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ABSTRACT

CRYSTALLIZATION STUDIES IN HOLLOW FIBER DEVICES

by Dimitrios Zarkadas

Crystallization was examined under a new perspective and in a flow environment much different from that available in currently used industrial devices. Three crystallization techniques were tested in the unique flow environment offered by hollow fiber devices. In addition, a new type of heat exchanger based on hollow fibers was tested as well as the potential use of porous hollow fiber devices as mixing devices. Hollow fiber devices are compact, extremely efficient on a volumetric basis, easy to scale up and control and their inherent characteristics promote the creation of homogeneous temperature and concentration conditions on a scale considerably smaller than existing industrial crystallizers without the necessity of a large energy input.

Porous hollow fiber heat exchangers (PHFHEs) were proven superior to conventional metal heat transfer equipment. For the liquid-liquid systems studied, they can transfer up to ten times more heat on a volumetric basis, achieve the same efficiency and number of transfer units at considerably smaller lengths; also, the height of a transfer unit achieved by them is 10-20 times smaller. In addition, they can transfer up to 20 times more heat at the same pumping power expenditure and need to utilize as low as 1 kPa for the achievement of one transfer unit compared to 30 kPa for metal heat exchangers. Considering their lower fixed cost, they can be considered suitable alternatives for metal and plastic heat exchangers at lower temperatures and pressures.

Solid hollow fiber cooling crystallization (SHFCC) was proved to be a promising technique for crystal size distribution control of both aqueous and organic systems. A combination of a solid hollow fiber crystallizer with a mixing device downstream was the most successful. For the aqueous potassium nitrate system, this combination provided crystal size distributions with 3-4 times smaller mean sizes compared to those mentioned in existing literature of Mixed Suspension Mixed Product Removal (MSMPR) crystallizers. In addition, 90% of the crystals produced were confined to sizes at least two times smaller, while the nucleation rates achieved were 2-3 orders of magnitude higher. Runs with aqueous paracetamol (4-acetamidophenol) solutions showed that an SHFC-static mixer assembly can be operated successfully up to 30-40°C below the metastable zone limit, a capability not existent in industrial cooling crystallizers. This ability allows the achievement of very high nucleation rates and the decoupling of nucleation and growth, an opportunity offered currently only by impinging jet mixers for antisolvent crystallization.

Porous hollow fiber devices proved efficient mixing devices, which unlike other tubular devices offer the opportunity for substantial radial mixing and hence the production of good micromixing. By proper rating they can potentially be utilized for reaction purposes, especially for liquid-liquid reactions on a 1:1 stoichiometric ratio, a task never performed before in membrane reactors.

Porous hollow fiber emulsion crystallization (PHFEC) of a system with an immiscible solvent-antisolvent pair, salicylic acid in 1-octanol and water, encountered difficulties. While an emulsion of droplets smaller than 50 μ m was obtained, crystallization at the droplet surface or interior was strongly hindered probably due to the

presence of the emulsifier. The latter, although beneficial for droplet stabilization and size control, prevents contact of the solute and the antisolvent and consequently the generation of supersaturation conditions.

Polymeric hollow fiber antisolvent crystallization (PHFAC) was found to be a promising crystallization technique for miscible solvent-antisolvent pairs. When crystallization was performed at the tube side of the device, the crystal size distributions obtained for the system aqueous L-asparagine monohydrate and 2-propanol as the antisolvent were confined below 200 μ m. However, prolonged operation of the membrane hollow fiber crystallizer was problematic due to pore and/or fiber blockage. The same was not true when crystallization was performed at the shell side of the device. Crystallization runs with the same system showed that, apart from stable operation, mean sizes as low as 30-40 μ m can be achieved. The crystal size distribution was confined between 70 and 150 μ m, a size range suitable for most pharmaceutical crystalline products and about 2-4 times smaller compared to 200-300 μ m achieved in stirred crystallizers for the same system. In addition, 1-5 orders of magnitude higher nucleation rates were obtained at the same levels of supersaturation.

CRYSTALLIZATION STUDIES IN HOLLOW FIBER DEVICES

by Dimitrios Zarkadas

A Dissertation Submitted to the Faculty of New Jersey Institute of Technology In Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Chemical Engineering

Otto H. York Department of Chemical Engineering

January 2005

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- Zarkadas, D. M. and Sirkar, K. K. (2004). "Polymeric Hollow Fiber Heat Exchangers (PHFHEs): A new type of heat exchanger for lower temperature applications." paper 198h, AIChE Annual Meeting, November 7-12, Austin, TX.
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- Zarkadas, D. M. and Sirkar, K. K. (2004). "Membrane Crystallization." paper 142e, AIChE Annual Meeting, November 16-21, San Francisco, CA.

