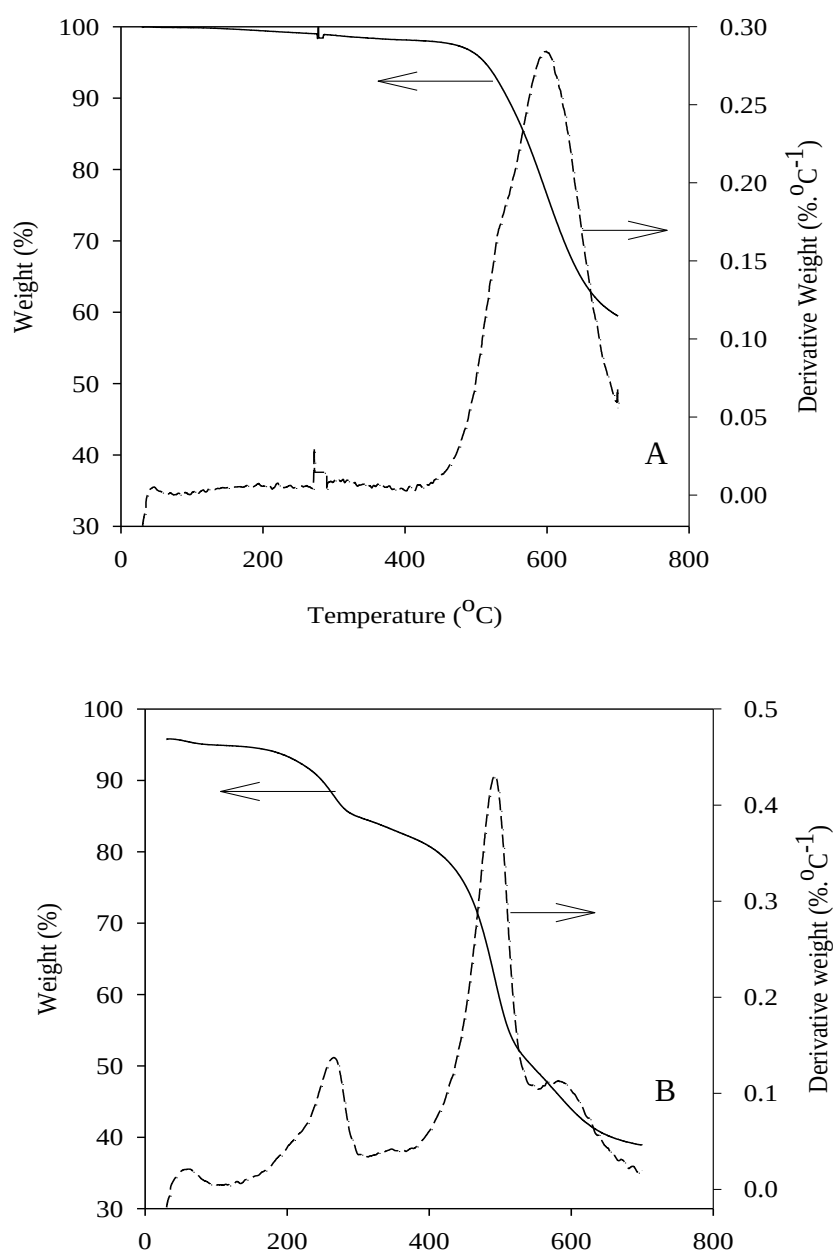


Figure 5.8: Thermal gravimetric analysis of (A) a P84 membrane (M2 formulation, in chapter 3) and (B) a P84 membrane crosslinked with HDA (M6 formulation). Both membranes were prepared without non woven material.

The P84 membrane (M2, in chapter 3) shows little weight loss with good thermal stability up to 400 °C (Figure 5.8 (A)). For the HDA crosslinked P84 membrane (M6), the initial weight loss at < 50 °C (Figure 5.8 (B)) was attributed to residual solvent IPA bound to the membrane

matrix. The second peak observed at around 250 °C (Figure 5.8 (B)) is at a much higher temperature than would be expected for the boiling point of HDA (B_p HDA: 205 °C) and this peak is most likely due to the energy required for re-imidisation of the imide bonds in the crosslinked P84 which then subsequently releases the reformed HDA. Similarly, an endothermic peak was also measured via DSC at a temperature range of 250 to 270 °C for the crosslinked P84 membrane (see Figure 5.9) and the FT-IR spectra (Figure 5.10) of the crosslinked membranes annealed at 100 °C and 150 °C for 0.5 h show that with increasing temperature, the spectral intensity of the imide bands decreased. This strongly indicates that re-imidization and loss of crosslinking in the membrane occurs. Further evidence for this hypothesis was noted as membranes annealed at 100°C were observed to remain insoluble in DMF, while membranes annealed at 150°C were observed to re-dissolve in DMF (symptomatic of non-crosslinked or partially crosslinked membranes).

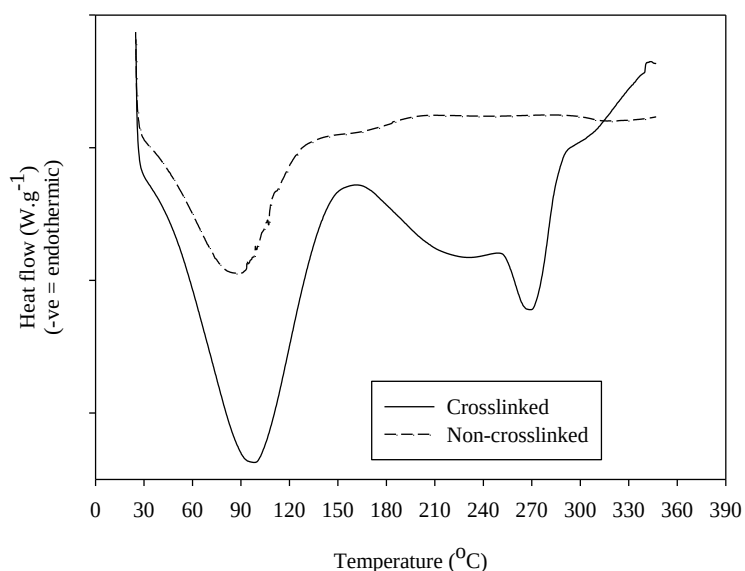


Figure 5.9: DSC analysis of P84 (M2 formulation, in chapter 3) and crosslinked P84 membrane (M6 formulation).

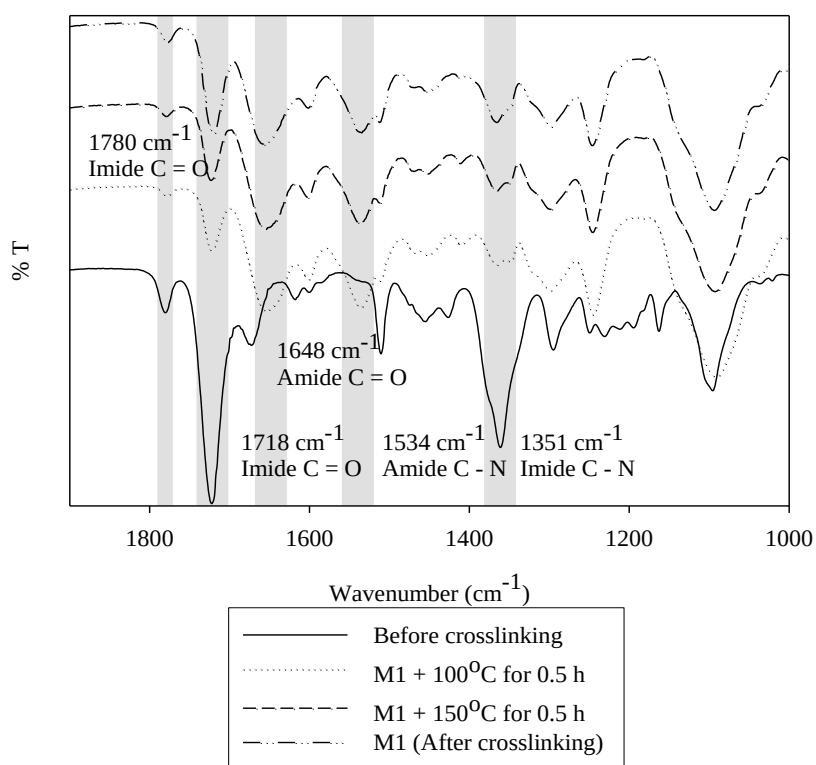


Figure 5.10: FTIR-ATR spectra of HDA crosslinked membranes (M6 wet dried, in Table 5.1) annealed at different temperatures for 0.5 h.

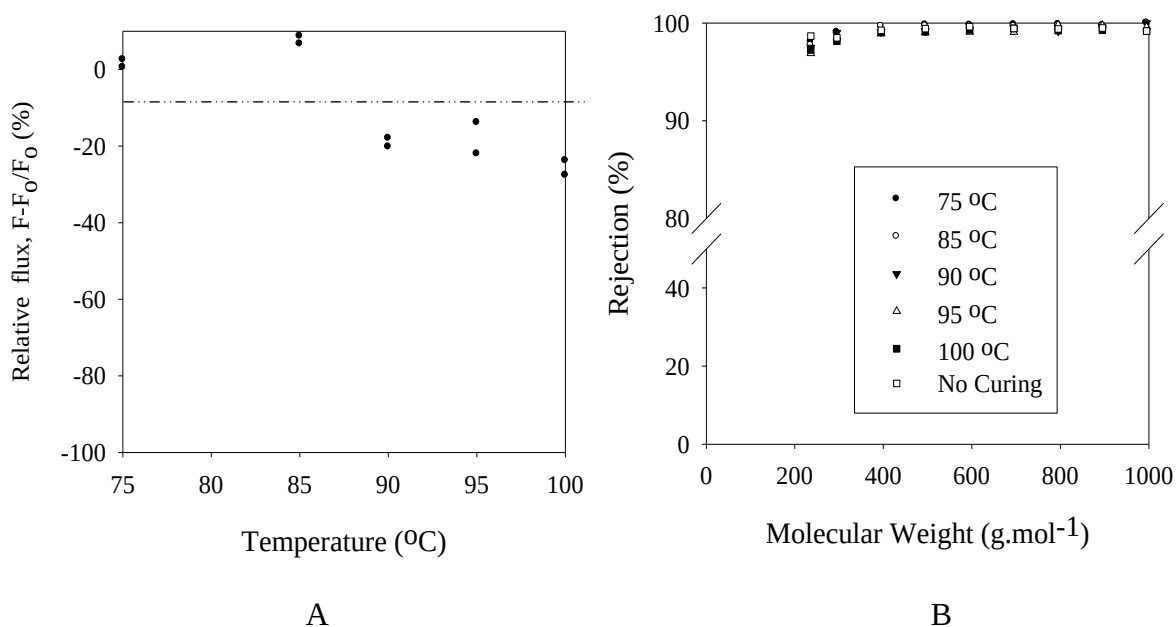


Figure 5.11: Effect of thermal energy on (A) acetone flux and (B) MWCO of M6 membranes, measured at 30 bar filtration pressure and 30 °C.

The results from the thermal gravimetric analysis suggest that the non crosslinked and chemically crosslinked P84 membrane should be stable up to 400 °C and 150 °C respectively (Figure 5.8). In Figure 5.9, the DSC analysis showed that energy is absorbed (endothermic peak) by both P84 and crosslinked P84 membrane at 85 °C and 90 °C respectively. The filtration results in Figure 5.11 for thermally cured crosslinked P84 membranes (M6), show a decline in acetone flux at temperatures ≥ 90 °C. Given that the evaporation of IPA from these membranes was measured to occur below 50 °C, it is believed that the strong energy flow into the membrane at 85-90 °C (DSC analysis, Figure 5.9) may be as a result of the activation temperatures for (i) evaporation of water strongly bound to the membrane matrix or (ii) rearrangement of the polymer chains to a thermodynamically stable state, leading to the densification behaviour reported by See-Toh et al. [32]. If (i) occurs, then water molecules are clearly shown to be bound more strongly to the crosslinked membrane than the non crosslink membrane. This is quite likely to be the case due to the increased hydrophilicity of the crosslinked membrane (as described in chapter 3) and the consequent increase in hydrogen bonding sites.

Membrane performance

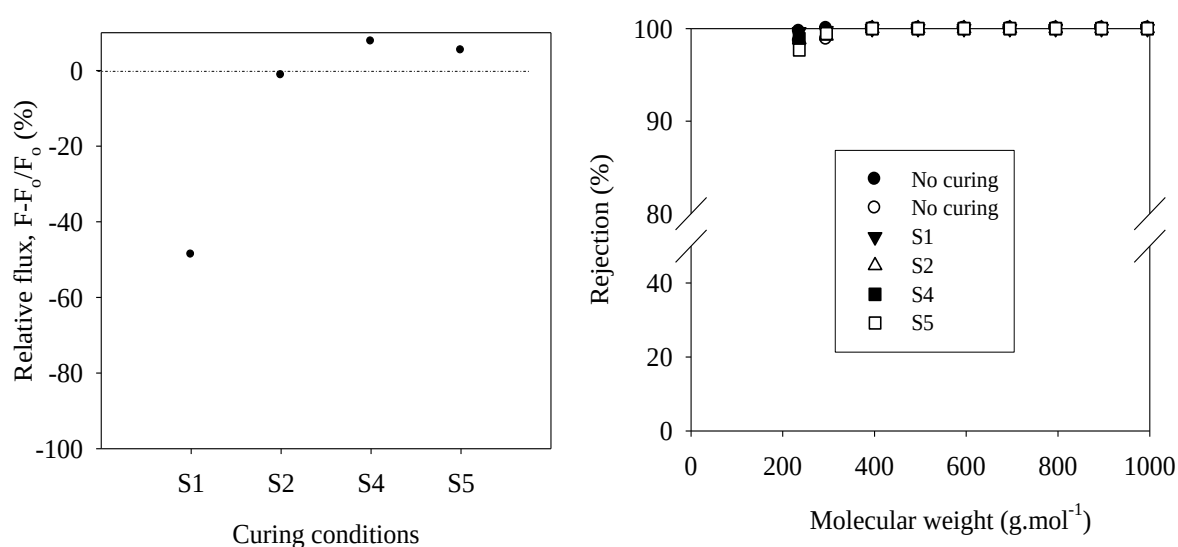


Figure 5.12: Influence of curing conditions (Thermal: S1 and S2; Microwave: S4 and S5) on (A) toluene flux and (B) MWCO of ST122 membranes, at filtration conditions of 30 bar and 30 °C.

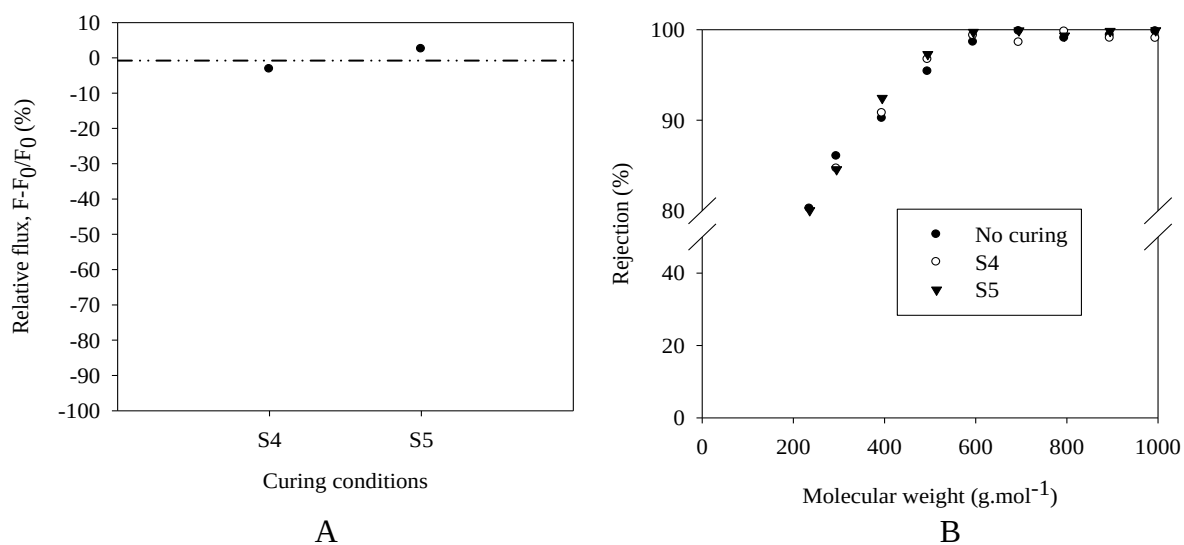


Figure 5.13: Influence of curing conditions (Microwave: S4 and S5) on (A) toluene flux and (B) MWCO of ST240 membranes, at filtration conditions of 30 bar and 30 °C.

Figures 5.12 and 5.13 present the effect of the optimal curing conditions for adhesive A16 on the flux and MWCO of StarmemTM 122 (ST122) and StarmemTM 240 (ST240) membranes

respectively. The flux across ST122 membrane was observed to decrease under curing condition S1 (100 °C for 2 hours), whereas S2 (75 °C for 19 hours), S4 (600 W for 0.5 hours) and S5 (1200W for 0.25 hours) had insignificant impact on the membrane's performance. Remarkably, the MWCO remain unaltered under curing condition S1. See-Toh et al. [32] had demonstrated similar observations on PI membranes produced in-house. This suggests that both the solute and solvent flux are reduced at the same rate, so that while flux decreases, rejection remains constant. SEM pictures (Figure 5.14 (A) and (C)) of the membranes before and after curing at 100 °C show a gradual loss of nanoporosity in the top separating layer and bottom supporting layer of the membranes. The nodular structure observed in membranes without annealing was replaced with a continuous non-porous dense layer interspersed with nodules, indicating that perhaps some of the nodules have repacked to form a continuous layer. An obvious shrinkage of the membrane was also observed. Similarly, toluene flux and MWCO curve remained unchanged for ST240 when subjected to microwave curing (S4 and S5). In conclusion, PIs are inert to microwave radiation at frequency of 2.45 Hz.