In memory of my father

To my wife Catherine

ACKNOWLEDGEMENT

I would like to express my deepest appreciation to Dr. Kamalesh K. Sirkar for giving me the opportunity to work in such a challenging project and providing me with valuable advice, insight and guidance throughout the duration of my research. I am also indebted to Dr. Lisa Axe, Dr. Dana Knox, Dr. Robert Pfeffer and Dr. Marino Xanthos for actively participating in my committee.

This study was funded by Pfizer Inc., Global Research & Development, Groton CT and the Center for Membrane Technologies at New Jersey Institute of Technology, Newark, NJ. Financial support was also provided from the Otto H. York Department of Chemical Engineering. Polypropylene nonporous hollow fibers for heat transfer and solid hollow fiber cooling crystallization studies were donated by Celgard, Charlotte, NC.

I also want to express my gratitude to Mr. Yogesh Gandhi who helped me promptly numerous times to fulfill various immediate needs in materials and apparatuses. Special thanks are given to Dr. Reginald Tomkins for allowing me to use the Anton Paar DMA-46 density meter for a prolonged period of time and Dr. Doug Wei for his initial guidance on the laser diffraction crystal sizing method.

I would also like to thank my mother and my late father for providing me a solid education and above all, for shaping my personality with the motivation, determination and perseverance necessary in life. But mostly, I want to thank my wife and life companion, Catherine for her fervent and unconditional support throughout my graduate and undergraduate studies. She has been a constant source of inspiration and encouragement and always motivated me to pursue my dreams without ever settling for anything less.

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LIST OF SYMBOLS

A	heat transfer area, m ²
A_{frontal}	ratio of frontal to total cross-sectional area of a heat exchanger, dimensionless
b	plate spacing, m
В	nucleation rate, no $m^{-3} s^{-1}$
C	actual concentration, kg/kg, kmol m ⁻³
ΔC	concentration difference or supersaturation, kg/kg, kmol m ⁻³
C^*	saturation concentration, kg/kg, kmol m ⁻³
Ċ	heat capacity rate, mC_p , W K ⁻¹
Ċ*	heat capacity rate ratio, $\frac{C_{\min}}{C_{\max}}$, dimensionless
Cı	constant in Equation (2.33); 0.866 for a 30° layout and 1 for 45° and 90° layouts
C _c	crystal molar density, kmol m ⁻³
C _p	specific heat, J kg ⁻¹ K ⁻¹
CUV	conductance per unit volume, Wm ⁻³ K ⁻¹
d ₁₀	crystal size corresponding to the 10^{th} percentile of the cumulative undersize curve
d ₅₀	crystal size corresponding to the 50^{th} percentile of the cumulative undersize curve
d ₉₀	crystal size corresponding to the 90^{th} percentile of the cumulative undersize curve
D	tube/shell diameter, m

D*	Aris-Taylor dispersion coefficient, m ² s ⁻¹
D _{AB}	molecular diffusion coefficient, m ² s ⁻¹
d _m	molecular diameter, m
d _p	pore diameter, m
D _s	inside shell diameter, m
E	friction power expended per unit surface area, W m ⁻²
f	Fanning friction factor, dimensionless
fhet	heterogeneity nucleation factor, dimensionless
G	linear growth rate, $\mu m s^{-1}$
Gz	Graetz number, $Gz = \frac{\pi}{4} \operatorname{Re} \operatorname{Pr} \frac{D}{L}$
ΔH	pressure head difference, psi
ΔH_c	heat of crystallization, J kg ⁻¹
Н	plate height, m or pressure head, psi
h	heat transfer coefficient, Wm ⁻² K ⁻¹
HTU	height of transfer unit, m or cm
J	volumetric flux, m ³ m ⁻² s ⁻¹
јн	Colburn factor for heat transfer St Pr ^{2/3} , dimensionless
k	thermal conductivity, Wm ⁻¹ K ⁻¹
К	pressure loss coefficient or constant in Equation (E.4), dimensionless
k _B	Boltzmann's constant, $1.381 \times 10^{-23} \text{ J K}^{-1}$
k _v	crystal volume shape factor, dimensionless
ΔL	crystal class size interval, µm
L	length or crystal size, m