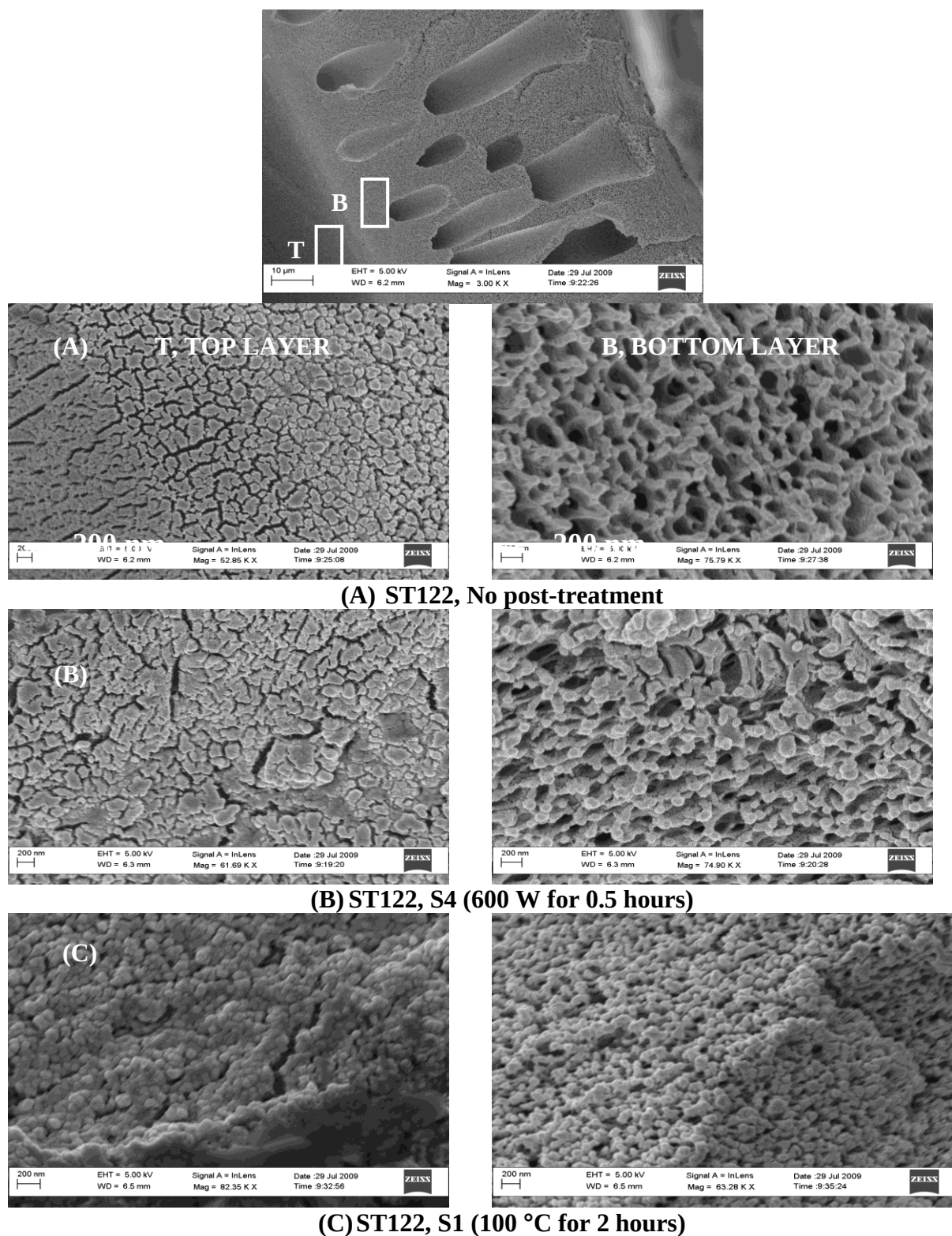


Figure 5.14: Cross section SEM pictures of the top separating layer and supporting bottom layer of Starmem™ 122 (ST122) membranes (A) before, (B) after being subjected to microwave curing (S4 – 600 W for 0.5 hours) and (C) after being subjected to thermal curing (S1 - 100 °C for 2 hours).

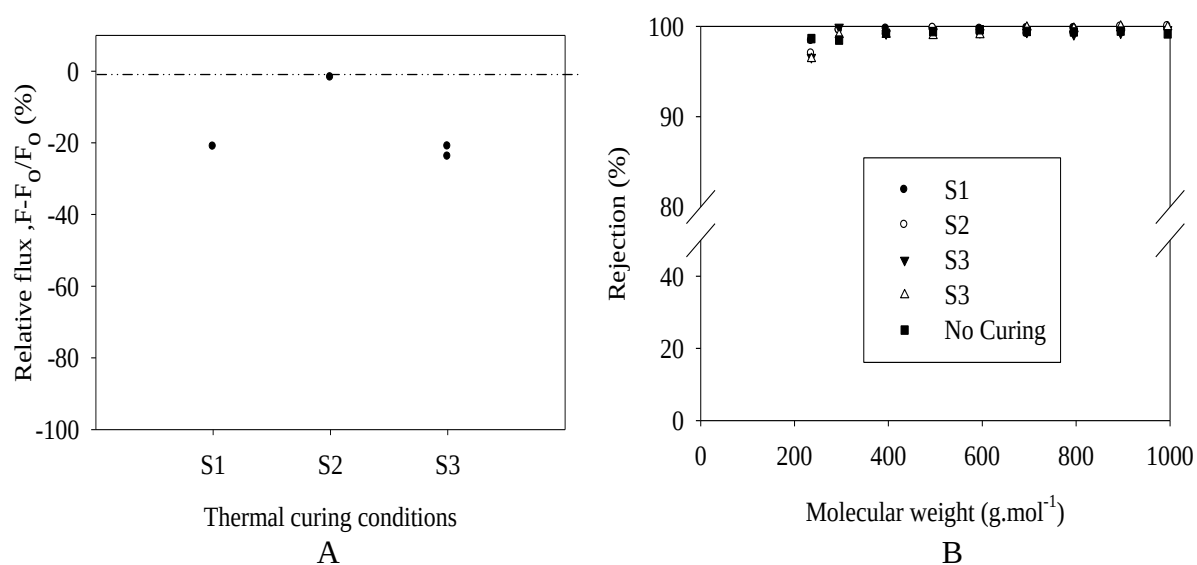


Figure 5.15: Influence of thermal curing conditions (S1, S2 and S3) on (A) acetone flux and (B) MWCO of M6 membranes, at filtration conditions of 30 bar and 30 °C.

Parallel results to StarmemTM 122 were obtained for M6 membranes (crosslinked and with PEG400 used as the preserving agent) when subjected to thermal curing (Figure 5.15). Curing conditions below the activation temperature (90 °C), S2, showed insignificant differences in flux. Concomitantly, curing conditions above the activation temperature, S1 and S3 suffer about 21 -25 % reduction in flux, whilst the MWCO remains unaffected.

Figure 5.16 presents the influence of microwave curing conditions, S4 and S5, on the acetone flux and MWCO for membrane M7 (crosslinked with PMP as the conditioning agent). Under microwave curing, the behaviour was the opposite of that observed for non crosslinked membranes (StarmemTM 122). Reduction of the solvent flux was measured for M7 membranes when subjected to microwave curing. As the power of the microwave energy was increased from 600 W (S4) to 1200 W (S5), the relative flux decline was also observed to increase with power without any affect on the MWCO. The decrease in flux was more pronounced than expected and it was found that free HDA was still present in the membrane

matrix. The -NH_2 groups in the HDA molecules are also highly susceptible to microwave heating and thus a more aggressive wash protocol was implemented to remove as much free HDA as possible.

For the enhanced wash protocol, IPA (HDA has a solubility up to 100 g.L^{-1} in IPA) was permeated through the membrane at low operating pressure, 5 bar, until no HDA was detected in the permeate. The Kaiser test was used to detect any unreacted amino groups in the permeate, which would be present due to any free HDA flushed from the M7 membrane. Special care must be taken during the analysis, to make sure all solid residues (e.g. P84 and P84 crosslinked with HDA) are removed from the liquid phase before the Kaiser test is carried out. The lower limit of detection of the Kaiser test is approximately 1 ppm. Once the free HDA in the membranes was removed, as confirmed by the Kaiser test performed on the permeate from the washes (see Figure 5.17), the relative flux drop improved from 37 % to 11 % when subjected to 1200 W microwave curing (S5).

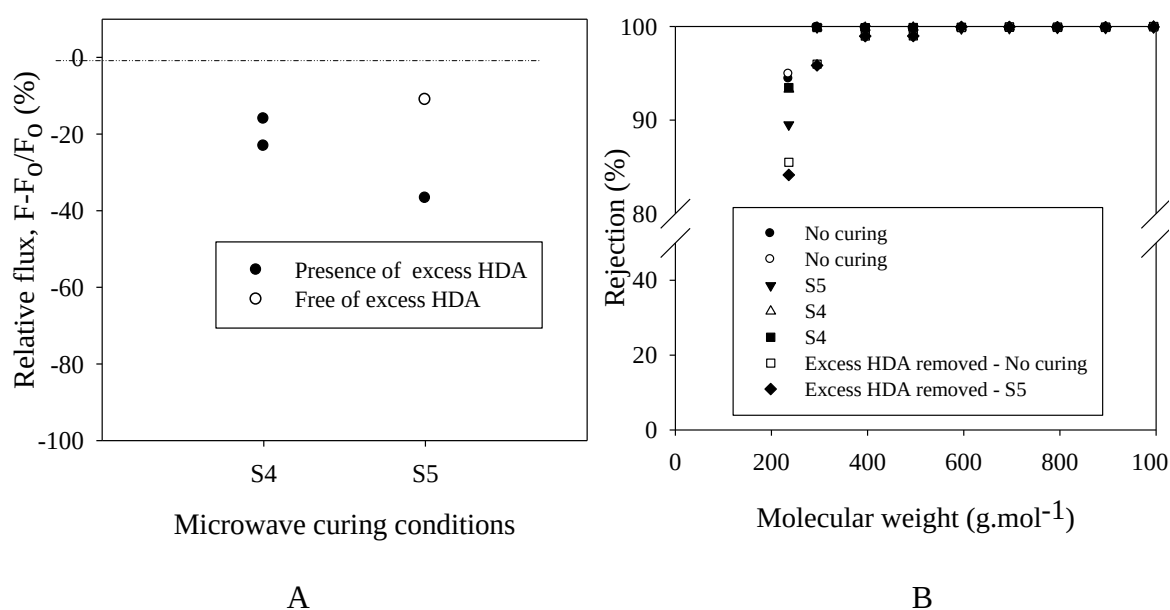
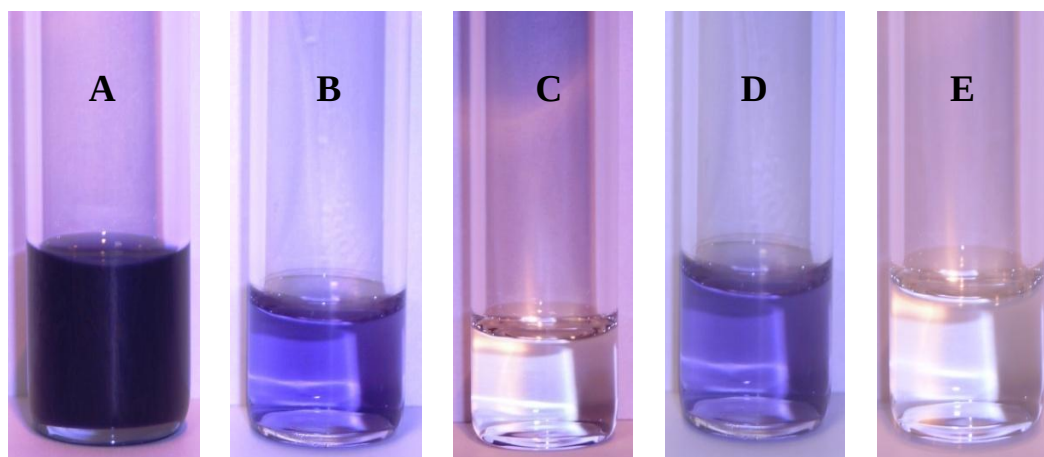


Figure 5.16: Influence of microwave curing conditions (S4 and S5) on (A) acetone flux and (B) MWCO at filtration conditions of 30 bar and 30 °C for M7 membranes.



Sample name	Sample
A	1 g.L ⁻¹ of HDA in IPA
B	10 ppm of HDA in IPA
C	IPA
D	Permeate after filtration of 7.1 L of IPA per m ⁻²
E	Last 10 mL of permeate after 17.6 L of IPA wash per m ⁻²

Figure 5.17: Kaiser test for the presence of free hexanediamine (HDA) in the permeate during washing of M7 membranes with IPA at 5 bar and 30 °C. Blue colour indicates the presence of amino groups.

Table 5.6: Microwave absorbance of different components of the M7 membranes at 1200 W for 0.25 hours (2.45 GHz).

Material	ΔT (°C)	Loading (g.m ⁻²)	Microwave absorbance		
			per g of material (J.g ⁻¹)	per m ² of membrane (J.m ⁻²)	Contribution (%)
P84	0.8	-	0.9	-	-
^a P84-HDA	4.5	58.7	5.1	299.4	27
HDA	96.8	3.1	249.4	773.1	70
PMP	0.6	37.4	1.0	37.4	3

^a P84-HDA solids were prepared by suspending P84 into 100 g.L⁻¹ HDA in IPA solution for at least 18 hours. The solids were then washed thoroughly with IPA until no HDA were detected in the IPA washes. The sample was analysed using elemental analysis, which confirmed 100 % crosslinking was obtained.

Clearly for the M7 membranes, free HDA in the membrane is a very strong absorber of microwave energy at 1200 W (2.45 GHz). The ability of each material present in M7 to absorb 2.45 GHz microwave energy at 1200 W was further investigated according to the procedure described in section 5.3.10. Table 5.6 presents the microwave absorbance of all materials in the M7 membrane exposed at 1200 W for 0.25 hours. In line with the characterisation results, free HDA is the primary source of heating, with a total energy

contribution of 70 %. This is followed by the backbone of the M3 membrane material, crosslinked P84 with HDA (P84-HDA). Unlike P84, after chemical crosslinking with HDA the P84-HDA backbone polarises in response to the electromagnetic field at 2.45 GHz and heating due to microwave absorption was measured.

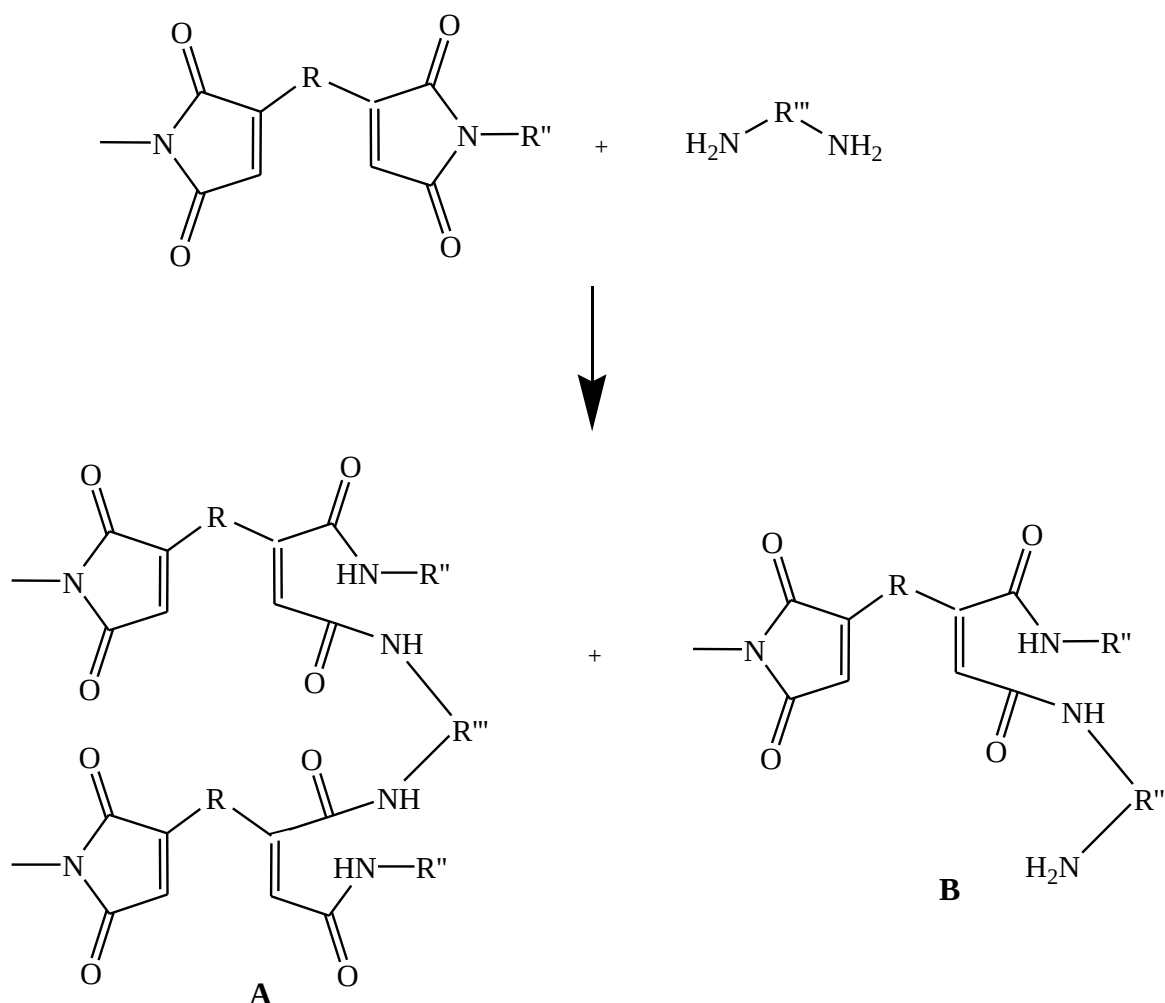


Figure 5.18: (A) Crosslinking of PI by reaction of imide bonds with diamines [120] and (B) reaction of diamines with PI precursor .

The proposed crosslinking mechanism by Liu et al. [120] suggests that the imide moieties in the polymer are susceptible to a ring opening reaction resulting in the formation of species A (in Figure 5.18). This species has some potential for microwave heating due to the potentially polarisable N-H bond in the amide groups. However, it is also highly likely that competitive

reactions at the ring opening sites in the presence of excess amines might also result in the formation of species B (in Figure 5.18) which gives a similar FTIR-ATR spectra. Species B is likely to have strong microwave absorbance due to the polarisable pendant NH_2 group. To test if the observed heating effect can be solely due to the presence of formation A in the crosslinked P84 structure, filtration experiments were carried out with M8 membrane made from Torlon 4000T-HV. Torlon 4000T-HV (Figure 5.19) consists of both the imide and amide groups present in formation A. Figure 5.20 presents the relative permeate flux and MWCO curves of M8 membranes before and after microwave curing (S5). A decrease in the permeate flux of M8 membrane was measured when exposed to microwave radiation following curing schedule S5, whilst maintaining its separation characteristics. These results suggest that even if 100 % crosslinking was achieved between polyimide and diamine following the proposed mechanism of Liu et al. [120], then it is likely that the membrane will still be susceptible to microwave radiation.

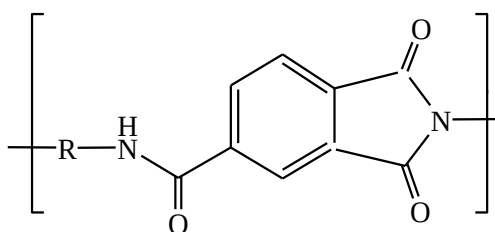


Figure 5.19: General chemical structure of Torlon 4000T-HV [222].

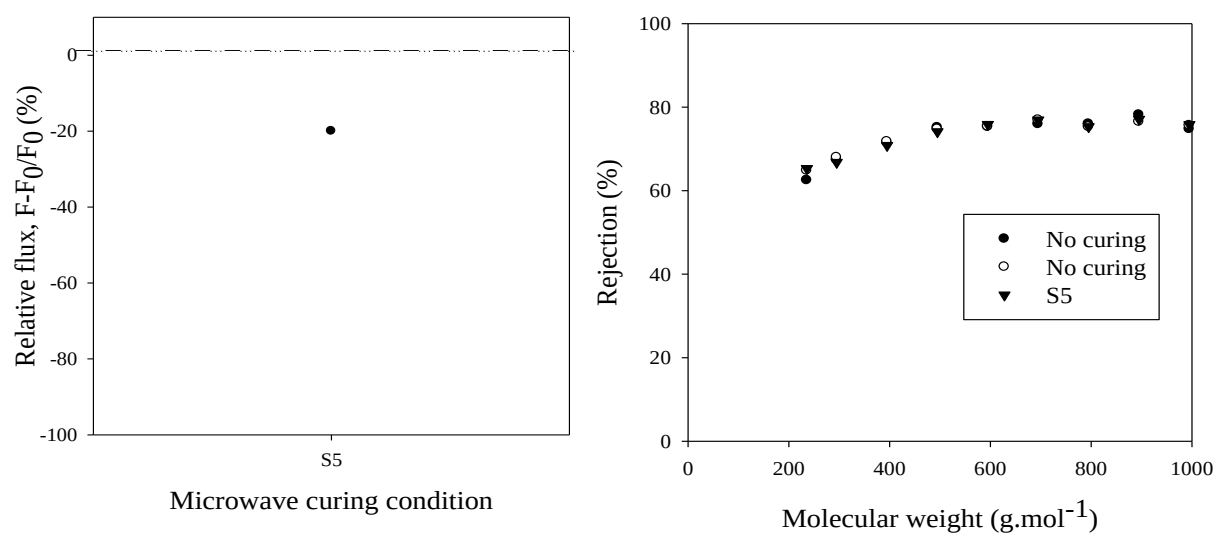


Figure 5.20: Influence of microwave curing condition S5 on the toluene flux and MWCO at filtration conditions 30 bar and 30 °C of M8 membranes.