L _e	hydrodynamic entrance length, m
L ₁	lower crystal size measured, µm
L ₂	upper crystal size measured, µm
m	mass, kg
m	mass flow rate, kg s ⁻¹
M _T	magma density, kg/m ³
n	population density, no $m^{-3}\mu m^{-1}$
n ^o	population density of crystal nuclei, no $m^{-3}\mu m^{-1}$
Ν	number of fibers/tubes or plates
N _A	Avogadro's number, $6.023 \times 10^{23} \text{ mol}^{-1}$
N_c	number of crystals generated per unit volume, no m ⁻³
$N_{\rm H}$	incremental heat transfer number
Nu	Nusselt number, $\frac{hD}{k}$
Nu _{T3}	inside Nusselt number for the T3 boundary condition
NTU	number of transfer units, dimensionless
ΔP	pressure drop, Pa
P _T	tube pitch, m
Pr	Prandtl number $\frac{C_p \mu}{k}$, dimensionless
Q	rate of heat transfer, W
q_w	wall heat flux, Wm ⁻²
r	tube radius, m

Re	Reynolds number $\frac{Du\rho}{\mu}$, dimensionless
S	thermal energy generated per unit volume of the fluid, W m^{-3}
S	supersaturation ratio, $\frac{C}{C^*}$, dimensionless
S*	thermal energy source number, dimensionless
St	Stanton number St = $\frac{Nu}{RePr} = \frac{h}{\rho u C_p}$, dimensionless
Т	temperature, K
t	time
ΔΤ	temperature difference, K
T_{α}	surrounding medium temperature, K
t _{cen}	time required for the permeate to be transported convectively to the centerline of a hollow fiber, s
t _p	plate thickness, m
t _{samp}	sampling time, s
u	velocity, m s ⁻¹
U	overall heat transfer coefficient, Wm ⁻² K ⁻¹
V	volume, m ³
• V	volumetric flow rate, m ³ s ⁻¹
W	flat duct half width, m
W _p	plate width, m
W	weight, kg
x*	dimensionless axial distance for thermally developing flow, $\frac{z/D}{\text{RePr}}$

x ⁺	dimensionless axial distance for hydrodynamically developing flow, $\frac{z/D}{Re}$
X _w	weight fraction
Y _n	n th eigenfuction
Z	axial distance, m

Greek Symbols

α	surface area to volume ratio of heat exchangers based on total volume, equal to ND_o/D_s^2 , m^2/m^3
α_{for}	volumetric surface area of foreign particles responsible for heterogeneous nucleation, m^2/m^3
β	surface area to volume ratio of heat exchangers based on the volume of one side, $m^2\!/m^3$
δ	wall thickness, m
3	heat exchanger effectiveness, dimensionless or mean specific power input, W kg ⁻¹
ε _m	membrane porosity, dimensionless
θ	dimensionless temperature
λ_{K}	Kolmogorov scale, µm
λ_n	n th eigenvalue
μ	viscosity, kg m ⁻¹ s ⁻¹
V	number of ions in a molecule, dimensionless
ξ	dimensionless radial displacement, m
ρ	density, kg m ⁻³
σ	relative supersaturation, dimensionless

φ	packing fraction of a PHFHE equal to ND_o^2/D_s^2 , dimensionless
ϕ_{het}	heterogeneity factor, dimensionless
τ	mean residence/retention time, s
τ_{m}	membrane tortuosity, dimensionless

Subscripts/Superscripts

AS	antisolvent
b	bulk
bc	boundary condition
c	crystal
С	clean
calc	calculated
cr	cross flow
CST	completely stirred tank
d	dispersed phase
D	dirty
en	entrance
ex	exit
exp	experimental
het	heterogeneous
hom	homogeneous
f	feed
fil	filtrate
i	inside or crystal class

in	inlet
lm	logarithmic mean
m	membrane or mean
max	maximum
mean	mean
min	minimum
0	outside
out	outlet
ov	overall
p	pore
S	shell side
solv	solvent
t	tube side
Т3	convective boundary condition at the inside surface of the duct
tot	total
w	wall
wat	water
x	local
*	saturation condition

LIST OF ACRONYMS

circle equivalent diameter CED CSD crystal size distribution CST completely stirred tank **CSTR** continuous stirred tank reactor CV coefficient of variation HTN high temperature nylon ID inside diameter IPA isopropanol **MSMPR** mixed suspension mixed product removal **MWCO** molecular weight cut off OD outside diameter PAT process analytical technology PE polyethylene PEEK polyetheretherketone PES polyethersulfone PHFAC polymeric hollow fiber antisolvent crystallization PHFEC polymeric hollow fiber emulsion crystallization PHFHE polymeric hollow fiber heat exchangers PP polypropylene PPS polyphenylene sulfide polytetrafluoroethylene PTFE PVC polyvinyl chloride

- PVDC polyvinylidene chloride
- PVDF polyvinylidene fluoride
- RO reverse osmosis
- SD standard deviation
- SEM scanning electron microscopy
- SHFC solid hollow fiber crystallizer
- SHFCC solid hollow fiber cooling crystallization

CHAPTER 1

INTRODUCTION

1.1 Crystallization from Solution – Current Art

Crystallization and precipitation processes are widely used in the chemical and pharmaceutical industries for the separation, purification and/or production of bulk or fine chemicals. The role of crystallization in the production of crystalline commodity products, such as bulk chemicals, sugar, salt and many fertilizers is important and the process itself is reasonably well established and understood, as summarized in the related literature (Mersmann, 2001; Mullin, 2001; Myerson, 2002). In recent years the importance of fine chemicals and special products and their high added value have shifted the interest in crystallization research towards organic materials, an area relatively undeveloped until the late 1980s (Tavare, 1995).

A good example of an industry where crystalline products of high value are produced is the pharmaceutical industry. Over 90% of all pharmaceutical products contain an active ingredient in particulate, generally crystalline, form (Shekunov and York, 2000), while 65% of the FDA-approved new drug entities in 2000 and 2001 were in solid form (Davis and Vinson, 2001a; 2001b; 2002a; 2002b). The properties of the crystallized product that are important are crystal size distribution (CSD), which should be as narrow as possible and crystal shape/habit. Also, small crystal sizes are preferred, since smaller particles dissolve more readily according to the Noyes-Whitney Equation and can increase the speed of action of the drug (Ansel et al., 1999). All these properties are determined from a variety of factors such as crystallization technique employed, type and size of equipment used, operating conditions and choice of solvent.

Crystallization/precipitation from a solution is far more common than melt crystallization and will be the focus of this dissertation. Four ways are commonly used to induce crystallization: cooling, solvent removal (i.e., evaporation), antisolvent addition and chemical reaction (precipitation) (Nyvlt, 1992). Another way, often neglected in the literature due to its scarcity, is heating (Dirksen and Ring, 1991). This is applicable for compounds for which solubility decreases with temperature and can be placed together with cooling in a more general category of temperature-driven crystallization. The technique used to induce crystallization dictates to a certain extent the type of equipment to be used. Good reviews of the different types of crystallizers encountered can be found in crystallization handbooks (Mersmann, 2001; Mullin, 2001; Myerson, 2002). The majority of them can in general be characterized as mixed vessels, with the degree of mixing, however, varying to a significant degree.

As such, one can consider them as variations of an ideal crystallizer, the Mixed Suspension Mixed Product Removal (MSMPR) crystallizer (Randolph and Larson, 1988). The latter is essentially a Completely Stirred Tank (CST) operating in a batch or continuous mode, in which perfect mixing of both the liquid and the generated solid phases is assumed to hold, particle breakage, attrition or agglomeration is negligible and reaction might (precipitation) or might not (crystallization) take place. From the above description it follows that the MSMPR crystallizer is directly analogous to Completely Stirred Tank Reactors (CSTR) and will therefore follow the same operating characteristics. For example at steady state, the population density curve of an MSMPR
crystallizer follows a simple exponential decay law, similar to the dimensionless residence time distribution of a CSTR. The theory of MSMPR crystallizers is simple, enables the simultaneous determination of the nucleation and growth kinetics by simple experiments (Garside and Shah, 1980) and is probably one of the most attractive features of this type of crystallizer. Another advantage of MSMPR crystallizers is the high solids loading they can handle.

Industrial crystallizers have been successfully used for the production of common inorganic and organic chemicals with narrow Crystal Size Distributions (CSDs) and a large mean size (Bennet, 1962). However, in the same study, broad CSDs were also reported, often for the same compounds, revealing a considerable variability in the process outcome. In addition, industrial crystallizers cannot in general meet the targets of a narrow CSD and a small mean crystal size, often desirable in the production of pharmaceuticals and specialty chemicals, due to imperfect mixing and the resulting supersaturation conditions inside crystallizer. Non-uniform non-uniform the supersaturation can lead to uncontrolled nucleation and non-uniform growth, effects that are clearly undesirable.

Imperfect mixing is an inherent characteristic of MSMPR crystallizers. It has been repeatedly reported in the literature for industrial crystallizers, whose performance is often different from that obtained at laboratory scale and frequently characterized by segregation effects (Tavare, 1989). It is also not uncommon even at a small scale. Figure 1.1 shows the CSDs obtained during potassium nitrate cooling crystallization in a 10 liter laboratory MSMPR crystallizer (Juzazsek and Larson, 1977). In this case, sampling was performed at two points inside the crystallizer: from the bulk of the crystallizer and a



Figure 1.1 Potassium nitrate cooling crystallization. CSD broadening in a 10L laboratory MSMPR crystallizer (reproduced based on data from Juzazsek and Larson, 1977).

dead zone, a zone of poor mixing. It is evident that even at such small scale the difference in the CSDs and their characteristics is large: 116 μ m in mean size and over 300 μ m in the size range of the crystals produced. Upon scale up, such mixing problems will become even more pronounced leading to a broad CSD. Scale-up problems are probably the only major disadvantage of the antisolvent addition technique compared to the other crystallization techniques. In this case, mixing should be good at both the addition point and the bulk of the suspension and micromixing and macromixing issues should be carefully addressed (Mersmann, 1999).