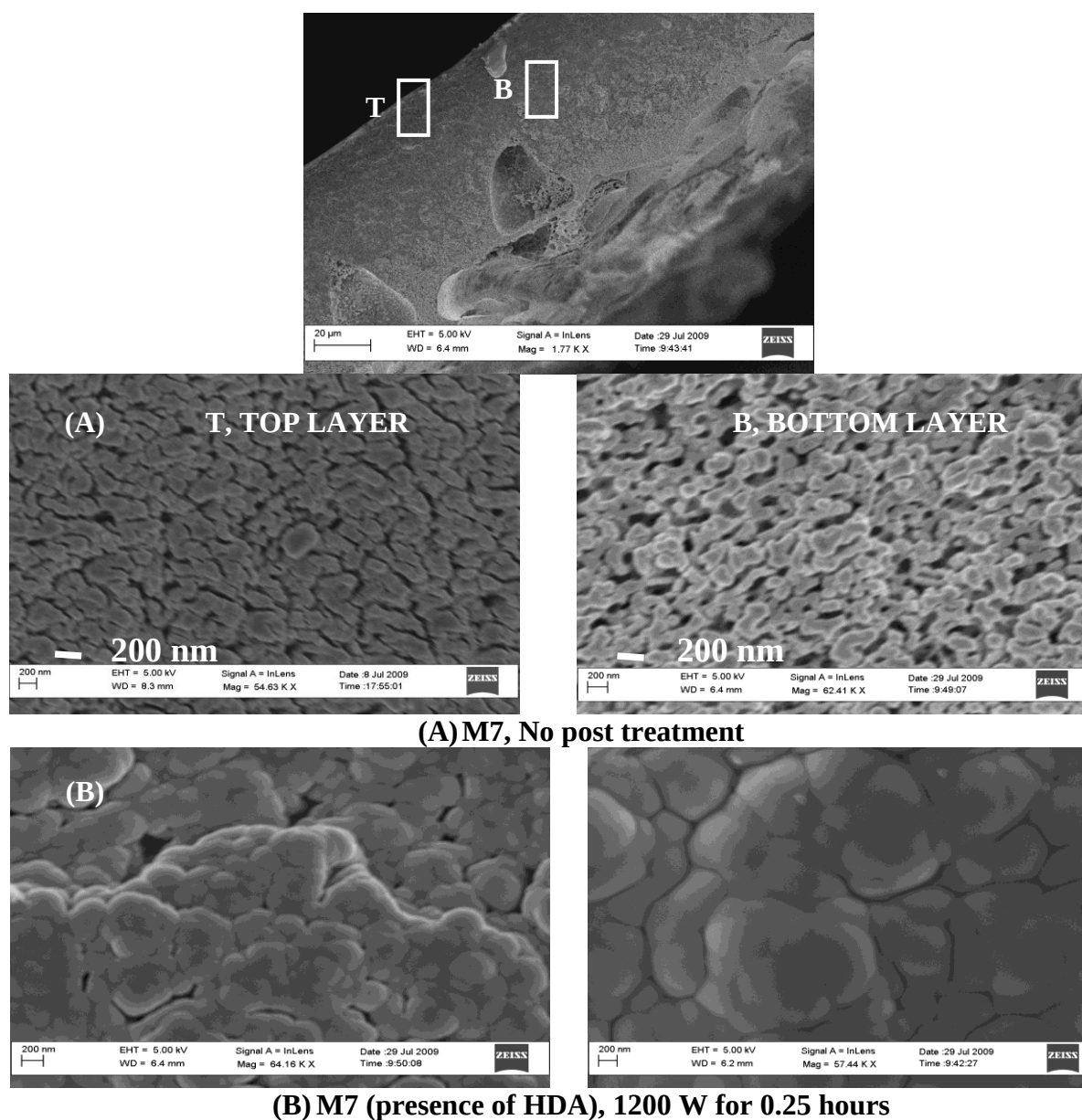


Figure 5.21: Cross section SEM pictures of the top separating layer and bottom layer of M7 membranes (A) before and (B) after being subjected to microwave curing (S5 – 1200 W for 0.25 hours)

Similarly, the SEM pictures in Figure 5.21 of the M7 membrane before and after being subjected to microwave curing (S5) show a loss in the porosity of the top separating layer, as well as the bottom supporting layer.

5.4.5 The curing process

In this section, the temperature profile within a spiral-wound module was studied following curing cycles as described in Figure 5.22; (i) *Cycle 1*: room temperature at 25 – 26 °C for 28 hours, (ii) *Cycle 2*: elevated temperature curing at 75 °C for 19 hours and (iii) *Cycle 3*: cooling at room temperature. A MicroLogix1500 programmable logic control (PLC) system integrated with a thermocouple input module and RSLogix500 software (Rockwell Software, Allen Bradley, USA) was used in this study. The output from the temperature transducers was logged using RSView32 software (Rockwell Software, Allen Bradley, USA). The positions of the *type K* thermocouple temperature probes are illustrated in Figure 5.23, with probe P1, P2, P4-P6 placed on top of the membrane surfaces and P3 located on the glue line. This study is highly relevant to provide insight to several important factors in designing and optimising the curing cycles of spiral-wound modules. The factors include:

- (i) *Temperature distribution within the module*: Since curing reactions of A13 and A16 are exothermic [160], internal heat will be generated by the adhesives in the module. Poor heat dissipation and high volume of adhesives within the module matrix may accelerate the chemical reaction and result in thermal runaway and hot spots. This phenomenon is not desirable for the curing mechanism of the adhesive and the impact it may have on the membrane itself.
- (ii) *Actual temperature of adhesive bond lines*: Large assemblies will act as a heat sink and may require substantial time for the adhesive within the joints to reach the specified temperature.

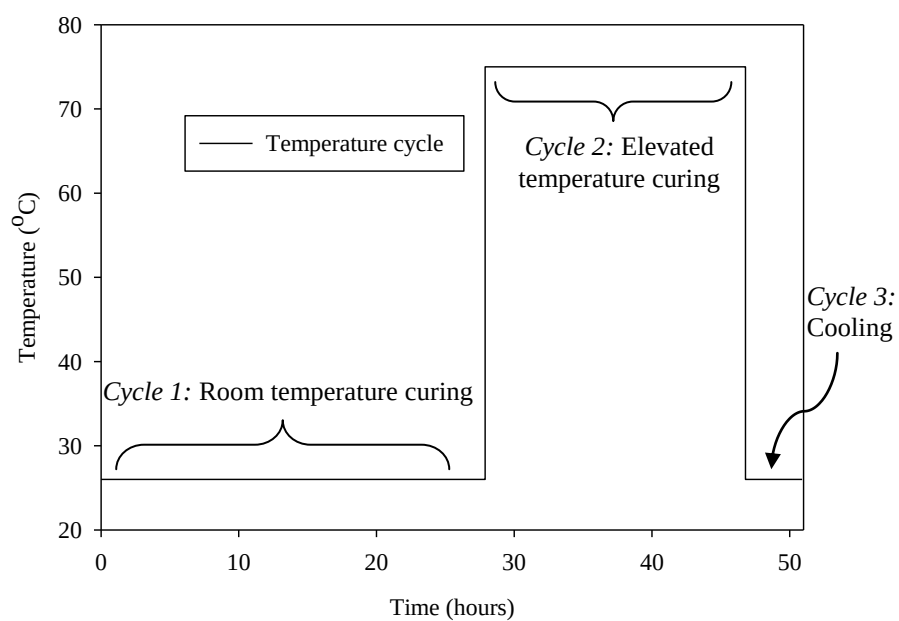


Figure 5.22: Curing cycle for spiral-wound membrane modules made from polyimide membranes and A13/A16 adhesive systems.

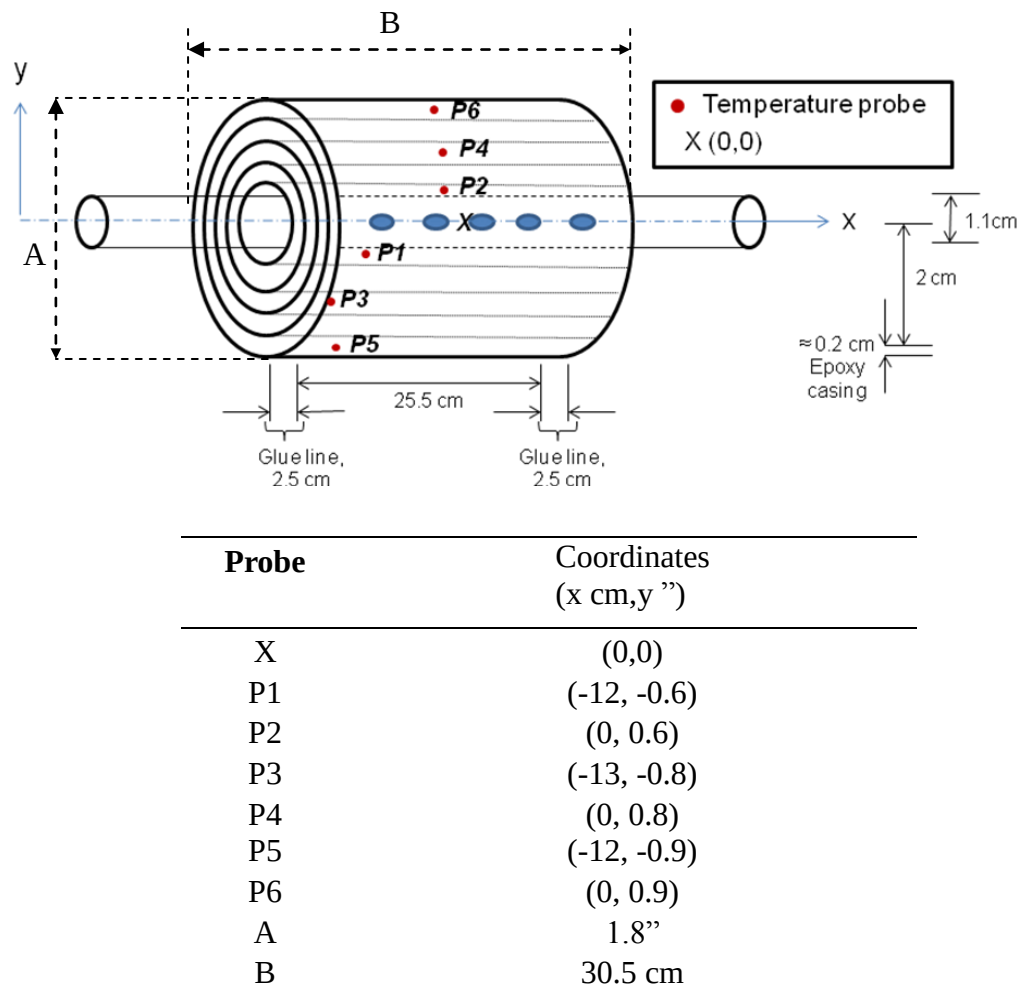


Figure 5.23: Positions of the temperature probes used to study the temperature profile during curing temperature cycles of a spiral-wound module.

The actual temperature profiles within a spiral-wound module consisting of M1 membrane which was assembled using A13 adhesive are shown in Figure 5.24. Similar temperature trends were measured by all probes during cycle 1 (room temperature, at 25 to 26 °C), with a maximum temperature peak at ≈ 37 °C on the glue line (P3) and on the membrane (P1) over a period of 0.75 hours. As expected, the temperature distribution near the glue lines, P1 and P5 are slightly higher than in the core of the module, P2, P4 and P6. Surprisingly, the temperature at the permeate tube (P2) is also insignificantly higher than the sections near the epoxy casing (P6), since a larger area is available on the outer casing for heat to convect and

radiate to the atmosphere. More importantly, during the elevated temperature curing phase (cycle 2, in Figure 5.24), the module was placed into the oven which was already at the curing temperature and it took less than 1 hour to achieve the specified temperature of 75 °C from room temperature 25 °C. Likewise, the temperatures within the module were also measured to be approximately 75 °C to 76 °C within 1 hour of being placed in the curing oven. Approximately 4 hours was taken to cool a 1.8'' × 12'' spiral-wound module to room temperature from 75 °C. In considering all the factors observed in the study, Figure 5.25 presents the optimal curing cycles for spiral-wound modules with elevated temperature curing at 75 °C for 19 hours (S2) and 100 °C for 2 hours (S1). The initial curing at 25 °C for 4 hours is necessary to avoid runaway reactions which could cause significant damage to both adhesives and membranes. An additional 1 hour and 1.5 hours in the oven at elevated temperatures of 75 °C and 100 °C respectively is required to allow heating of the adhesives to their specified temperatures from 25 °C.

This study also suggests that exothermic heat generated by the epoxy adhesives is readily conducted throughout the module, as indicated by the temperature at P3 (glue line) and P1 or P5 (membrane surfaces) with $\Delta T \leq 1$ °C. Considering a fixed mass of adhesives are spread on a fixed area, a larger diameter module with a fixed length would experience similar heat distribution, thus exhibiting comparable ΔT to a 1.8'' spiral-wound module. Therefore, the curing cycles proposed above would be suitable for curing spiral-wound modules of all sizes.

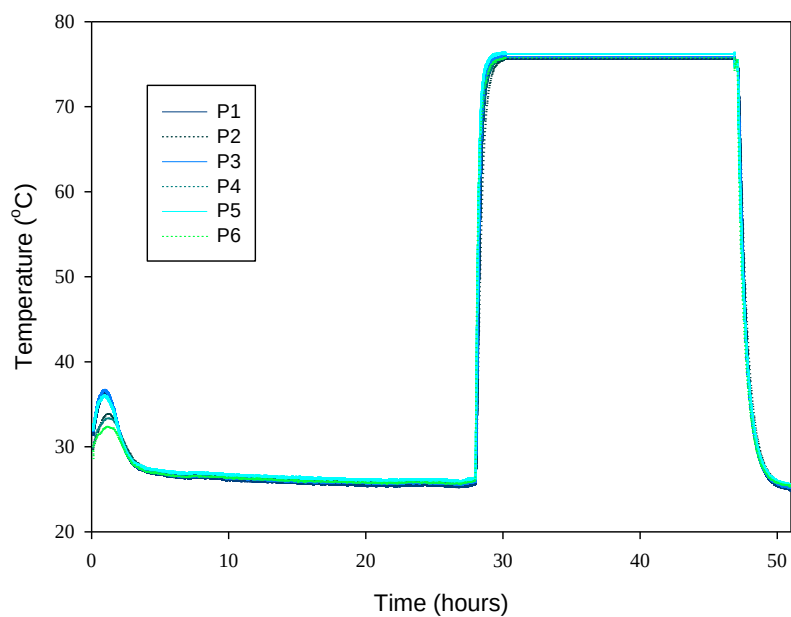


Figure 5.24: Actual temperature profiles of a spiral-wound module made from M1 membrane using A13 adhesive following the curing cycles described in Figure 5.21.

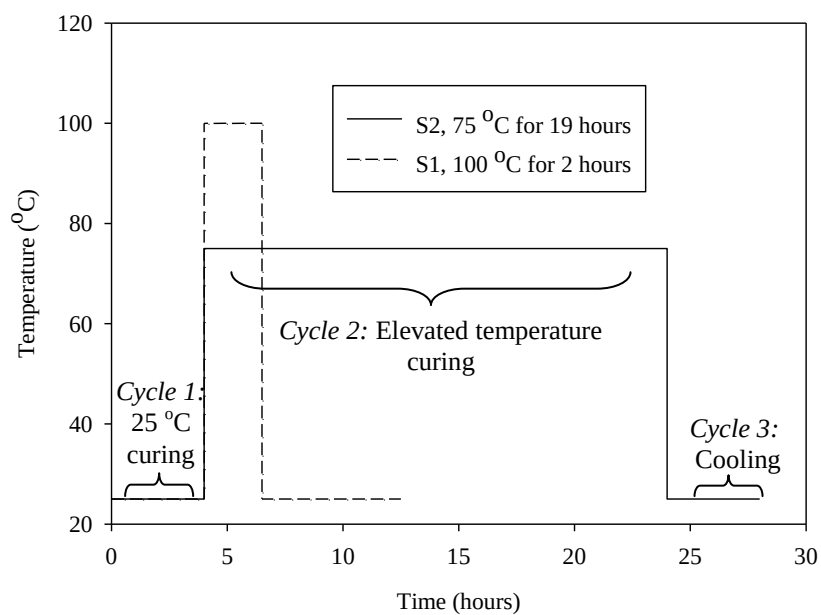


Figure 5.25: Optimal curing cycles for 1.8'' × 12'' spiral-wound modules with elevated temperature curing at 75 °C for 19 hours (S2) and 100 °C for 2 hours (S1).

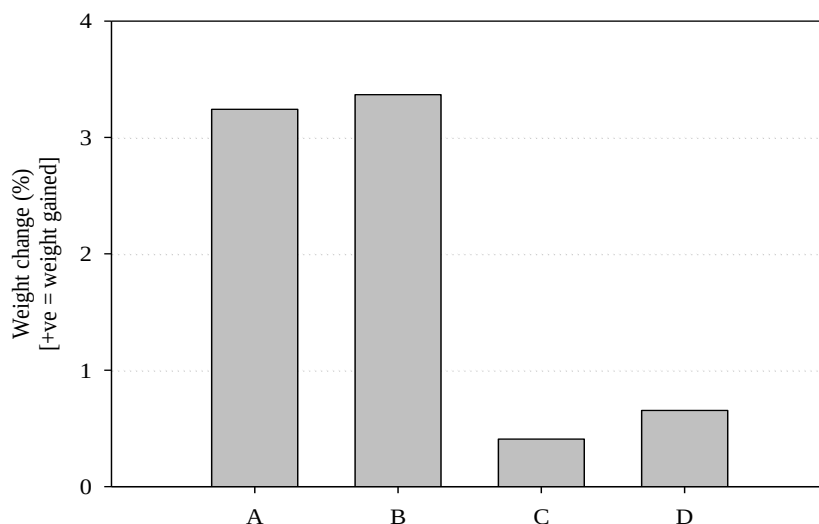


Figure 5.26: Effect of conditions during curing cycle 1 on A13 adhesive before elevated temperature curing: (A) 25 °C for 24 hours at 0 % humidity, (B) 25 °C for 24 hours at 60-70 % humidity, (C) 25 °C for 4 hours followed by 100 °C for 2 hours at 0 % humidity, and (D) 25 °C for 4 hours followed by 100 °C for 2 hours at 60-70 % humidity. The chemical stability was studied using methanol as solvent and weight uptake measurements were taken after 14 days of immersion.

The effect of environmental conditions during curing cycle 1 on A13 adhesive before elevated temperature curing is shown in Figure 5.26. The effect of humidity during curing cycle 1 is shown to have an impact on the chemical stability of the A13 adhesive. It is postulated that the absorbed water molecules on the uncured/curing materials has a tendency to attach directly to the available lone pair in the nitrogen of the aliphatic amines through hydrogen bonding, as presented in Figure 5.27 [194]. The stabilisation of the formation is promoted by the electron donating effect of the alkyl group(s) in the aliphatic amines [194]. The resultant formation hinders the nucleophilic substitution reaction of the epoxy – amine and subsequently reduces the degree of crosslinking. As such, it is both crucial to have a controlled humidity and temperature environment during curing to minimise chemical stability variation [160].