Apart from the mixing issue, conventional crystallizers present additional disadvantages, which are more case specific. In thermally-driven crystallization, cooling and evaporative, current design practices for heat transfer devices (external shell and tube heat exchangers, cooling coils and jackets) impose a large temperature difference between the cooling/heating medium and the crystallizing solution, typically between 5-10°C (Myerson, 2002; Price, 1997). This temperature difference is responsible for uncontrolled supersaturation generation and depletion near the cooling/heating surfaces, which leads to excessive nucleation and incrustation formation. In evaporative crystallization, other problems apart from excessive nucleation and incrustation include vapor disengagement at the heating surfaces and the possibility of product disintegration (Paul, 1997). The former introduces further nucleation as well as high and localized supersaturation at the vapor-liquid interface, while the latter is unacceptable if the product properties have to meet stringent specifications as in the case of pharmaceuticals and fine chemicals.

Two approaches have been followed to overcome the above-mentioned shortcomings. The first is to improve existing facilities by applying new in-situ monitoring techniques that can lead to better prediction and control of the applied supersaturation and hence better control of the final CSD (Fevotte, 2002; Grön et al., 2003; Monnier et al., 1997; Togalidou et al., 2002; Yu et al., 2004). This approach is very popular nowadays, especially in the pharmaceutical industry where the Process Analytical Technology (PAT) initiative is expected to transform the way the process is operated. However, as already explained, well-mixed crystallizers are intrinsically inclined towards a spectrum of local conditions in time and space, and consequently a relatively broad CSD.

The second approach is to develop new crystallization techniques where supersaturation can be created and depleted on a microscale, resulting therefore in a narrow CSD and a small crystal size. Probably, the most well-known of these techniques is the impinging-jet mixer technique, where two high velocity streams are brought into contact to effect high nucleation rates, followed by growth in a well-mixed vessel or a tubular precipitator (Midler et al., 1994). Although this technique can result in narrow CSDs with a small crystal size, it has certain limitations. It often suffers from jet alignment problems and its applicability is limited to streams with a viscosity ratio smaller than 3.5, since for larger values of this ratio, mixing is poor (Kirwan et al., 2003). Another technique suitable for the production of pharmaceutical solids is spherical crystallization (Kawashima et al., 1982). In spherical crystallization, only the goal of a narrow CSD is obtained; the produced crystals are spherical agglomerates of relatively high porosity, consisting of smaller, usually needle-like crystals. Other approaches undertaken include emulsion crystallization (Davey et al., 1995; Davey et al., 1996) and precipitation with supercritical fluids (York, 1999); although the latter shows promising results, it has not been commercialized yet.

1.2 Membrane-based Crystallization

Due to their small diameter, membrane hollow fibers can be potentially used for the creation and depletion of supersaturation on a microscale, which can lead to narrow and reproducible CSDs. Probably the observation of crystal formation on the surface of polymeric membranes is as old as the process of reverse osmosis (RO). However, the interest in this case is primarily to prevent crystal formation (Boerlage et al., 2000; 2002) and not to produce crystals of a desired CSD and/or crystal shape. Crystallization in reverse osmosis is induced by solvent (water) removal achieved via the application of a high pressure difference.

The first study of reverse osmosis as a crystallization technique was performed by Azoury et al. (1986a; 1986b; 1986c; 1987). They studied the precipitation of calcium oxalate in hollow fiber reverse osmosis modules in order to simulate the early stages of stone formation in the renal tubules. They reported the dependence of the mean crystal size and its standard deviation (SD) on the residence time of the feed solution. The mean crystal size ranged from 3.9-5.1 µm and its SD from 0.3-0.5 µm, yielding a low coefficient of variation (CV) of only 10%. Calcium oxalate is a sparingly soluble system; hence, a low mean size and coefficient of variation should be anticipated (Mersmann, 2001). However, the SD and CV values achieved in these studies are extremely low and indicative of the level of supersaturation generation and control that hollow fiber

membrane devices can achieve. It was also reported that about 10% of the formed crystals remained inside the reverse osmosis module. Since the concentration of calcium oxalate in the feed was low, it seems that scaling problems will be more severe for a readily soluble system. This would result in pore blockage and consequently a reduction in the flux and the generated supersaturation.

Another membrane technique used recently in crystallization is membrane distillation, which is a solvent removal method like reverse osmosis. In this case, the solvent (water) is removed by evaporation through the pores of a hydrophobic membrane. Crystallization phenomena in membrane distillation have been observed by various researchers (Wu and Drioli, 1989; Wu et al., 1991a; Wu et al., 1991b; Tomaszewska, 1993; Gryta, 2000; Gryta et al., 2001). However, in all these studies, crystallization was at best a secondary phenomenon if not a side effect. In some of the studies (Wu et al., 1991a; Wu et al., 1991a; Wu et al., 1991b; Gryta, 2000), membrane distillation accompanied by crystallization served as a polishing step of wastewater streams followed by downstream recovery of the crystallizing solute, while in others (Tomaszewska, 1993; Gryta et al., 2001), crystallization was merely a hindering factor in membrane distillation introducing flux decline due to fouling.

The use of membrane distillation as a means of CSD control has been proposed only recently (Curcio et al., 2001). In this study a hydrophobic porous hollow fiber membrane was used as the device creating uniform supersaturation, while crystallization took place in a magma circulating crystallizer. The salt NaCl was the model compound used and relatively narrow CSDs were obtained; CV values between 42-57% were reported, representative of the values obtained in magma crystallizers. However, flux declined with time due to pore blockage. The situation was better in a later study of fumaric acid crystallization in aqueous L-malic acid solutions, where flux decline was small (Curcio et al., 2003a). However, it was still present and can be easily attributed to the much lower solubility of fumaric acid compared to NaCl. The CV values of around 40% reported were similar to the previous study.

Membrane distillation was also applied to the growth of single macromolecular crystals (i.e., proteins), suitable for X-ray diffraction measurements (Curcio et al., 2002; Curcio et al., 2003b). This technique utilizes both flat and hollow fiber membranes and is also suitable for the determination of the crystallization kinetics (Di Profio et al., 2003). It should be mentioned, however, that a similar technique, osmotic dewatering (Todd et al., 1991), has been proposed earlier for the same purpose using RO membranes.

Membrane reactors have been proposed recently for precipitation applications (Zhiqian and Zhongzou, 2002). Barium sulphate precipitation was studied with ultrafiltration hollow fiber membranes of various molecular weight cut off (MWCO) sizes. In this configuration, one of the reactants (Na₂SO₄) is introduced from the shell side, which is kept at a higher pressure, to the lumen side, where it reacts with BaCl₂ to form barium sulphate. Nanosized particles having a primary size of about 70 nm were produced with the smaller MWCO membranes. However, no quantitative information on the CSD was given, while particle aggregation was evident in the transmission electron microscopy images presented. Agglomeration was found to increase with MWCO due to the transmembrane flux increase caused by the larger pores. Fouling problems were also reported, which due to the low reactant concentrations used, must be more pronounced at higher concentrations.

From the above discussion, it is obvious that hollow fiber membrane devices have the potential to achieve supersaturation creation and control. The main problem with solvent removal methods (reverse osmosis and membrane distillation) is fouling and pore blockage, which lead to flux decline and consequently a decrease in the applied supersaturation with time. Pore blockage has been confirmed experimentally by SEM photographs in the case of membrane distillation (Gryta, 2000; Gryta et al.; 2001). Flux decline with increased feed concentration is an inherent characteristic of membrane distillation. As the concentration of the solute increases, the vapor pressure of the solution decreases according to Raoult's law and the driving force for solvent removal, the partial pressure difference, is reduced (Wu and Drioli, 1989; Gryta et al., 2001). For concentrations higher than a specific value, which is different for each solute (i.e., about 1.5M for NaCl), flux decreases sharply and even negative fluxes (dialysis effect) have been observed for more concentrated solutions (Wu and Drioli, 1989). Pore blockage also seems to be an issue in the case of membrane precipitators; however, sufficient data for a final assessment are not yet available. In addition, reverse osmosis has the disadvantage of requiring a high operating pressure, while solvent resistant RO membranes are not available. Finally, membrane distillation can only be applied to aqueous solutions due to wetting of the hydrophobic membrane pores by organic solvents.

1.3 Objectives and Dissertation Organization

Despite the problems that membrane hollow fiber devices presented in the past, they do offer certain advantages. The most important of them is the ability to split the feed into numerous relatively identical fluid packets, which travel through the device with the same velocity and are exposed to the same boundary conditions. This uniformity in flow and boundary conditions, should in principle, lead to a uniformity in crystallization conditions and consequently to a narrow CSD. The ability to pack a large number of fibers in the same device makes them suitable for processing of industrial streams of various capacities. They can also be easily scaled-up and their performance will not differ substantially whether at bench or industrial scale.