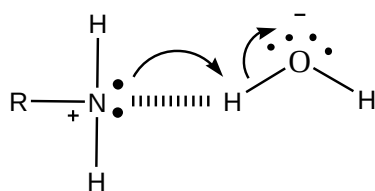


Figure 5.27: Protonation of aliphatic secondary amine with water through hydrogen bonding [194].

5.4.6 Long-term stability

The chemical and mechanical stability of the membrane modules was evaluated in two difficult solvents, DMF and THF. Figures 5.28 and 5.29 present (a) the MWCO and (b) the flux of M7 modules cured under curing condition S2 following curing cycles proposed above in DMF and THF at 30 bar and 30 °C respectively. The testing programme was carried out over 10 days in DMF and 120 days in THF with flux and rejection measurements taken periodically. The M7 membrane modules reached a stable permeate flux after 5 hours of compaction, giving a final flux of 65 L.m⁻².h⁻¹ and 70 L.m⁻².h⁻¹ in DMF and THF respectively. Maximum compaction of the membrane in the modules is observed in the first 0.5 hours of filtration, with about 24 - 27 % reduction in permeate flux in both cases. The membrane modules and flat-sheets showed comparable MWCO of 300 g.mol⁻¹ in DMF and 200 g.mol⁻¹ in THF. The data unequivocally demonstrates the stability over an extended test period of the membrane module in these harsh conditions whilst still affording good separation performance.

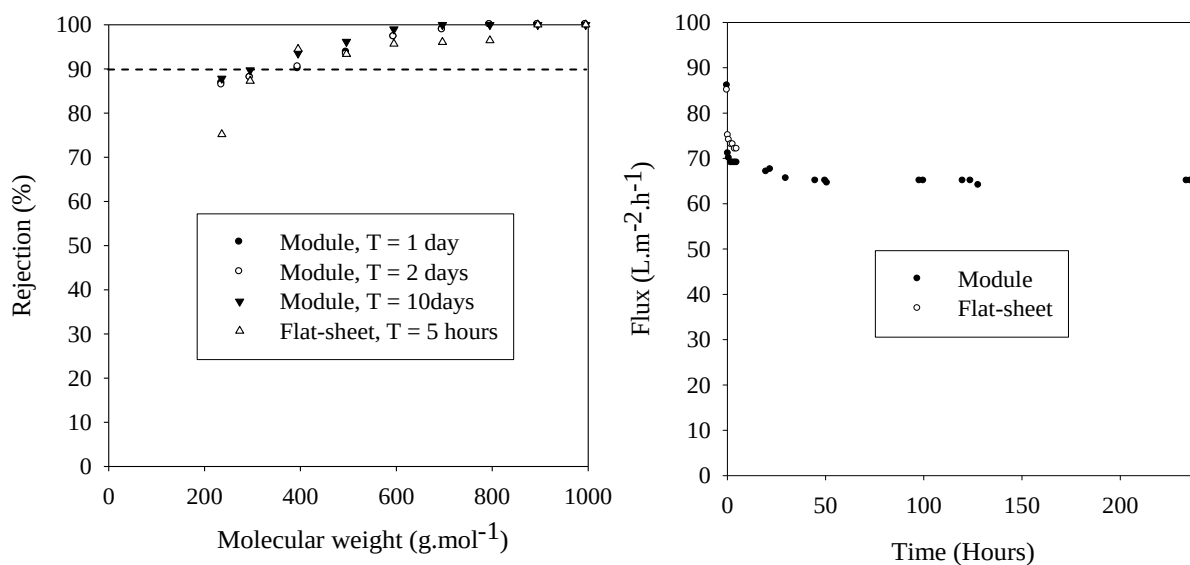


Figure 5.28: (a) MWCO and (b) DMF flux of a 1.8'' × 12'' M7 membrane module at 30 bar and 30°C over a period of 10 days in DMF.

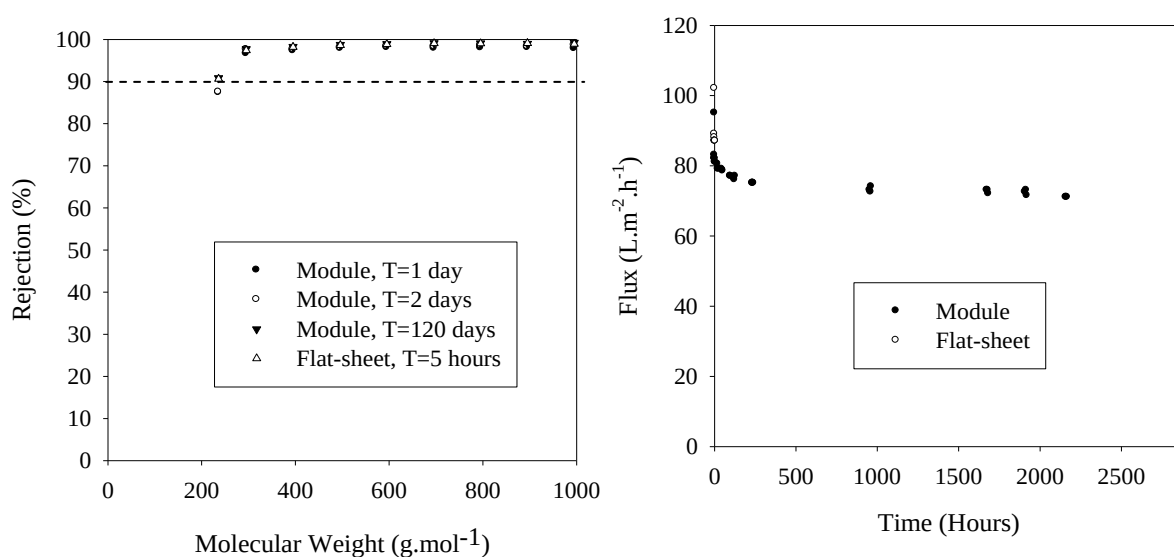


Figure 5.29: (a) MWCO and (b) THF flux of a 1.8'' × 12'' M7 membrane module at 30 bar and 30°C over a period of 120 days in THF.

As discussed in Chapter 4, the control of extractables is at least as important as chemical stability in the pharmaceutical industries. Table 5.7 summarises the percentage of extractables and leachables from A16 cured under S2 in DMF and THF. As expected, the percentage of extractables and leachables in DMF and THF from A16 cured under S2 were

measured to be higher than for A16 when cured under S1 curing conditions. This is due to the lower extent of cure achieved under S2 conditions and hence there are more unreacted materials still present in the cured network. Nevertheless, the amount of extractables in both DMF and THF are still below the acceptable limit [204,205].

Table 5.7: Extractables extracted from A16 epoxy – amine adhesives cured under S2 conditions in DMF and THF.

Solvent	Boiling point (°C)	Extractables, g of dry mass. g of sample ⁻¹ (%)	
		Wash 1	Wash 2
THF	66.0	0.04 ± 0.05	0.02 ± 0.02
DMF	153.0	^a 0.14 ± 0.08	^a 0.08 ± 0.03

5.4.7 Conclusion

This chapter identifies the potential of microwave radiation to cure epoxy adhesives for assembling polyimide membranes into spiral wound modules. The resultant A16 adhesive showed comparable chemical stability across a broad range of organic solvents, including harsh solvents such as methanol and DCM, to A16 cured traditionally at 100 °C for 2 hours. Advantageously, microwave curing (i) reduces the curing process time from 2 hours to 19 minutes (with a total exposure time of 15 minutes at 1200 W and 2.45 GHz) and (ii) selectively curing the epoxy adhesive without affecting the performance of polyimide membranes (StarmemTM 122 (P84) and StarmemTM 240 (Matrimid 5218)) given these membranes are susceptible to temperatures >100 °C. It is also essential to select a preserving agent that is transparent to microwave radiation for preserving the membrane structure. However, once P84 polyimide membranes are crosslinked with a diamine, the membranes are found to be vulnerable to microwave radiation. The effect was contributed to by the presence of excess diamine (R-NH₂) in the membranes, as well as the core chemical structure of the

modified polymer – amide groups due to their ability to polarise in the applied microwave field.

The activation temperature for the densification of P84 and diamine crosslinked P84 membranes were found to be at 85 °C and 90 °C respectively, which may be attributed to the evaporation of strongly bound water molecules in the membrane matrices. At temperatures above the activation temperatures, the performance of these membranes was found to show reduced permeability, but unchanged separation characteristics. A loss in nanoporosity is seen in the SEM. Consequently, a trade-off needs to be reached between preventing the loss of performance in the membranes and ensuring that the epoxy adhesives are sufficiently cured to provide good chemical stability. Apart from chlorinated solvents, a curing temperature of 75 °C for a minimum exposure time of 18 hours is the optimal condition for both polyimide and crosslinked polyimide membrane modules for applications in all organic solvents. The curing process proposed here is suitable for curing spiral wound modules of all sizes. Extended testing periods in DMF and THF for 10 days and 120 days respectively show that the membrane modules cured following the proposed temperature curing technique are stable, and afford good and leak free separation.

Chapter 6

OSN solutions to classic purification issues in the pharmaceutical industry

6.1 Abstract

This chapter describes the application of OSN using the second generation PI membranes and modules in typical purification problems encountered in the pharmaceutical industries with polar solvents such as DMF, acetone, ethanol, DMSO, water and THF, as well as solvent mixtures. The purification processes examined include:

- A. the integration of OSN into removing a by product (ammonium salt, TEA.HCl) formed in the synthesis of an API or its intermediate through acylation, elimination or alkylation of secondary amines with halogenides,
- B. solvent exchanges of API from high boiling point solvent (HBS) to low boiling point solvent (LBS) and from an azeotropic mixture to high purity solvent, and
- C. removing undesired oligomeric impurities from an expensive API intermediate to produce a developmental drug for Hepatitis C.

Case study C is a tedious separation problem which standard separation techniques (including chromatography, crystallisation and charcoal treatment) cannot achieve. In case study A, the first generation PI membranes showed a better selectivity and permeability in milder solvents like ethanol to provide a more efficient process. The purification process targets were achieved, but a major limitation associated with the membrane characteristics (also reported

with traditional technologies) was also identified and addressed by coupling the purification process with a downstream OSN-solvent recovery system (Dual Membrane Diafiltration (DMD)). This provides a solvent-efficient process, which does not generate large volumes of waste and/or does not provide a dilute product solution that would require further processing.

6.2 Introduction

Most pharmaceutical drugs on the market today are made by synthetic organic processes involving multi-step reactions and separation processes. The separation and isolation of a desired pharmaceutical compound or intermediate from impurities receives significant attention from chemical engineers and process chemists in the pharmaceutical industry, since purification processes are often the major hurdle in pharmaceutical manufacturing. In many cases, the impurities are unused reactants that remain with the desired product, or side/by-products from the synthesis, or compounds that form due to aging of the product. The presence of these unwanted materials, even in small amounts, may influence the efficacy and safety of the pharmaceutical products [223,224].

In the pharmaceutical industries, state-of-the-art purification and separation technologies primarily rely on extraction, crystallisation and column chromatography. There are limitations to these purification/separation techniques and they sometimes require research and development to change the synthesis route to accommodate the process target, as well as process economics [225-227]. Membrane technology, particularly nanofiltration, has attracted a great deal of attention as an alternative molecular purification technology for APIs [9,39,101-104,228]. By selecting suitable MWCO membranes, this technology can be used to separate molecules in the molecular weight range of 200 to 1,000 g.mol⁻¹ which have similar physical properties. The newly improved second generation PI membrane and reliable

modules from this work has opened up future possibilities for further applications of OSN in a larger range of organic solvent environments, especially in polar solvents.

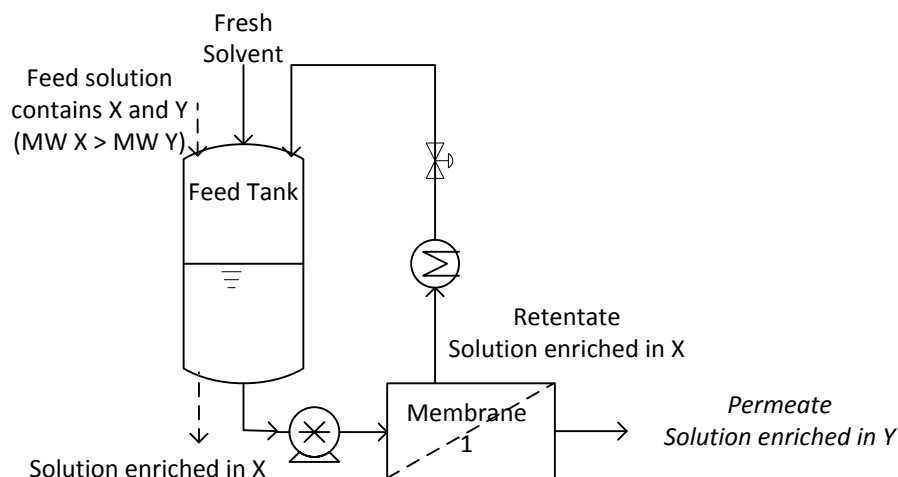


Figure 6.1: Schematic diagram of an Organic Solvent Nanofiltration (OSN) membrane purification process of a mixture comprising compounds X (higher MW) and Y (lower MW).

In membrane technology, diafiltration is a common technique used for purifying materials [229]. There are numerous applications of diafiltration processes in aqueous solution in the food and beverage, biotechnology and pharmaceutical industries [1,103,230,231]. The concept of membrane purification by diafiltration is depicted in Figure 6.1. Fresh solvent is added to a batch of feed which is undergoing filtration, so that the lower molecular weight species, compound Y, is flushed through the membrane whilst retaining the higher molecular weight species, compound X. The retained solute (compound X) concentration is not allowed to increase during the diafiltration, minimising concentration polarisation effects and enabling the permeating species to be flushed through the membrane more effectively. In contrast, diafiltration in organic solvent solutions is rather unexplored. The use of OSN membranes in diafiltration processes for solvent exchanges has been reported [40,103]. To our knowledge, no literature has reported the use of OSN for diafiltration separations of two or more solutes in organic solvent solution. In this chapter, the potential of the second

generation PI membranes and modules developed in the preceding chapters as a separation tool in the chemical production process of APIs is evaluated.

To represent typical purification and/or separation problems in organic synthesis in the pharmaceutical industry three different separation case studies are investigated. The case studies include:

Case study A

Proton scavengers (*N,N*-diisopropylethylamine, triethylamine, tributylamine, methylmorpholine, etc.) are employed in the synthesis of active pharmaceutical ingredients (APIs), including chemical reactions such as acylation, elimination and alkylation of secondary amines with halogenides [232-235], where the respective halogen acid is generated in the course of the reaction. The halogen acids react with the nitrogen function of the base scavenger and ammonium salts form accordingly. Without the presence of the proton scavenger, some of the synthesised tertiary amine would take on the role of proton scavenger and hence reduce the reaction yield [233].

Typical separation technique:

Extraction of undesired ammonium salts (of Br, Cl and I) into an aqueous phase from organic reaction mixtures that are not miscible with water are practiced in industry. For organic reaction mixtures that are miscible with water, solvent extraction is often applied. But, this separation step can lead to additional yield loss, as well as high solvent consumption and consequently a high volume of waste will be generated [233]. Concomitantly, this separation technique (aqueous/solvent extraction) limits the possibility of acylation and/or alkylation reactions in solvents such as methanol, ethanol, acetone, THF, DCM, DMF and DMSO,

which are also desirable for the reaction yield [235,236]. Due to their good miscibility with water, these reaction routes are usually eliminated in the early stages.

OSN:

The feasibility of removing the ammonium salt triethylamine hydrochloride (TEA.HCl) from model reaction solutions containing a model API compound (rosmarinic acid (model API-1, with MW of 360 g.mol⁻¹)) in water miscible solvents via OSN is demonstrated. OSN can reduce the total amount of solvent required, facilitate separation by using fewer different solvents and minimise the number of post processing operations.

Case study B

Solvent exchange is a common unit operation in pharmaceutical manufacturing since many sequential organic synthesis reactions are carried out in different organic solvents. Generally, this is one of the major solvent consumption processes in the industry [40,91].

Typical separation technique:

Distillation is commonly applied in industry to swap solvents. However, distillation is only able to swap solvents with differing boiling points when the solvent to be removed has a lower boiling point than the replacing solvent. It is difficult to exchange target compounds from a high boiling point solvent (HBS) to a lower boiling point solvent (LBS), although Chung et al. [237] have demonstrated that ‘put-and-take’ distillation at lab scale using rotary vacuum evaporation can eventually exchange the desired compound into LBS using frequent additions of the LBS. There are several drawbacks to this operation, but the main ones are that it consumes significant energy, and generates a vast quantity of intermediate solvent

mixtures (waste). Last but not least, distillation is not the best solution for APIs since the vast majority of APIs are susceptible to thermal degradation.

OSN:

The benefit of nanofiltration processes compared to conventional thermal separation techniques is that the separation can be performed at near ambient or sub-ambient temperatures which offer a considerable advantage for thermolabile compounds. This can minimise the loss of activity of APIs due to thermal degradation. Since the separation discrimination via OSN is based on size, shape, solute-solvent and solvent-membrane interactions [1,9], it is feasible to exchange target solutes from HBS to a replacing LBS or from LBS to a replacing HBS or even from solvent mixtures with similar boiling points [40,103] and azeotrope mixtures [103]. Here, two typical solvent exchange processes are demonstrated and they are:

- (i) exchanging target solute (sucrose octaacetate, model API-2 with molecular weight of $678.59 \text{ g.mol}^{-1}$) from 100 wt% HBS – dimethyl sulfoxide (DMSO) to replacing LBS – acetone; and
- (ii) exchanging target solute (rosmarinic acid, model API-1) from an azeotrope mixture of ethanol-water (96 wt% ethanol in water) to ethanol.

Case study C

This case study is a current separation challenge encountered at Janssen Pharmaceutica to produce a developmental drug for Hepatitis C. In the synthesis of a macrocyclic intermediate of a new drug candidate at Janssen Pharmaceutica (API-3, $\text{MW}=675 \text{ g.mol}^{-1}$), its isomer (Isomer B) and a series of oligomeric impurities based on API-3 with $\text{MW} > 1000 \text{ g.mol}^{-1}$ (i.e. dimers, trimers, tetramers, pentamers, etc.) are also formed. Isomer B, dimers and trimers

of API-3 can be separated using conventional techniques such as preparative high pressure chromatography. However the presence of oligomeric impurities, especially the tetramers and higher oligomers of API-3, block the active sites of the stationary phase and make this separation step tedious. For a feasible process, 100 % removal of the tetramers and pentamers from API-3 is essential.

Typical separation techniques:

All the separation techniques typically applied in the pharmaceutical industries, including crystallisation and charcoal treatment, have been investigated to remove tetramers and pentamers of API-3. However, these techniques offer low removal of these oligomeric materials and the loss of significant quantities of expensive API-3 into the waste stream is one of the main contributors to the manufacturing cost of the new drug. The API-3 yield and removal of oligomers of API-3 will be reported in the following section in this chapter. In addition, both separation techniques also generate a vast amount of waste and make them unfeasible. In the case of charcoal treatment, 50 wt% (relative to API-3) of charcoal is required for every batch, and the volume of waste generated from crystallisation is double the process volume in each batch (comprising of mother liquor and anti-solvent). Crystallisation can be a rather complex process that is difficult to control and scale-up due to the interlinked nature of chemical and physical effects, and also requires significant optimisation to generate acceptable process yields [225,226].

OSN:

The key parameters of the purification process (API-3 yield, removal of high MW oligomers and product purity) are compared between OSN and the classic separation techniques – crystallisation and charcoal treatment applied in case study C.

One of the main challenges facing the OSN diafiltration processes in case studies A and B is that a considerable amount of fresh solvent is required to achieve the process targets (i.e. purity and/or yield). This is a generic problem in membrane separation technology, since the permeating molecule is usually retained to some degree. This limitation in case study C is eliminated through using the Dual Membrane Diafiltration (DMD) process, as demonstrated by Figure 6.2. The DMD process combines two diafiltration stages – e.g. a purification stage combined with a solvent recovery stage. Here, instead of adding fresh solvent to the process in every diafiltration volume, recovered solvent from the solvent recovery stage is fed to the purification stage to allow further purification to be carried out.

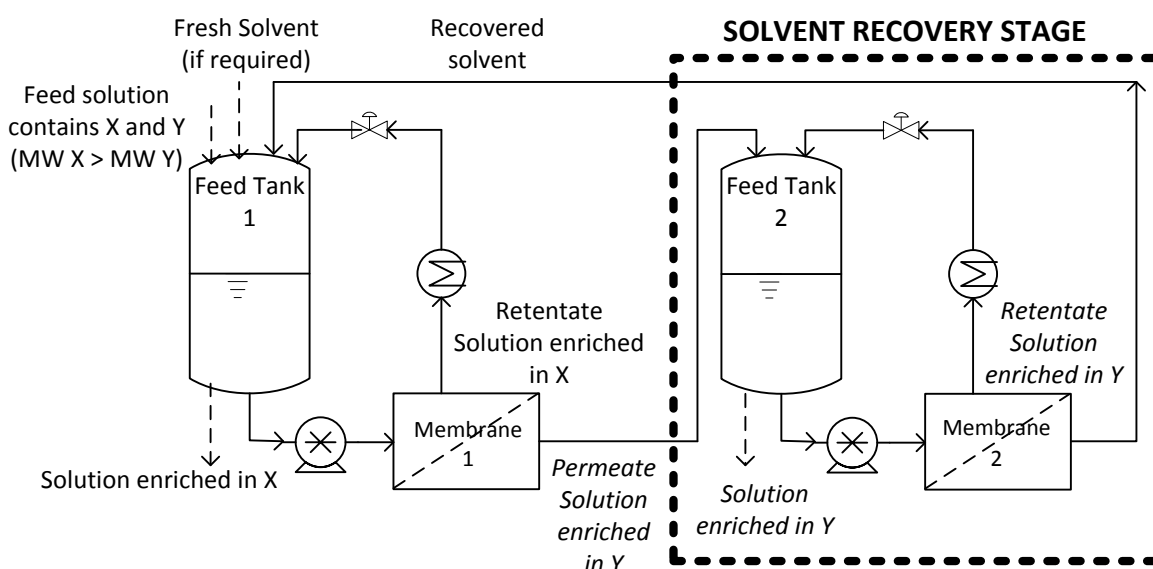


Figure 6.2: Schematic diagram of Dual Membrane Diafiltration (DMD) process, compound Y (lower MW) is separated from compound X (higher MW) in the primary stage using Membrane 1. In the secondary stage, compound Y is retained using Membrane 2, allowing solvent to be recycled back into the primary stage.

(Case study C has been published in Organic Process Research and Development [238].)

6.3 Experimental

6.3.1 Process description

The schematic overview of case studies A, B and C are presented in Figure 6.3. Case study A mimics a typical separation challenge in the pharmaceutical industry where purification of a reaction mixture containing a desired compound (rosmarinic acid – API-1, a model API with MW of 360.31 g.mol⁻¹) and 0.1 wt% of undesired ammonium salt – triethylamine hydrochloride (TEA.HCl with MW of 137.69 g.mol⁻¹), a by-product from acylation/alkylation reactions is required. Three water miscible reaction solvents were chosen in this study; DMF, acetone and ethanol. The aim is to purify a solution containing 0.1 wt% of the desired compound, API-1, and 0.1 wt% of the unwanted impurity, TEA.HCl, to give a final product containing less than 0.005 wt% of TEA.HCl ($\geq 95\%$ removal) whilst recovering $\geq 95\%$ of API-1. The yield of product i (Y_i) and removal of impurity i (R_i) are calculated using the following equations:

$$Y_i = \frac{M_{p,i}}{M_{F,i}} \times 100\% \quad (\text{Equation 6.1})$$

$$R_i = \frac{M_{R,i}}{M_{F,i}} \times 100\% \quad (\text{Equation 6.2})$$

Case study B, solvent swapping processes involves (i) the exchange of the desired compound (sucrose octaacetate, API-2 with MW of 678.59 g.mol⁻¹) from HBS, DMSO, to more than 99.99 wt% of the replacement LBS, acetone, and (ii) the exchange of desired compound (rosmarinic acid, API-1 with MW of 360.31 g.mol⁻¹) from 94.4 wt% ethanol in water (an azeotrope mixture) to more than 99.9 wt% of ethanol. In both cases, $\geq 95\%$ of the APIs have to be recovered.

Case study C involves the separation of API-3 (with MW 675 g.mol⁻¹) from oligomeric impurities based on API-3 (with MW>1000 g.mol⁻¹, e.g. dimers, trimers, tetramers, pentamers, etc.). The main objective of this case study is to remove $\geq 99\%$ of the tetramers and higher oligomeric impurities from API-3, while recovering $\geq 95\%$ of API-3. Advantageously, by removing these oligomeric impurities to $\leq 3.0\%$, just one chromatography stage rather than multiple chromatography stages is required to generate high purity API-3 for subsequent reaction steps in the production process. Reducing the number of chromatography stages is a major saving in time, equipment occupancy and material cost. In case study C, the DMD concept is introduced for solvent recycle (refer to Figure 6.2). Permeate containing the purified product from the primary membrane filtration (Membrane 1) is fed into the solvent recycle stage (Membrane 2). API-3, isomer B and the oligomeric impurities are retained by Membrane 2 in the solvent recovery stage, whilst the solvent freely passes through the membrane. The permeate from the solvent recovery stage (stage 2) is then returned to the purification stage (stage 1). This closed-system configuration allows solvent to be recycled and minimises the use of fresh solvent. The yield of API-3 (Y_{API-3}) and impurity level in the OSN product (I) after the purification processes are calculated based on equations 6.3 and 6.4 respectively. The impurity level in the purified product is based on the relative mass of API-3 and the oligomeric impurities (i.e. dimer, trimer, tetramer and pentamer of API-3) present in the product.

$$Y_{API-3} = \frac{M_{R2,API-3}}{M_{F,API-3}} \times 100\% \quad (\text{Equation 6.3})$$

$$I = \frac{M_{R2,Oligomeric\ impurities}}{M_{R2,API-3} + M_{R2,Oligomeric\ impurities}} \times 100\% \quad (\text{Equation 6.4})$$

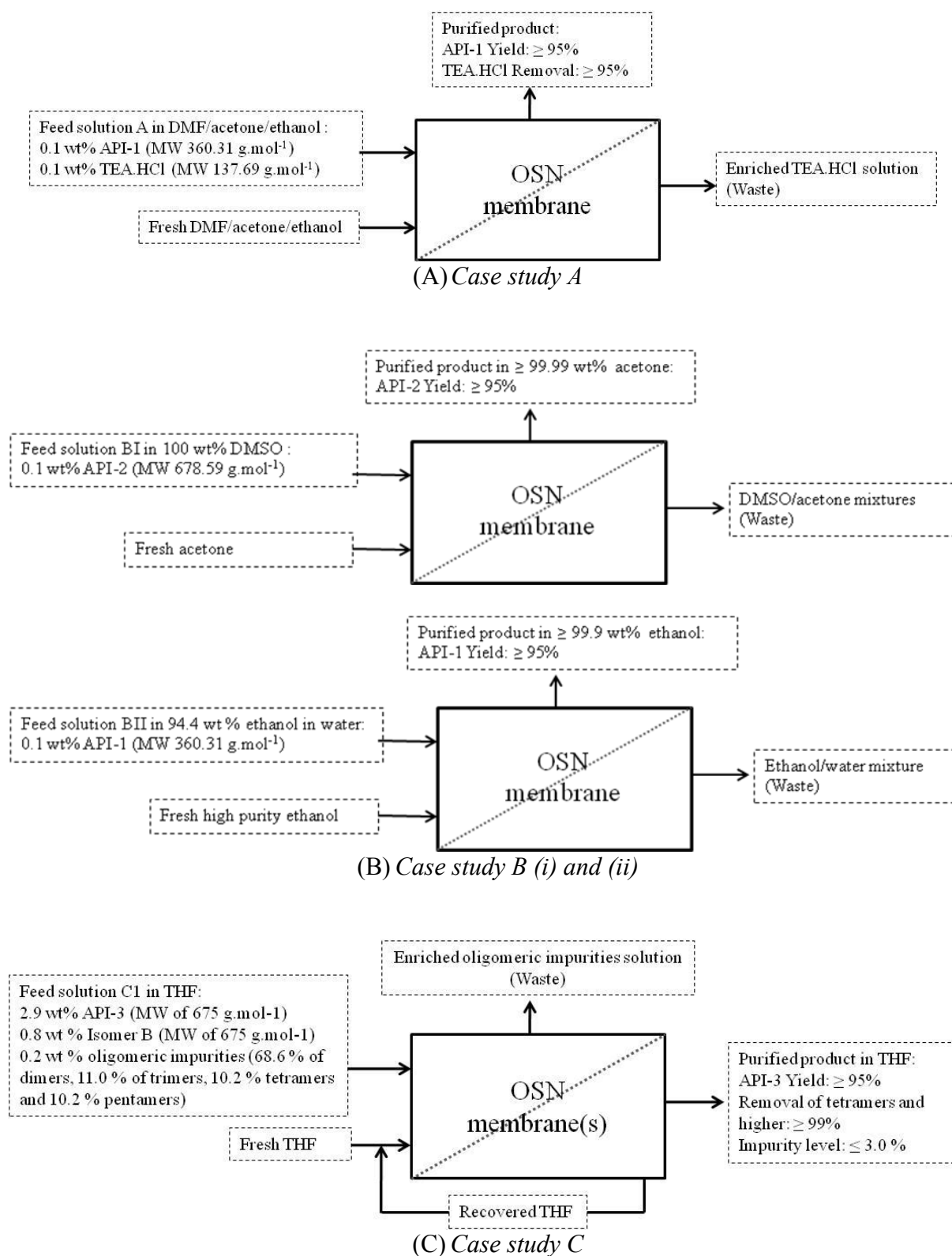


Figure 6.3: Schematic overview of case studies A, B and C.

6.3.2 Chemicals and reaction mixture solution

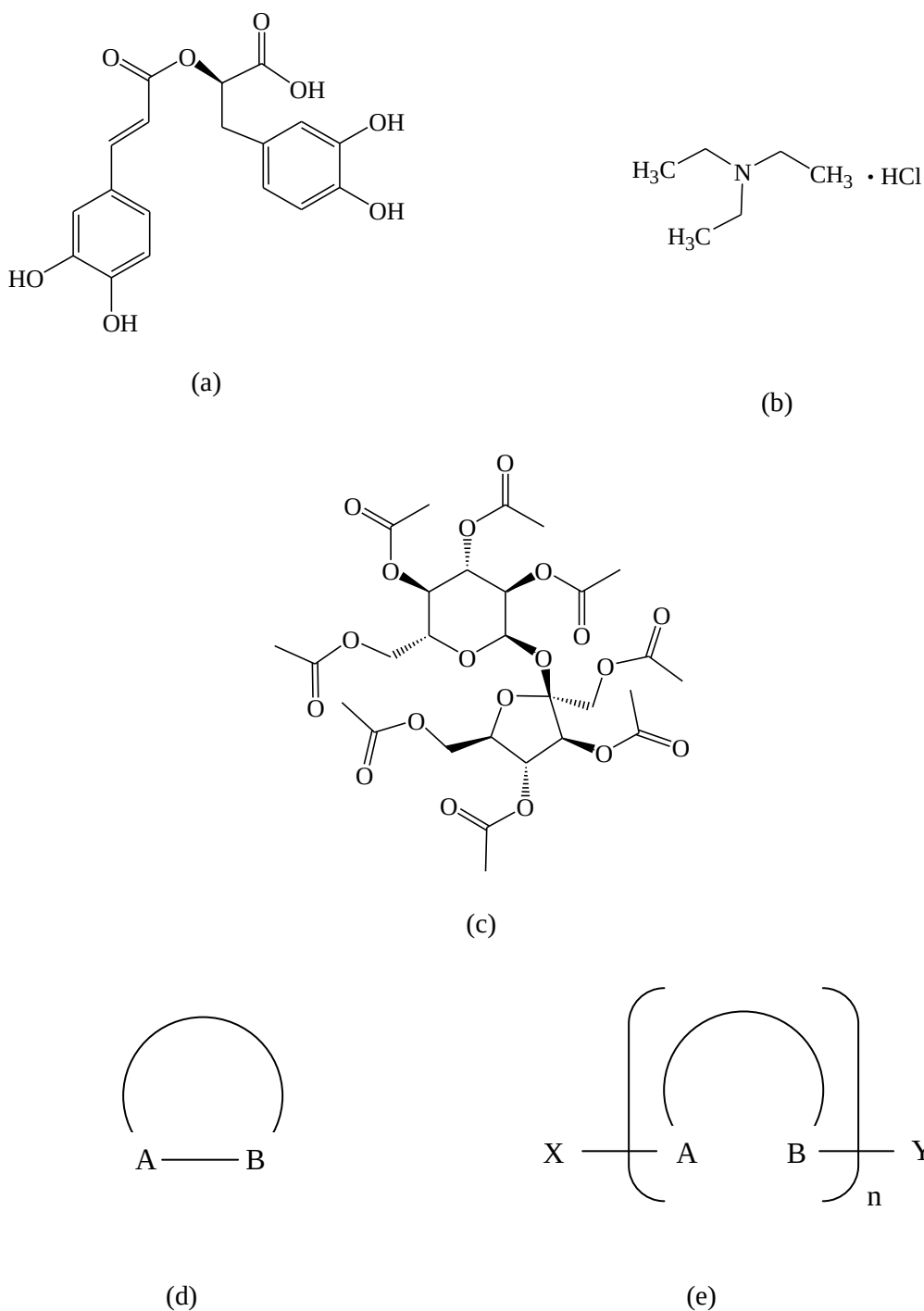


Figure 6.4: Chemical structures of (a) rosmarinic acid – API-1, (b) triethylamine hydrochloride – TEA.HCl, (c) sucrose octaacetate – API-2, (d) API-3 and (e) oligomeric impurities of API-3.

Rosmarinic acid, triethylamine hydrochloride, sucrose octaacetate, absolute ethanol and Hydranal – Coulomat A (reagent for Karl-Fischer titration) were purchased from Sigma-

Aldrich (UK). All other organic solvents used in this study, including DMF (Rathburn, UK), ethanol (VWR, UK), acetone (Rathburn, UK), THF (Rathburn, UK), DMSO (Rathburn, UK), methanol (VWR, UK), acetonitrile (VWR, UK) were HPLC grade and used without any further purification. The Ring-Closed Metathesis (RCM) mixture containing the desired macrocyclic intermediate (API-3), Isomer B and oligomeric impurities was synthesised and kindly supplied by Janssen Pharmaceutica, Belgium. Figure 6.3 presents the chemical structure of the model APIs (API-1 and API-2), model impurity (TEA.HCl), API-3 and oligomeric impurities of API-3 (as the drug substance derived from API-3 is still in development, the detailed structure of API-3 cannot be disclosed at this time). The composition of the synthetic feed solutions for case studies A and B, and RCM mixture supplied by Janssen Pharmaceutica (Belgium) for case study C are summarised in Table 6.1.

Table 6.1: Composition of synthetic feed solutions (Case studies A and B) and the Ring-Closed Metathesis (RCM) mixture supplied by Janssen Pharmaceutica (Case study C).

Case study	Feed solution	Composition	Solvent(s)
A	AI	0.1 wt% API-1 + 0.1 wt% TEA.HCl	DMF
	AII	0.1 wt% API-1 + 0.1 wt% TEA.HCl	Acetone
	AIII	0.1 wt% API-1 + 0.1 wt% TEA.HCl	Ethanol
B	BI	0.1 wt% API-2	DMSO
	BII	0.1 wt% API-1	96 wt% ethanol in water
C	CI	2.9 wt% API-3 + 0.8 wt % Isomer B + 0.2 wt % oligomeric impurities (68.6 % of dimers, 11.0 % of trimers, 10.2 % tetramers and 10.2 % pentamers)	THF
	CII	0.9 wt% API-3 + 0.2 wt % Isomer B + < 0.02 wt % oligomeric impurities (89.8 % of dimers, 9.8 % of trimers and 0.4 % of tetramers)	THF

6.3.3 Analytical methods

Concentration of rosmarinic acid (API-1) in solutions was determined using a high performance liquid chromatography (HPLC) method reported by Peshev et al. [239]. The concentration of sucrose octaacetate (API-2) was measured using a gel permeation chromatography (GPC) system equipped with evaporative light scattering detector (ELSD). The separation was carried using two PLgel3 μ m 100Å, 300mm $\times$ 7.5 mm columns (purchased from Polymer Laboratories, UK) connected in series. The analysis had a total run time of 30 minutes and was performed at 40 °C with 0.7 ml.min⁻¹ of THF effluent and 100 μ l injection volume.

Triethylamine hydrochloride (TEA.HCl) was determined using a HI-8733N auto temperature compensation conductivity meter (Hanna Instruments, UK). Solvents were evaporated from all samples using a rotary evaporator and re-dissolved into water before measurement. Together with the known concentration of rosmarinic acid (API-1) in the samples, the concentration of TEA.HCl in solutions was calculated based on the following equation:

$$\kappa_T = \kappa_{API-1} + \kappa_{TEA.HCl} \quad (\text{Equation 6.5})$$

where κ_T , κ_{API-1} and $\kappa_{TEA.HCl}$ are the conductivity of the sample, API-1 and TEA.HCl respectively. The analysis provided a linear response of API-1 and TEA.HCl standard solutions in the concentration range from 15 ppm to 1 g.L⁻¹, and at any given concentration the error was found to be within ± 2 %.

DMSO and water content in DMSO/acetone and water/ethanol mixtures were determined by gas chromatography (GC) and Karl Fischer titration (KF) respectively. The GC system (6850 Series II, Agilent Technologies, UK) was fitted with an Agilent J.W. DB-FFAP column 30 m $\times$ 0.25 mm nominal diameter, 0.25 mm film thickness and a flame ionisation detector (FID).

The temperature programme selected was as previously published by Rocheleau et al. [240] for measuring residual solvents in pharmaceutical samples. The coefficient of variation was 3 % for three independent measurements. This analytical method allowed detection of DMSO content to as low as 10 ppm. A C20 Compact Karl Fischer Coulometer (Mettler Toledo, UK) together with titration agent Hydranal – Coulomat A was used for measuring water content. The Karl Fischer analysis provided less than 2 % variation of standard water solutions based on absolute ethanol (the ethanol contained 153 ± 2 ppm) at concentrations of 0.30 wt% to 0.15 wt% of water.

The concentrations of API-3 and Isomer B were measured using HPLC. The oligomeric impurities of API-3 such as dimers, trimers, tetramers and pentamers were determined by GPC. In addition, the presence of tetramers and pentamers of API-3 was also determined by means of thin layer chromatography (TLC). As the compounds are still under development, the public release of their detailed structure and analytical methods is not possible at the present time.

6.3.4 Membranes

Table 6.2: List of membranes used in this study. All are crosslinked polyimide membranes, except PuraMemTM280 which is a non-crosslinked polyimide.

Membrane	Membrane Type	Nominal MWCO
M6	DuraMem TM 300	^a 300
M9	DuraMem TM 200	^a 200
M10	PuraMem TM 280	^b 280
M11	DuraMem TM 500	^a 500
M12	DuraMem TM 900	^a 900

^a Determined using a series of styrene oligomers in acetone at 30 bar and 30 °C.