The objective of this dissertation is to study three new crystallization techniques based on hollow fiber devices, porous or nonporous. These techniques can be certainly used with aqueous systems as all previously reported membrane crystallization techniques. However, their application range is far more extended: miscible aqueousorganic, immiscible organic or aqueous-organic and purely organic systems can be processed with the proposed techniques. The latter include the following:

- 1. Solid Hollow Fiber Cooling Crystallization (SHFCC). This technique is based on nonporous hollow fibers. The crystallizing solution is passed through the lumen side of the hollow fiber device and cooled below its saturation point by circulating a cooling solution at the shell side. The hollow fiber device acts in this case as a heat exchanger and a plug/laminar flow crystallizer.
- 2. **Porous Hollow Fiber Antisolvent Crystallization (PHFAC).** In this technique the antisolvent is permeated under pressure through the pores of a hydrophobic or hydrophilic membrane to the side where the crystallizing solution is flowing continuously. Miscible systems can be processed by this technique, in which the hollow fiber device acts simultaneously as a mixer and a crystallizer.
- 3. **Porous Hollow Fiber Emulsion Crystallization (PHFEC).** Here, an emulsion of the crystallizing solution in the antisolvent is created by permeating the crystallizing solution under pressure through the pores of hydrophobic or hydrophilic membranes. Immiscible systems can be processed with this technique.

The dissertation is organized as follows. Each technique is presented separately in self-contained chapters, which include their own theory, experimental and results/discussion sections. The fact that Solid Hollow Fiber Crystallizers (SHFC) are essentially heat exchangers prompted a study of their heat transfer performance. During this investigation it became clear that Polymeric Hollow Fiber Heat Exchangers (PHFHEs) are very efficient devices compared to conventional metal and plastic heat exchangers. The theory describing their operation and the intriguing results obtained are presented in Chapter 2. Solid Hollow Fiber Cooling Crystallization is presented in Chapter 3. Chapters 4 and 5 describe Porous Hollow Fiber Antisolvent Crystallization and Porous Hollow Fiber Emulsion Crystallization respectively. Chapter 6 provides conclusions and recommendations for future studies.

CHAPTER 2

POLYMERIC HOLLOW FIBER HEAT EXCHANGERS

The heat transfer performance of Polymeric Hollow Fiber Heat Exchangers (PHFHEs) is examined in this Chapter. The theory and results shown here are important in two ways. First, they can be used to predict the temperature profiles obtained when PHFHEs are used for cooling crystallization, the subject of Chapter 3. Second, they illustrate the superior heat transfer performance of PHFHEs for low temperature/pressure applications compared to existing metal and plastic heat exchangers; they also justify the serious consideration of PHFHEs as alternatives to metal and plastic heat exchangers of both the shell-and-tube and plate type and their more detailed presentation in this dissertation.

2.1 Plastic Heat Exchangers – A Review

Recognized over 40 years ago (Whitley, 1957; Weaver, 1960), polymeric materials offer numerous advantages over metals in the construction of heat exchangers. They are less expensive, easier to shape, form and machine than metals and their densities are 4-5 times lower (Bandelier et al., 1992) resulting in much lower construction, transportation and installation costs. Moreover, the energy required to produce a unit mass of plastics is about two times lower than common metals, making them environmentally attractive (El Dessouky and Ettouney, 1999). The surface of plastics is smooth leading to smaller friction factors and pressure drops and less fouling than commercial metal tubes (Bandelier et al., 1992). However, no long-term fouling data are available except a 76 hr test with hard water (Githens et al., 1965). The smooth surface of hydrophobic plastics also promotes dropwise instead of filmwise condensation and consequently much higher heat transfer coefficients. Plastics possess excellent chemical resistance to acids, oxidizing agents and many solvents. Bigg et al. (1989) have summarized the performance of various polymers under highly corrosive conditions.

The main disadvantage of polymer materials is their low thermal conductivity, between 0.1-0.4 Wm⁻¹K⁻¹, which is 100-300 times lower than metals and necessitates the use of thin walled tubes if performance comparable with metal heat exchangers is to be achieved (Bandelier et al., 1992). Yet, there is another disadvantage: the lack of extensive experience and testing data with plastic heat exchangers accompanied by a disinclination of the chemical industry to depart from well established practices. Also, the operation of plastic heat exchangers is confined below about 200°C, while the thermal expansion of plastics is ten times higher than metals, requiring special design considerations (Bandelier et al., 1992).