^b Determined using a series of alkanes in toluene at 30 bar and 30 °C.

The membranes selected for use in this study are listed in Table 6.2. All membranes were made from P84 polymer and the nominal MWCO were varied by varying the solvent:co-solvent composition as published in See-Toh et al. [11]. Crosslinked membranes were prepared following the procedure as discussed in chapter 3. All membranes were preserved with PEG 400 as demonstrated in chapter 3.

6.3.5 Filtrations

Flat-sheet membrane and spiral-wound module filtration experiments were conducted using a METcell crossflow and bench-top module apparatus as discussed in chapters 3 and 5 respectively. Two filtration modes were used in this section of work for two different purposes; (i) membrane screening in the METcell crossflow system to indentify a suitable membrane for the specific application, where the permeate was continuously recycled back into the feed tank using a HPLC pump and (ii) diafiltration to demonstrate the proof of concept, where fresh/recycled solvent was added into the feed tank at the same rate as solution permeated the membrane.

6.3.6 Process modelling

A mathematical model was developed to predict process performance during diafiltration. The model is based on mass balances at steady state using simplifying assumptions. The process parameters, variables and equations are elaborated in Appendix A. The yield of the desired APIs and removal of unwanted impurities for the processes of case studies A and B (single-stage filtration) were calculated using the predicted concentration profiles obtained from equations 6.6 and 6.7:

$$C_{R,i} = C_{F,i} \cdot e^{-N(1-R_i)} \quad (\text{Equation 6.6})$$

$$C_{P,i} = \frac{C_{F,i} \cdot V_F \cdot (1 - e^{-N(i-R_i)})}{J_p \cdot A_m \cdot t} \quad (\text{Equation 6.7})$$

Similar to a single-stage filtration model, by assuming the same volume and permeate flux of both filtration stages in a DMD process (purification combined with membrane-based solvent recovery), the yield and impurity level of the process of Case Study C can be determined by equations 6.3 and 6.4 using the concentration profiles of species i at time t in stage 1 and 2 derived from equations 6.8 and 6.11 respectively:

$$C_{R1,i,t} = \frac{(\Omega_i \cdot C_{R1,i,0} + \Phi_i) \cdot e^{(J_p \cdot A \cdot \Omega_i \cdot t / V_1)} - \Phi_i}{\Omega_i} \quad (\text{Equation 6.8})$$

where

$$\Omega_i = -[(1 - R_{i2}) + (1 - R_{i1})] \quad (\text{Equation 6.9})$$

and

$$\Phi_i = (1 - R_{i2}) \cdot C_{R1,i,0} \quad (\text{Equation 6.10})$$

$$C_{i,R2,t} = \frac{V_1 (C_{R1,i,0} - C_{R1,i,t})}{V_2} \quad (\text{Equation 6.11})$$

6.4 Results and Discussion

6.4.1 Case study A: Removal of unwanted halide scavenger

Membrane screening

Table 6.3: Summary of membrane screening results for the removal of TEA.HCl from API-1 at 40 bar and 30 °C.

Entry	Feed solution	Solvent	Membrane	Rejection (%)		Flux (L.m ⁻² .h ⁻¹)
				API-1	TEA.HCl	
1	AI	DMF	M9	99.5 ± 0.1	41.3 ± 1.2	12.9 ± 0.5
2	AII	Acetone	M9	99.9 ± 0.1	85.0 ± 0.8	40.7 ± 0.7
3	AIII	Ethanol	M9	99.8 ± 0.1	89.5 ± 3.5	25.5 ± 3.1
4	AIII	Ethanol	M10	99.7 ± 0.2	80.5 ± 1.3	68.3 ± 1.1
5	0.1 wt% TEA.HCl	DMF	M9	N/A	58.0 ± 1.2	14.6 ± 0.4
6	0.1 wt% TEA.HCl	Ethanol	M9	N/A	93.0 ± 0.7	31.2 ± 1.2

Table 6.3 presents the membrane screening results for removing TEA.HCl from API-1 in three solvents: DMF, acetone and ethanol at 40 bar and 30 °C. Since the aim of this purification process is to separate TEA.HCl (lower MW impurity) from API-1, the ideal membrane should completely retain API-1 whilst allowing TEA.HCl to pass through the membrane unhindered. Of all the membranes and systems tested, the M9 and M10 membranes achieve > 99 % rejection of API-1 and < 90 % rejection of TEA.HCl (entries 1-4, in Table 6.3). The mathematical model suggest that all three solvent systems will provide a purified material by removing 95 – 99% of TEA.HCl and achieving ≥ 95 % recovery of API-1 (as presented in Table 6.4), thus achieving the process targets.

Table 6.4: Predicted key process parameters for removing TEA.HCl from feed solutions AI, AII and AIII (the removal of TEA.HCl is fixed at 95% and 99 %).

Entry	Feed solution	Solvent	Membrane	Removal of TEA.HCl (%)	Predicted process parameters	
					API-1 yield, Y_{API-1} (%)	Diafiltration volume (-)
1	AI	DMF	M9	99	97	6
2	AII	Acetone	M9	99	97	30
3	AIII	Ethanol	M9	99	92	44
4	AIII	Ethanol	M10	99	93	23
5	AIII	Ethanol	M9	95	95	28
6	AIII	Ethanol	M10	95	96	15

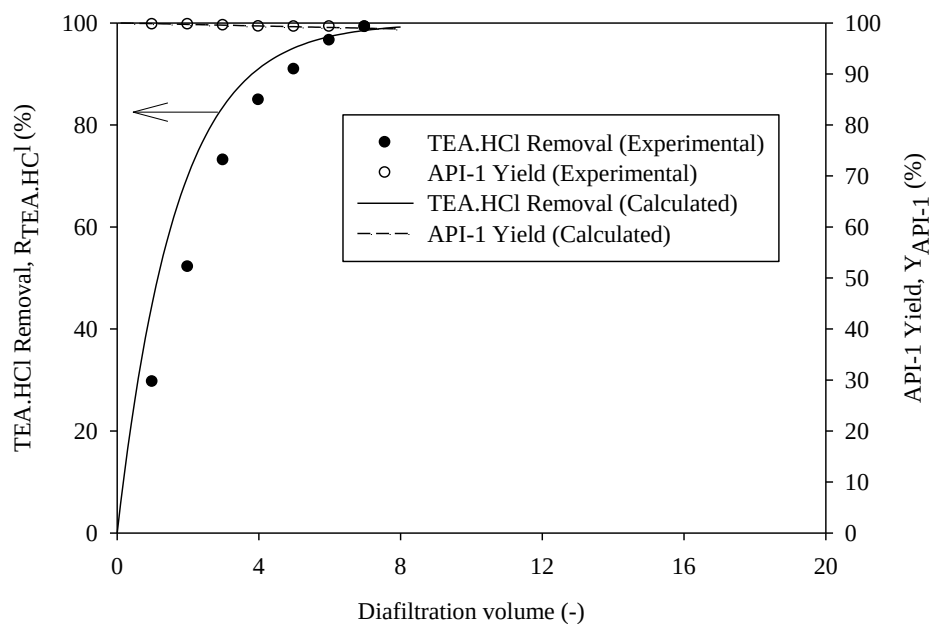
The number of diafiltration volumes required for this purification process is a function of the TEA.HCl rejection. This effect was most pronounced for the filtration in ethanol with the M9 membrane, for which TEA.HCl rejection is the highest (Table 6.3). To test the reason behind this effect, filtrations were carried out solely with TEA.HCl in DMF and acetone (entries 5 and 6, in Table 6.3). The similarity in TEA.HCl rejection to systems with the presence of API-1 suggests that the different TEA.HCl rejection measurement in DMF, acetone and ethanol is attributable to the conformation of TEA.HCl in these solvents and/or interaction between the solvents and M9 and M10 membranes. The major drawback of high diafiltration volume processes is that large volumes of solvents are required, which in turn creates a large volume of solvent waste. However, this limitation can be eliminated by implementing a solvent recovery system downstream of the membrane purification process via distillation or possibly OSN.

Purification process

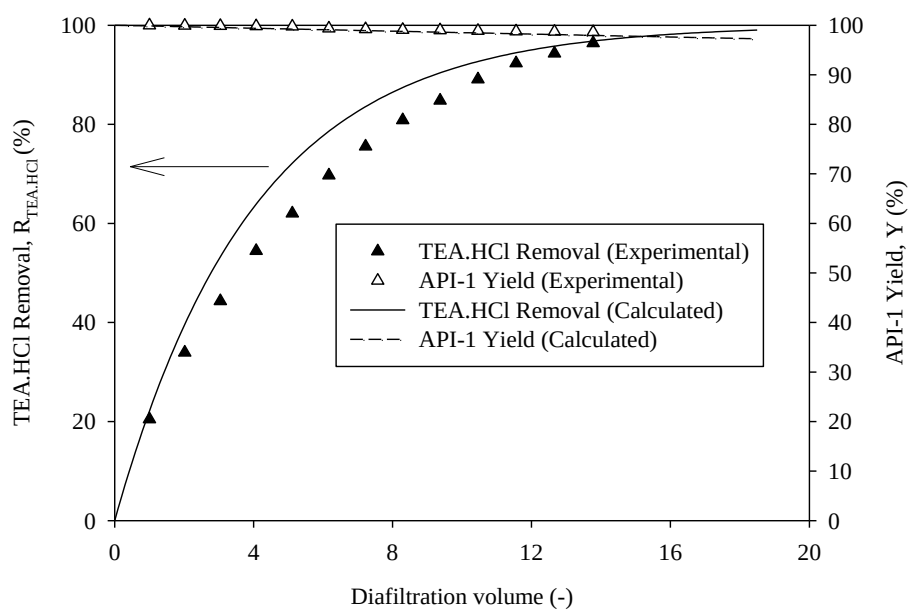
The experimental yield and purity profiles during the purification of a solution mixture containing 0.1 wt% API-1 and 0.1 wt% TEA.HCl in DMF (feed solution AI) and acetone

(feed solution AII) are plotted along with their calculated values as a function of diafiltration volume in Figure 6.5 (a) and (b) respectively. Both permeate flux and rejections of API-1 and TEA.HCl remained constant during the purification processes. The average permeate flux for DMF and acetone systems were $14.2 \pm 3.1 \text{ L.m}^{-2}.\text{h}^{-1}$ and $37.9 \pm 1.8 \text{ L.m}^{-2}.\text{h}^{-1}$ respectively. The average rejections of API-1 in both DMF and acetone were $99.9 \pm 0.1 \%$. On the other hand, the average rejections of TEA.HCl in DMF and acetone were $40.1 \pm 8.4 \%$ and $70.4 \pm 5.6 \%$.

From Figure 6.5(a), after 7 diafiltration volumes, 99.1 % of TEA.HCl was removed from Feed solution AI while yielding 99.2 % of API-1. Additionally, 96.4 % of TEA.HCl was removed from feed solution AII after 14 diafiltration volumes, while yielding 98.6 % API-1. In both processes, the calculated removal and yield are in good agreement with experimental values, suggesting that the model is valid for predicting the process. The calculated profiles show that after 19 diafiltration volumes, it is possible to remove 99 % of TEA.HCl from feed solution AII whilst recovering 97 % of API-1.



(a)



(b)

Figure 6.5: Removal of TEA.HCl ($R_{\text{TEA.HCl}}$) and API-1 yield ($Y_{\text{API-1}}$) profiles during the purification process of (a) feed solution AI (DMF) and (b) feed solution AII (acetone) via OSN using M9 membranes at 40 bar and 30 °C.

6.4.2 Case study B: Solvent exchange of solution(s) containing API

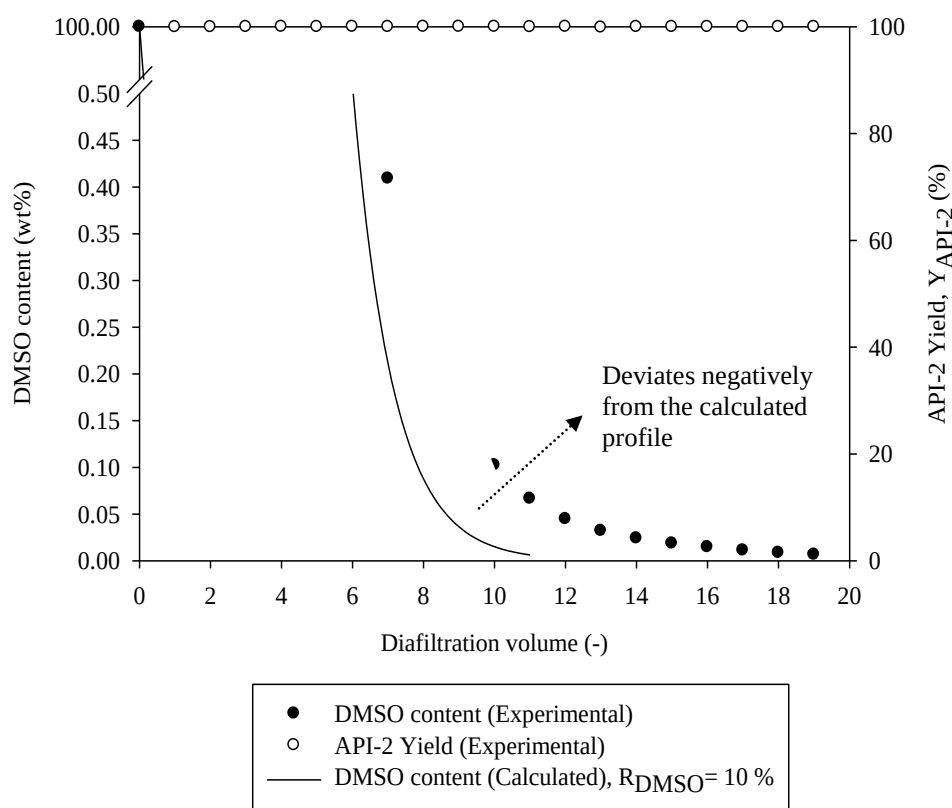
From High Boiling-Point Solvent (HBS) to Low Boiling-Point Solvent (LBS)

Figure 6.6: DMSO content and API-2 yield (Y_{API-2}) profiles during the exchange of API-2 from DMSO into acetone, with M9 membrane at 40 bar and 30 °C.

Figure 6.6 presents the DMSO content and API-2 yield profiles during the exchange of API-2 from DMSO (feed solution BI) into acetone using the M9 membrane at 40 bar and 30 °C. As shown in the graph, the experimental DMSO content in the retentate deviates negatively away from the postulated DMSO content when DMSO rejection is assumed to be constant at 10 % (initial value measured) throughout the purification process. Consequently, an extra 8 diafiltration volumes were required to reduce the DMSO content in the retentate from 100 wt% to less than 50 ppm. The increasing diafiltration volumes corroborates with the increasing rejection for DMSO observed in Figure 6.7. The permeate flux also follows the same trend as the rejection for DMSO (Figure 6.7). It was also observed that the permeate

flux from diafiltration volume 11 onwards appears to have similar values to pure acetone as presented in Figure 6.7.

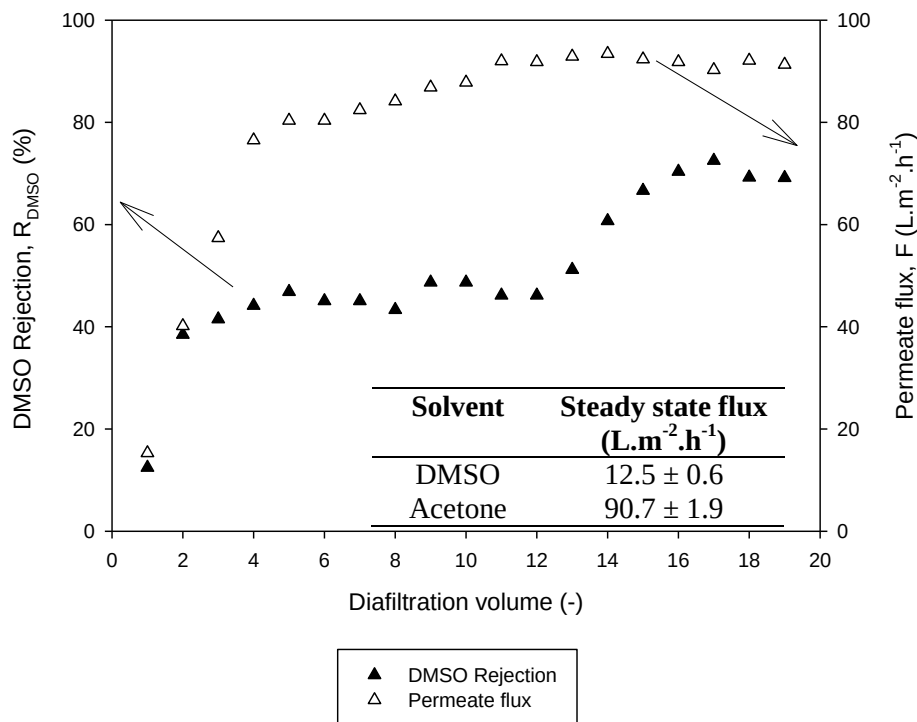


Figure 6.7: DMSO rejection and permeate flux profiles during the exchange of API-2 from DMSO into acetone.

Assuming there is no interaction between (i) the membrane and solvent(s) and (ii) the solvents themselves (DMSO and acetone), the rejection of DMSO as a function of DMSO concentration in the retentate was calculated based on the pure solvent fluxes. Figure 6.8 presents the comparison between the predicted and actual DMSO rejection as a function of DMSO concentration in the retentate. The actual DMSO rejections deviate significantly from the predicted values, importantly however, the calculations did predict an increasing DMSO rejection trend. For further understanding, improvements are required:

- (i) investigate the interaction between both the membrane and solvents, and between the solvents,

(ii) a more highly controlled system used for testing (e.g. automation).

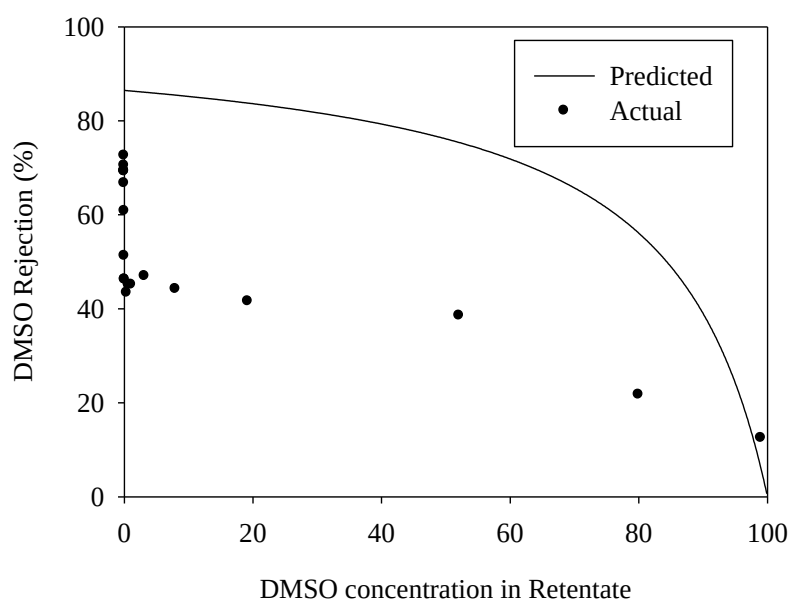


Figure 6.8: Predicted and experimental rejection of DMSO as a function of DMSO concentration in retentate.

From azeotrope to high purity solvent

Figure 6.9 presents the water content and API-1 yield ($Y_{\text{API-1}}$) profiles during the exchange of API-1 from a solvent mixture consisting of 5.6 wt% water in ethanol (feed solution BII) through its azeotrope to ethanol via OSN with M9 membrane at 30 bar and 30 °C. After 4 diafiltration volumes, more than 99.9% of API-1 was recovered in the OSN process with the solution containing less than 0.1 wt% of water. The rejections of API-1 and water remain constant throughout the purification process; the average rejections of API-1 and water were $99.9 \pm 0.1 \%$ and $1.5 \pm 5.1 \%$. As shown in Figure 6.9, the measured water content in the retentate (product) follows the calculated profile closely, suggesting that the model is valid for predicting the purification process. The calculated profile suggests that after 7 diafiltration volumes, API-1 yield will remain unchanged at $> 99.9 \%$, but the product containing API-1 will be in high purity ethanol containing less than 50 ppm of water. The permeate flux profile

during the purification process of feed solution BII is presented in Figure 6.10. In this case, the permeate flux also appeared to be consistent throughout the process.

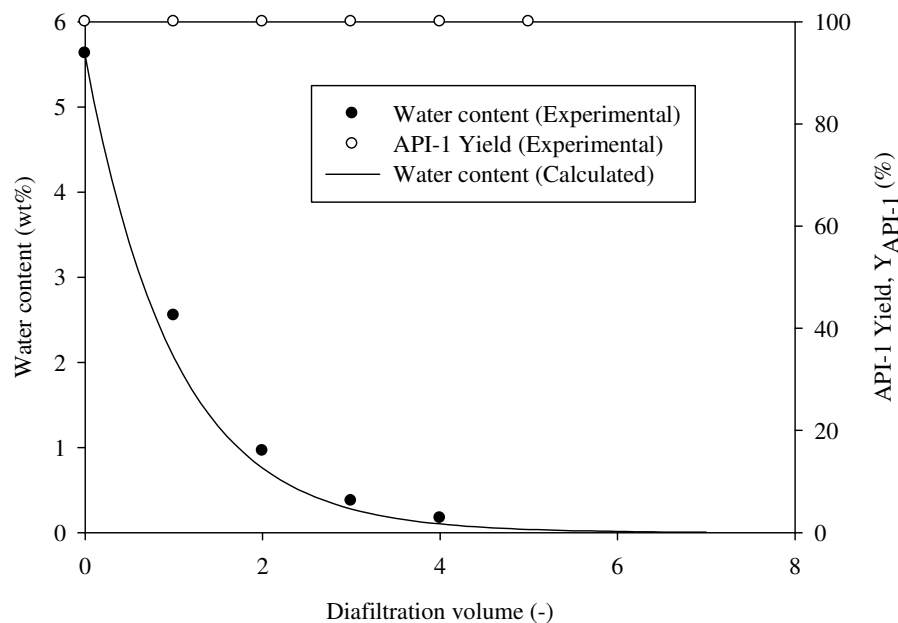


Figure 6.9: Water content in retentate and API-1 yield (Y_{API-1}) profiles during the purification process of feed solution BII with M9 membrane at 30 bar and 30 °C.

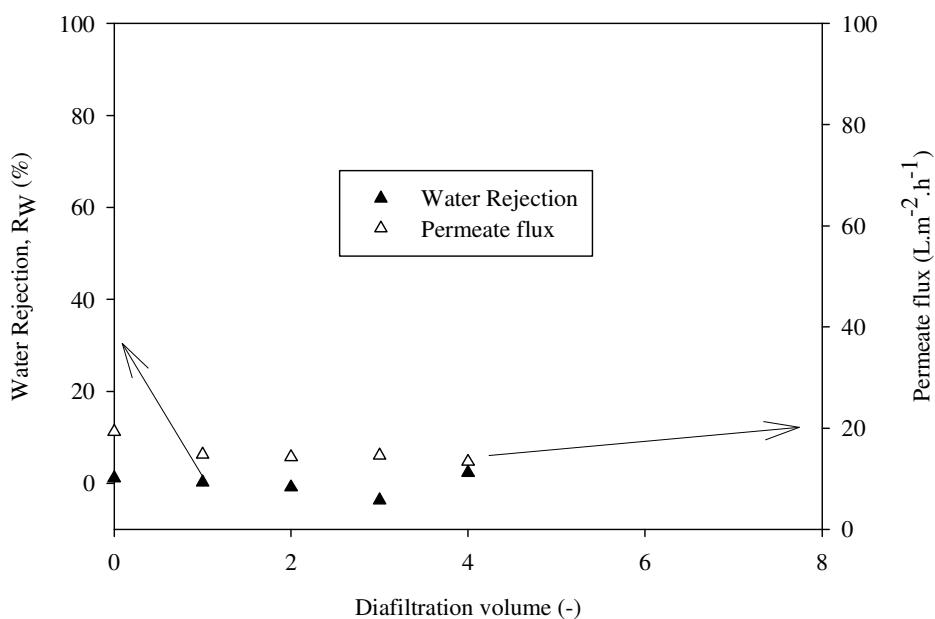


Figure 6.10: Permeate flux and water rejection profile during the purification process of feed solution BII with M9 membrane at 30 bar and 30 °C.

6.4.3 Case study C: Removal of high MW impurities

Membrane screening

The performance of selected crosslinked PI membranes with feed solutions CI and CII (in THF) at 30°C and operating pressures in the range 10 to 60 bar are presented in Table 6.5. Both M11 and M12 are suitable for removing tetramer and pentamer impurities from API-3 in feed solution CI, achieving tetramer and pentamer rejections $\geq 99.9\%$ (entries 1 to 6, in Table 6.5). TLC analysis (Figure 6.11) confirmed that there was no presence of tetramer or pentamer in the permeate of entry 3, suggesting that the membranes are able to highly retain these larger oligomeric species. Based on the mathematical model derived above and using the experimental results obtained in Table 6.5, two systems are predicted to provide a purified API-3 solution with $\leq 3.0\%$ of oligomeric impurities in the OSN product, while recovering $\geq 98\%$ of API-3. These are M12 at 10 bar (entry 3, in Table 6.5) and M11 at 20 bar (entries 4 and 5, in Table 6.5). However, the best membrane for removing $\geq 99\%$ of tetramer and pentamer of API-3 and purifying feed solution CI to the target purity while achieving the target yield is M12 at 10 bar. M11 at 20 bar is not able to achieve all the objectives of case study C, since it is only able to remove $\approx 95\%$ of the tetramers and pentamers of API-3 from feed solution CI. This is due to the higher number of diafiltration volumes required to achieve 98+ % recovery of API-3. Effectively, M11 at 20 bar is more viable for removing lower MW oligomeric impurities such as dimers and trimers.

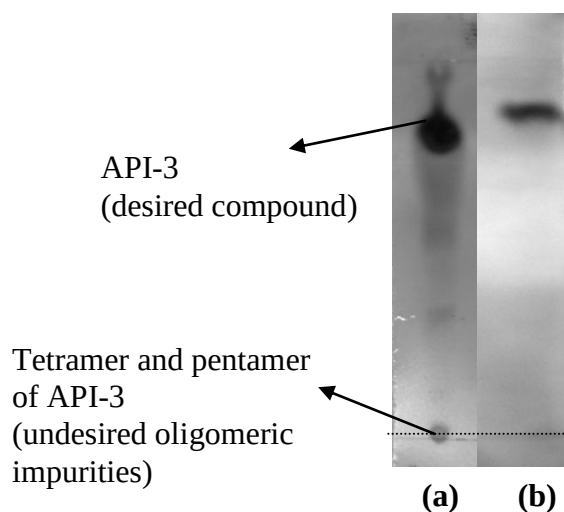


Figure 6.11: Thin layer chromatography (TLC) traces of (a) feed solution CI and (b) permeate collected from entry 3, in Table 6.5.

Table 6.5: Summary of screening results for flat-sheet membranes using feed solutions CI and CII. Filtrations were performed at 30°C in full-recycle mode (permeate and retentate returned to the feed tank). Rejections of each membrane disc were measured after 8 hours.

Entry	Feed Solution	Operating pressure (bar)	Membrane	Permeate flux (L.m ⁻² .h ⁻¹)	^a Rejection (%)				
					API-3	Dimer	Trimer	Tetramer	Pentamer
1	CI	10	M6	9	83.4	95.6	99.0	≥ 99.9	≥ 99.9
2	CI	10	M11	14	80.1	95.7	98.6	≥ 99.9	≥ 99.9
3	CI	10	M12	20	59.7	93.1	96.2	≥ 99.9	≥ 99.9
4	CI	20	M11	20	90.1	98.9	99.4	≥ 99.9	≥ 99.9
5	CI	20	M11	27	93.4	99.3	99.6	≥ 99.9	≥ 99.9
6	CI	20	M12	32	80.0	95.7	98.2	≥ 99.9	≥ 99.9
7	CII	30	M6	6	97.3	≥ 99.9	≥ 99.9	≥ 99.9	≥ 99.9
8	CII	30	M6	7	96.9	≥ 99.9	≥ 99.9	≥ 99.9	≥ 99.9
9	CII	60	M6	12	99.7	≥ 99.9	≥ 99.9	≥ 99.9	≥ 99.9
10	CII	60	M6	13	99.5	≥ 99.9	≥ 99.9	≥ 99.9	≥ 99.9

^a Analysed by HPLC (API-3 and dimer) and GPC (dimer, trimer, tetramer and pentamer) .

The potential for OSN technology to recover the process solvent from the dilute permeate generated from the purification process and to use the recovered solvent for further purification was evaluated. Figure 6.12 presents the results of a mathematical model showing the influence of API-3 rejection in the solvent recovery stage of a DMD process on API-3 yield when the impurity level is fixed at 3 %. It can be concluded that a minimum API-3 rejection of 99.4 % is sufficient to generate a product purity of 3 % whilst achieving the target API-3 yield of 95 %. From Table 6.5, M6 provides the highest rejection of API-3, 99.5 – 99.7 % at 60 bar (entries 9 and 10, in Table 6.5), with an average permeate flux of 12.5 L.m⁻².h⁻¹. This membrane at 60 bar can therefore be used for the solvent recovery stage. However, since the permeate flux from the purification of feed solution CI (entry 3, in Table 6.5) is 1.6 times the permeate flux of the solvent recovery of feed solution CII (entries 9 and 10, in Table 6.5), the membrane area required in the solvent recovery stage of the DMD process will be ≥ 1.6 of the membrane area used in the purification stage.

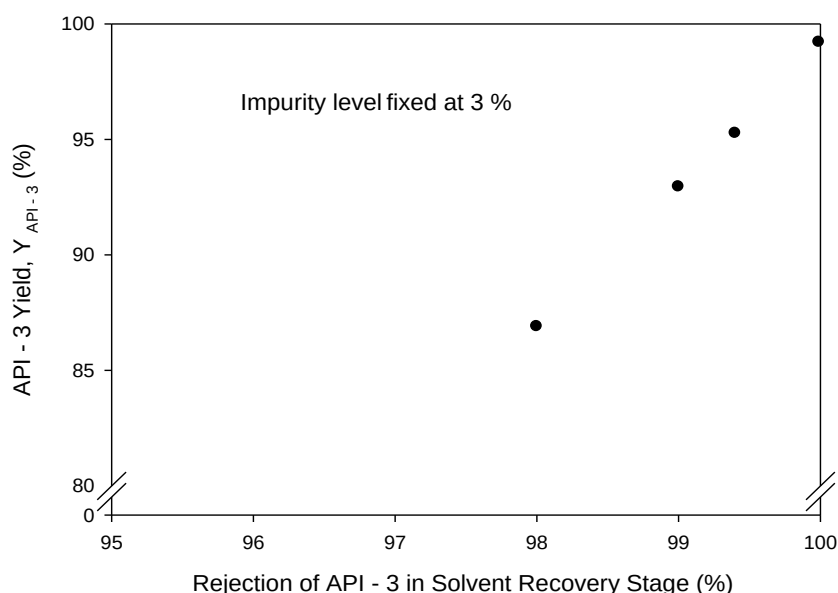


Figure 6.12: Effect of API-3 rejection on the solvent recovery stage in a DMD process on the API-3 yield at a fixed impurity level of 3 %.

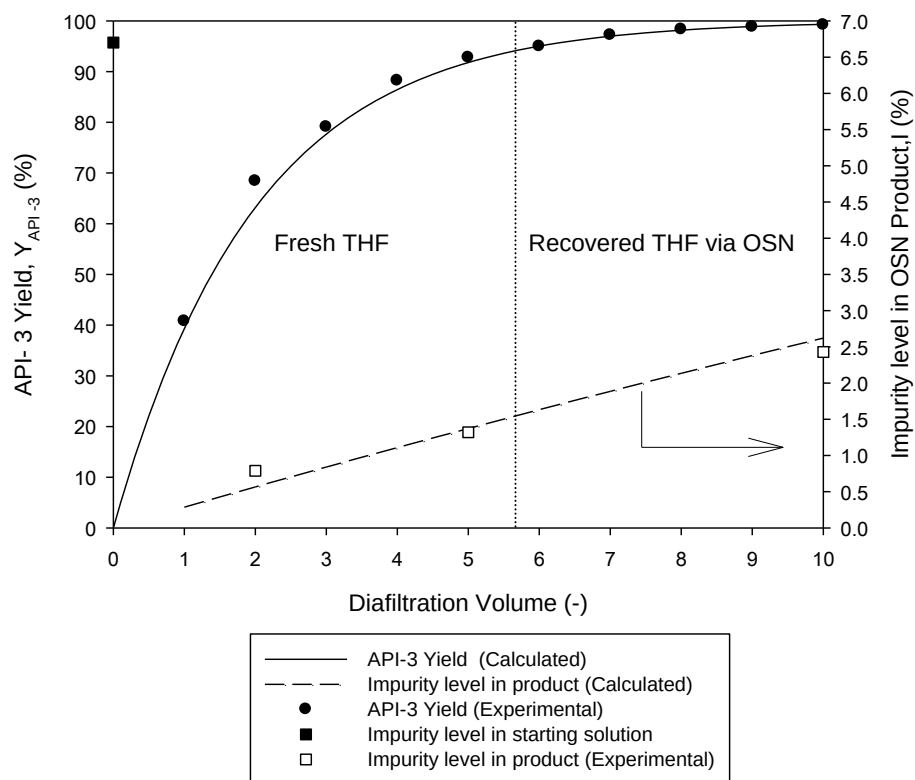
Purification process

Figure 6.13: Yield and purity profiles of case study C using the DMD process with a 1.8-inch $\times$ 12-inch spiral-wound M12 module operated at 30°C and 10 bar in the purification stage and two 1.8-inch $\times$ 12-inch spiral wound M6 modules operated at 30 °C and 60 bar in the solvent recovery stage.

In case study C, the purification process was initially performed using five diafiltration volumes of fresh THF ($N = 0$ to 5) and completed with recovered THF ($N = 6$ to 10) following the DMD process as described and shown in Figure 6.2 until the target yield was achieved. The yield of API-3 and impurity level in the purified product during the purification process is summarised in Figure 6.13. The experimental yield of API-3 and impurity level in the OSN product closely follows the projected values estimated from a single stage purification system without solvent recovery. In fact, the purity of the product from diafiltration volumes 5 to 10 deviates positively from the calculated values which are based on the initial rejection values. This is due to the improved rejections of the oligomeric

impurities in the purification stage over time. Meanwhile, the rejection of API-3 remains consistent at 59.4 ± 6.1 % during the purification process. This behaviour may be attributed by compaction of the membrane over time, which is often observed with PI membranes. A product with impurity level of 2.4 % oligomeric impurities and API-3 yield of 99.2% was achieved at the end of the purification process, whilst providing a consistent permeate flux of $28 \pm 2.8 \text{ L.m}^{-2}.\text{h}^{-1}$ in the purification stage and an average of $11 \pm 1.8 \text{ L.m}^{-2}.\text{h}^{-1}$ in the solvent recovery stage. The composition of oligomeric impurities in the purified material (OSN product) and the overall removal of each specific oligomeric impurity of API-3 is summarised in Table 6.6.

Table 6.6: The composition of oligomeric impurities in feed solution CI and purified material (OSN), and percentage removal of oligomeric impurities after purification through OSN using the DMD process.

Solution	Impurity level, I (%)			
	Dimer	Trimer	Tetramer	Pentamer
Feed Solution I	4.6	0.7	0.7	0.7
OSN Product	1.8	0.2	≤ 0.1	≤ 0.1
Removal (%)	60	69	99	99

As alluded to previously, the DMD process is feasible to operate, without affecting the yield of API-3 and the impurity level in the purified product, as long as the purity of the recovered solvent is ≥ 99.99 % and/or free of API-3, which is achieved here. The simple mathematical model employed can be used to assist in membrane selection, as well as in designing an efficient process configuration. The integration of solvent recovery in the DMD process can massively reduce the fresh solvent requirement for purifying a fixed mass of feed solution CI by up to 90 %, in an ideal process where 0 % of solvent is lost from the system via evaporation and/or no dead volume is present in the system. Figure 6.14 presents the mass balance of case study C ((a) without the solvent recovery stage and (b) with the solvent

recovery stage – DMD) to process 10 batches of 1 tonne of feed solution CI. Further reduction in the THF usage of case study C is possible with the DMD process by optimising the solvent recovery stage, i.e. removing the retentate of the solvent recovery stage after processing several batches of feed solution CI, which will not significantly affect the membrane performance (permeate flux, membrane fouling and etc.). Furthermore, DMD advantageously avoids generating a dilute product that would require further downstream processing. The efficiency of three optimised separation technologies (OSN, crystallisation and charcoal treatment) to remove oligomeric impurities from API-3 is shown in Table 6.7. Overall, these results show that OSN is a very promising technology as it successfully removed the problematic oligomeric impurities, while losing $\leq 1\%$ of the desired and expensive API-3 from feed solution CI.

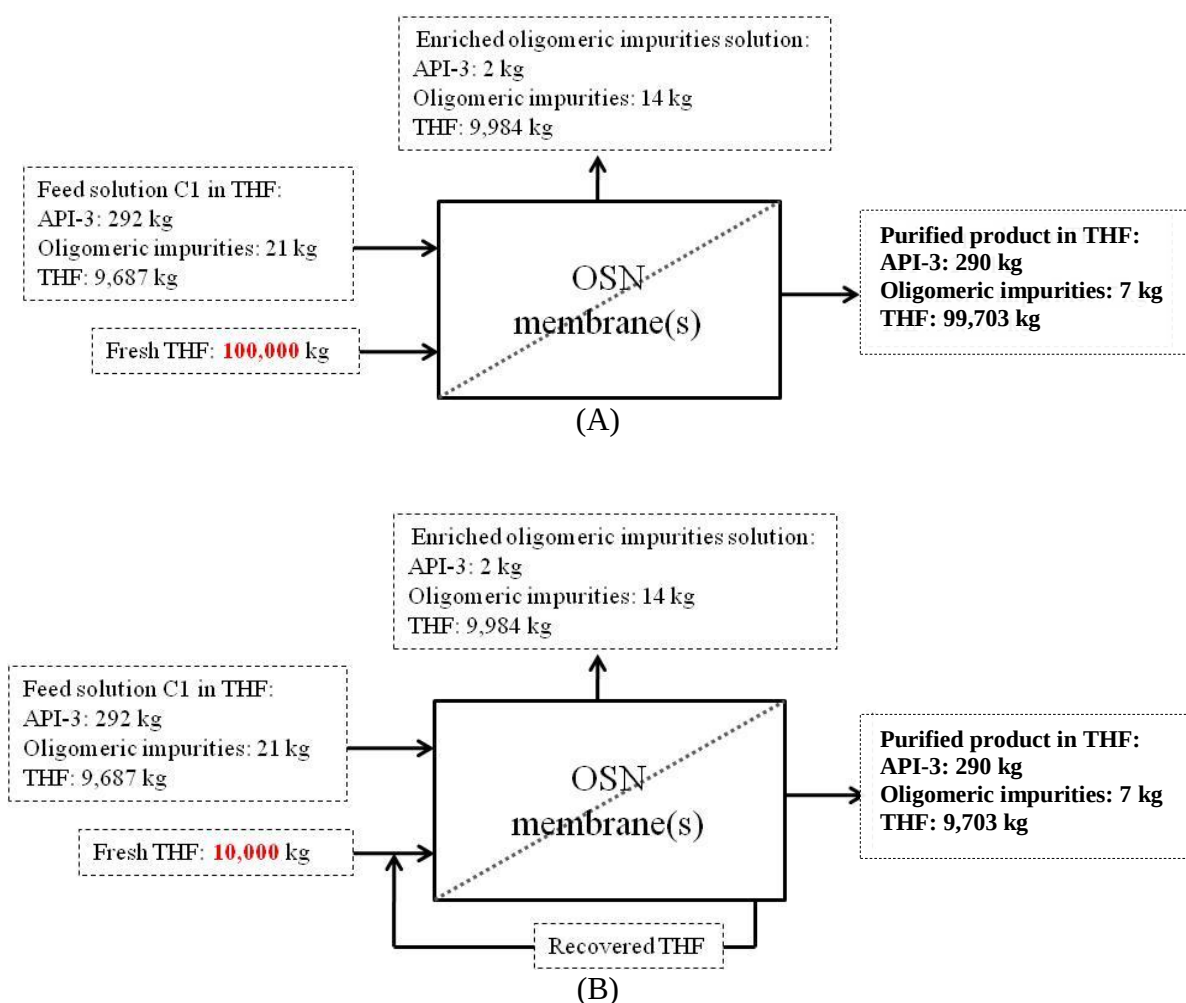


Figure 6.14: Mass balance of case study C based on experimental results, (A) without solvent recovery and (B) with solvent recovery – DMD process, to process 10 batches of 1,000 kg of feed solution CI.

Table 6.7: Efficiency of OSN, crystallisation and charcoal treatment in removing oligomeric impurities from feed solution CI and yield of API-3 after purification treatment.

Separation method	Removal of oligomeric impurities (e.g. dimers, trimers, tetramers and pentamers) (%)	Removal of tetramers and pentamers (%)	API-3 yield (%)
OSN (case study C)	67	99	99
Crystallisation	30	26	85
Charcoal treatment	45	60	98

6.5 Conclusion

The application of OSN to classic pharmaceutical purification issues using second generation PI membranes and modules has been demonstrated with three different case studies A, B and C. The following conclusions can be drawn from these case studies:

Case study A:

- Integration of OSN for the removal of a by product (TEA.HCl) during the synthesis of API through acylation, elimination and alkylation of secondary amines with alkyl halogenides in polar solvents like DMF, acetone and ethanol is possible.
- More than 99% of TEA.HCl was removed while yielding more than 99% of model API-1, in DMF.
- More than 96% of TEA.HCl was removed while yielding more than 98% of model API-1, in acetone.
- All three solvent systems able to achieve the process targets (removing $\geq 95\%$ of TEA.HCl and yielding $\geq 95\%$ of model API-1).
- The membrane selectively (separation characteristics between TEA.HCl and API-1) varies according to the solvent system and membrane type.
- First generation PI membrane (M10) presents better separation characteristics than the second generation PI membrane (M9), in terms of separation selectively (between TEA.HCl and API-1) and permeate flux.

Case study B:

From HBS to LBS

- Second generation PI membrane (M9) was used to successfully swap model API-2 from 100 wt% DMSO (HBS) to ≥ 99.99 wt% acetone (LBS), while yielding $\geq 99\%$ of model API-2.

- An extra 8 diafiltration volumes compared to the theoretically predicted value, were required to achieve the process targets due the increasing rejection of DMSO over time by the membrane.
- A model solely based on pure solvent flux is not capable of predicting DMSO rejection during the purification process, but showed the same trend as the experimental values. The interactions between membrane and solvents, and/or between the solvents are believed to play a role in this observation.
- Improvement of testing equipment is also required for further investigation (e.g. automation).

Separating via an azeotropic mixture

- M9 was successfully used in a separation which took the solution through the ethanol and water azeotrope point to ≥ 99.9 wt% ethanol, whilst yielding ≥ 99.9 % of model API-1.
- Membrane selectivity and permeate flux remained consistent throughout the purification process.

Case study C

- The application of OSN using the second generation PI membrane modules for purifying an organic synthesis solution containing API-3 from its oligomeric impurities such as dimer, trimer, tetramer and pentamer in THF has been shown to be feasible.
- The overall content of oligomeric impurities in an solution synthesised at Janssen Pharmaceutica was reduced from 6.8 % to 2.4 %, which is below the target limit of 3.0 % oligomeric impurities, as well as removing 99 % of the particularly challenging higher oligomeric impurities (i.e. tetramer and higher of API-INT).
- More than 99 % yield of API-3 was also achieved.

- In general, all three case studies demonstrated that a major drawback of OSN is the potential requirement for large volumes of solvent, which in turn creates a large volume of solvent waste. Integrating a downstream OSN-based solvent recovery system into the diafiltration purification process via Dual Membrane Diafiltration (DMD) massively reduced fresh solvent consumption. The DMD process also solves the problem commonly encountered in membrane purification techniques, i.e. by retaining the desired product with the solvent recovery membrane, the DMD process does not generate a dilute product solution that requires further processing.

The systems presented in this study mimic common industrial systems and the concept can be readily transferred to various applications in the pharmaceutical industry. Depending on the application, the process can be customised to deliver the target yield and purity. It is also shown that the mathematical model (based on mass balances) predicts the diafiltration process very well, when the membrane separation selectivity remain consistent throughout the process. Otherwise, it is a useful tool to select the optimal membrane for the purification process. The reliability and stability of these OSN membrane modules in harsh solvent environments was also established.

Chapter 7

Summary and future perspectives

The development of OSN membranes and modules for applications in common solvents (e.g. THF, acetone, DMF, DMSO, NMP and DCM) used in the pharmaceutical industries is the central theme of this work. The first generation P84 (PI) membranes (StarmemTM produced by W.R. Grace) are known to have superior separation performance in OSN. Further modification of these membranes (second generation PI membranes) through chemical crosslinking enhances the chemical stability of the polyimide membranes thus allowing them to be used in the common solvents listed above, in which the first generation solvents are not stable. The main focus of this thesis is in tackling various aspects involved during the transformation of flat sheet membranes into spiral wound modules (the final product used for industrial applications). Limitations in the production process could potentially eclipse the breakthrough of the second generation PI membranes into industrial applications.

Chapter 3 - Second generation PI OSN membranes: Towards production

The generation of a ‘dry’ membrane at production scale allows the membrane to be handled easily and provides a wider range of adhesive systems to select from, particularly when chemical stability is the main concern. Air-drying of water and solvents wetted membranes imposes considerable detrimental effects on the functional performance of polymeric membranes formed via phase inversion. The performance of both wetted P84 and wetted chemically crosslinked P84 membrane were affected by air-drying. Two phenomenon, (i) collapse of pores in the separating layer and (ii) rearrangement of polymer chains in the

Chapter 7 – Summary and future perspectives

separating layer and sub-layer, were postulated to occur upon air-drying based on the intrinsic membrane parameters - porosity and pore size distribution as determined from the pore flow model using experimentally derived solute rejections. The ability to relate NF membrane structure to their intrinsic transport properties utilising microscopic imaging techniques perhaps holds the future to a rational, structured approach to further membrane development and understanding. The chemical properties of preserving agents (e.g. hydrophilicity and solubility in solvents) and the interaction between the membrane and preserving agents are the dominating factors in the choice of a suitable material for maintaining the performance of membranes formed via phase inversion in a 'dry state'. PEG400 and undecanone were found to be suitable preserving agents for P84 membranes crosslinked with diamine. Improved repeatability and reproducibility of the membrane performance within and between batches was obtained through the chemical crosslinking process, at the expense of reduced solvent permeability (relative to non-crosslinked P84 membrane).

Chapter 4 – Design of epoxy adhesive formulation for OSN

Apart from the membrane itself, the adhesive is another key element required for attaching all components in the final OSN product (spiral wound module). Epoxy based adhesives were identified as potential precursors for the development of the adhesive system for applications in OSN. The chemical stability of epoxy-amine adhesive in a range of organic solvents (from apolar through polar to polar aprotic) was investigated through various formulation parameters. The chemical stability of epoxy-amine adhesive in organic solvents was found to be dependent on two key aspects, (i) the available free volume in the crosslinked matrix for the organic solvent to occupy and (ii) the chemical interaction between the functional groups within the epoxy matrix and the organic solvent. This understanding allows the epoxy – amine adhesive formulation to be tailored for specific applications. The adhesives developed

Chapter 7 – Summary and future perspectives

in this work demonstrated excellent stability in all organic solvents studied including hexane, toluene, methanol, ethanol, acetone, THF, DMF, NMP and DCM, as well as water. It is also suitable for use in regulated industries with $< 0.05\%$ extractables or leachables measured in key solvents and all components are compliant with FDA 21 CFR. This breakthrough is a major step towards developing the final industrial membrane module product.

Chapter 5 – Optimisation of epoxy adhesive for PI OSN membranes

The traditional curing methodology via thermal energy for epoxy adhesives is vital to enhance the chemical stability of the adhesives in organic solvents. In determining optimal curing conditions, a compromise needs to be reached between preventing the loss of performance in the membranes and ensuring that the epoxy adhesive is sufficiently cured to provide good chemical stability for specific applications. A novel curing methodology for curing epoxy adhesives via microwave energy was used with P84 and P84 chemically modified OSN membranes used with. This novel technique enables the curing of epoxy adhesives without affecting the performance of unmodified P84 membranes, but this technique cannot be utilised with chemically modified P84 membranes due to the polarisable amide groups of the polymer core. An optimal thermal curing cycle was proposed for the chemically modified P84 membranes, which retained excellent chemical stability of the adhesives in most organic solvents and maintained the functional performance of the membranes. The curing methodology was derived from fundamental analytical analysis and understanding of epoxy – amine adhesive chemistry and then experimentally demonstrated through performance testing membrane modules.

Chapter 6 – OSN solutions to classic purification issues in pharmaceutical industries

This chapter amalgamates the research presented in the preceding chapters by demonstrating the feasibility of applying the second generation PI OSN membranes and modules in classic purification processes in the pharmaceutical industries. In this chapter, three purification processes were described, these involve (A) removing a smaller reaction by-product formed during the synthesis of an API or intermediate, (B) exchanging API from a HBS to LBS and from an azeotropic mixture to a high purity solvent, and (C) removing unwanted oligomeric impurities from an API. The purification processes were successfully demonstrated by achieving the process targets, both in terms of purity or impurity removal and API yield. The use of Dual Membrane Diafiltration (DMD) in the purification process markedly improved the efficiency of the OSN purification process by reducing the solvent consumption and reducing the waste generated. The systems presented in this study mimic common industrial systems and the concept can be readily transferred to various applications in the pharmaceutical industry. Reliability and stability of the second generation PI membranes and modules was demonstrated through these separation processes.

Whilst the improvements developed in this work significantly open up more future possibilities for industrial OSN applications in the pharmaceutical industries, there still remain several areas where further work and development are required.

The first of these is to generate improvements in membrane selectivity so that compounds with similar chemical and physical properties can be separated. It is clear that many separations are feasible where there is a difference in chemical/physical properties with the membranes described in this work, which represents a significant fraction of the total possible separation opportunities. However, improvements are still required in the selectivity of the

membranes to access further separations in which the properties of the solutes are more similar. Potential opportunities for generating more selective membranes/membranes with different selectivity include:

- (i) adding different functionalities to the P84-based membranes described in this work, by for instance incorporating functional groups into the diamine crosslinker. This would generate different solute-membrane and solvent-membrane interactions that could increase the selectivity through providing a larger difference in membrane interactions between different solutes;
- (ii) generating interfacial polymerisation membranes stable in organic solvents. These membranes would be produced in a method analogous to the production of the vast majority of commercial reverse osmosis membranes, but generating a polymer layer on the membrane surface that would be solvent stable. The properties of the polymer (typically a polyamide) could be adjusted again to offer different solute-membrane interactions to the P84-based membranes and thus a different selectivity between solutes;
- (iii) depositing a rubbery layer on an ultrafiltration support layer, i.e. forming thin-film composite membranes. In this case, the membrane formed would be a true “solution-diffusion” membrane, which then means that the rubbery layer in effect acts as a solid-phase solvent and the solute most “dissolve” into this layer for it to be transported through the membrane. By using different rubbers (or using a generic monomer type and adding/remove functionalities) it may be possible to take advantage of this solubility effect change the relative mass transport (and hence selectivity) of the different solutes to provide the desired selectivity.

By addressing this issue, possibly through the strategies outlined above, this would provide a significant improvement in membrane performance that could rapidly accelerate the development of OSN applications.

The second area is the generation of low MWCO membrane(s) that could enable recovery of solvents via OSN, making OSN a much more attractive technology. As presented in chapter 6, purification processes via diafiltration generally require a large volume of solvents to reach the target product purity and yield due to the inefficient separation between the product and unwanted impurity provided by currently available membranes. Additionally, membranes formed via phase-inversion are unable to provide a ‘tight’ membrane without sacrificing solvent permeability. Therefore, the need to generate ‘tight’ NF membranes (with MWCO of less than 200 g.mol⁻¹) with good solvent permeability is desirable. This may be attained by the development of composite and interfacial polymerisation membranes (as described above), which are the most common type of reverse osmosis membranes used in membrane water treatment systems. The reason that these technologies may be of interest for OSN, is that they are used for forming high-permeability reverse osmosis membranes and thus potentially can generate high-permeability membranes. Assuming that these types of membranes can be formed from solvent-stable polymers, it is likely that low MWCO membranes will be generated and these would aid in the further use of OSN for solvent recovery.

The third area is to develop membranes with improved mechanical and chemical stability. Two areas that are currently challenging for P84-based membranes are applications in solvents with high swelling capability (e.g. DCM) and in strong acids and bases. Furthermore, these membranes are currently lacking from the market in the nanofiltration range. High swelling

solvents, such as DCM, are commonly used in many syntheses particularly in the pharmaceutical industry. The biggest problem with swelling solvents is that they make performance of the membrane quite variable. Sometimes physical damage is caused directly by the swelling, as the membrane folds on itself and catastrophic failure through cracking occurs. On other occasions, more subtle effects are observed, such as changes over time in membrane flux/rejection performance due to on-going changes in the separating layer through swelling or the formation of micro-scale cracks can occur that bypasses a portion of the retentate through the membrane and lowering the rejection. Applications with strong acids/bases are also common in the pharmaceutical industry, for instance strong acids are often used in small quantities as catalysts or they can be used in stoichiometric quantities for protection/deprotection of functional groups, and strong bases such as sodium methoxide are used in alkylation reactions. Strong bases in particular are problematic for P84-based membranes as they hydrolyse the polymer backbone, reducing the molecular weight of the polymer, and this leads to membrane failure. The impact of strong acids is more variable, but they too can lead to polymer hydrolysis and membrane failure. To address this issue of chemical/physical stability of OSN membranes will require (i) P84-based membranes crosslinked with a new generation of crosslinking agents or membranes made from new polymers to address the swelling issues, and (ii) a new non-polyimide generation of membranes made from polymers that do not contain bond readily attacked by strong acids and bases. If these membranes can be developed, then there are considerable opportunities for applying membranes stable in these solvents or at extreme pH.

Finally, there is a need to understand the transport phenomena that occur during the purification process and to be able to relate this to the morphological structure of the membrane. Currently, the relationship between morphological structure of the separating

layer and mass transport phenomena in the membrane cannot be established. The nominal pore size of OSN membranes is of the order 1nm and thus features of the separating layer at this dimension scale need to be resolved in order to establish if there is any correlation between what can be visualised with imaging techniques and actual membrane performance. To date, none of the standard imaging techniques (AFM, SEM, TEM, etc.) or variants of them has been able to offer any insights the pore structure of these membranes. It is clearly very important that even when techniques are available to allow imaging at the 1nm scale, that the preparation technique for the samples must maintain the state of the membrane as it is actually used and must not induce artefacts due to preparation. Assuming that these significant hurdles can be overcome, and the results correlated with actual membrane performance, then this would become a very powerful tool for the rational design of OSN membranes for particular applications.

Overall, this thesis has provided a major step forward in the application and use of OSN membranes, and has highlighted that there are still many new avenues of research that require considerable work to fulfil OSN's ultimate potential.

Appendix A

In this study, a process model was developed to calculate concentration profiles of each solute in the system. The model developed in the study employs the constant volume operation mode, and is based on mass balances at steady state using simplifying assumptions. Solute concentration effects, including concentration polarisation and osmotic pressure are neglected, and nanoscale aspects of mass transport through the membrane are not considered in this work. As a result, solute rejections and fluxes are all assumed to be constant with respect to time. It is assumed that the circulation rate in the system used in this study is sufficient to keep the liquid completely mixed, and thus feed and retentate concentration at any given time are equal. Additionally, assuming that there is no selectivity for solvent through OSN membranes, the solvent rejection is equal to zero.

The system of equations governing a single-stage filtration process, according to the above assumptions is:

$$V \frac{dC_{R,i}}{dt} = -J_p \cdot A C_{P,i} \quad \text{S-1}$$

$$C_{P,i} = (1 - R_i) \cdot C_{R,i} \quad \text{S-2}$$

The substitution and integration of Equations (S-1)-(S-2) with an initial condition:

$$\text{At } t = 0, C_{R,i} = C_F \quad \text{S-3}$$

gives concentration the concentration of the species in the retentate as a function of time:

$$C_{R,i} = C_{F,i} \cdot e^{-N(1-R_i)} \quad \text{S-4}$$

where N is diafiltration volume and is defined as:

$$N = \frac{V_P}{V_F} \frac{J_p \cdot A t}{V_F} \quad \text{S-5}$$

Therefore, the permeate concentration can be calculated based on mass balance:

Appendix A

$$C_{P,i} = \frac{C_{F,i} \cdot V_F \cdot (1 - e^{-N(i-R_i)})}{J_p \cdot A \cdot t} \quad \text{S-6}$$

Whereas, the system of equations governing a dual membrane diafiltration (DMD) process according to the above assumptions and assuming both stages have the same volume and permeate flux is:

$$V_1 \frac{dC_{R1,i,t}}{dt} = J_2 \cdot A \cdot C_{P2,i,t} - J_1 \cdot A \cdot C_{P1,i,t} \quad \text{S-7}$$

A mass balance over the system on species i gives:

$$C_{R2,i,t} = \frac{V_1(C_{R1,i,0} - C_{R1,i,t})}{V_2} \quad \text{S-8}$$

S-9 can be re-written by integrating equation S-2 and S-8:

$$\frac{dC_{R1,i,t}}{dt} = \frac{J_p \cdot A}{V} (\Phi_i + \Omega_i \cdot C_{R1,i,t}) \quad \text{S-9}$$

where $\Omega_i = -[(1 - R_{i2}) + (1 - R_{i1})]$ and $\Phi_i = (1 - R_{i2}) \cdot C_{R1,i,0}$

The integration of Equations (S-9) with an initial condition:

At $t = 0$, $C_{R1,i} = C_{R1,i,0} = C_{F,i}$

provides concentrations of i in the retentate of stage 1 as a function of time:

$$C_{R1,i,t} = \frac{(\Omega_i \cdot C_{R1,i,0} + \Phi_i) \cdot e^{(J_p \cdot A \cdot \Omega_i \cdot t / V_1)} - \Phi_i}{\Omega_i} \quad \text{S-10}$$

Therefore, the retentate concentration of I in stage 2 can be calculated based on equations S-8 and S-10.

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