On the other hand, the high thermal expansion of plastics can be beneficial in so far as fouling is concerned, since repeated expansion and contraction of the plastic channels can lead to scale detachment (Githens et al., 1965). If one further considers that fouling is essentially solids deposition on the heat transfer surfaces, then it follows that the reduction in heat transfer performance due to scaling in case crystallization is performed, will be much less for plastic heat exchangers. This feature has already been applied on a commercial scale in Swenson Teflon-tube crystallizers (Myerson, 2002), where the cooling surface consists of one or more Teflon immersion coils suspended in the interior of the crystallizer. An elaborate review of past and current developments in the plastic heat exchanger field is out of the scope of this dissertation. Details can be found in the literature (Zaheed and Jachuck, 2004; Davidson et al., 1999). Table 2.1 summarizes the most important details of past work in laboratory, pilot plant or commercial scale plastic heat exchangers; information presented includes the overall heat transfer coefficient obtained and the surface area to volume ratio, which is a measure of the compactness of the heat exchanger. It is apparent that the thermal performance of plastic heat exchangers is inferior to their metal rivals as compared to acceptable design values (Perry and Green, 1999). Also, the designs presented in Table 2.1 are not in general substantially more compact than metal heat exchangers. Therefore, plastics are a good choice for gas-to-gas applications, when corrosion is an issue or when ultra purity, is required.

2.2 PHFHE – A New Type of Heat Exchanger

The relatively low overall heat transfer coefficients achieved in plastic heat exchangers can be improved and reach values comparable to metal heat exchangers, if the tube thickness is kept below 100 μ m (Bandelier at al., 1992). Mechanical strength considerations, on the other hand, impose a minimum wall thickness to diameter ratio of about 10% (Raman et al., 2000). The above constraints clearly show that tubing with diameter smaller than 1 mm should be used if heat transfer comparable or better than metal heat exchangers were to be obtained. Such an approach would also have the additional advantage of obtaining substantially more compact designs.

Exchange	Material(s)		Q.	Application(s)	Reference
Туре		(Wm ⁻ K ⁻)	(m^{2}/m^{2})	and a second	<u> </u>
shell-and-tube, immersion coil	Teflon	30-570	< 340	gas-to-gas, liquid-to-liquid, steam heating	Githens et al., 1965
shell-and-tube, immersion coil	FEP, resin Q ¹	341-567	170-541	liquid-to-liquid, steam heating, corrosive media	Wharry Jr., 1995, www.ametek.com
shell-and-tube	PP, PVDF, PPS	50-500	< 600	liquid-to-liquid, gas-to-gas	Bandelier et al., 1992
shell-and-tube	PVC	90-150	35	water-water	Morcos and Shafey, 1995
plate, triangular channel	PE, PVDC	80-90	651	Gas-air	Hetsroni and Mosyak, 1994
plate, rectangular channel	PP, PVDF	55	500	Air-water	Brouwers and Van der Geld, 1996
plate in shell, rectangular channel	SPER 12 ²	150-230	64	gas-to-gas, gas- to-liquid	Deronzier and Bertolini, 1997
plate, cross flow, irregular channel	PEEK	60-900	< 1140	gas-to-gas, air- water, water- water	Jackhuck and Ramshaw, 1994; Burns and Jackhuck, 2001
spirally wound plastic film	N/A	1500-7000	N/A	evaporators, condensers	Lauro, 1979; Bandelier et al., 1992
shell-and-tube	РР	170	42	evaporators, condensers	Bourouni et al., 1997
Shell-and-tube	HTN	1100 ³	542	water-water, solar heating systems	Liu et al., 2000

Performance of Laboratory, Pilot Plant and Commercial Plastic Heat Table 2.1 Exchangers

¹ Proprietary Teflon based resin
 ² Super Polymer EniRicerce with 40% glass fiber or 40% silica.
 ³ Theoretical estimate based on wall resistance

Consequently, it is rather peculiar that nonporous hollow fiber devices have not yet been used or studied for heat transfer purposes; the only notable exception is their use in extracorporeal blood oxygenators (Drummond et al., 2003; Dueri et al., 2002; McFall et al., 1999; Elgas et al., 1997). It is one of the objectives of this dissertation to clearly illustrate that nonporous Polymeric Hollow Fiber Heat Exchangers (PHFHEs) can be potential substitutes for metal and plastic heat exchangers at low temperatures and pressures. Parallel flow shell-and-tube PHFHEs of solid/nonporous PP hollow fibers were fabricated and tested extensively between 0-75°C and 63<Ret<2537 with water/water and water/organic systems. It will be clearly illustrated that PHFHEs achieve overall coefficients close to the design values of metal heat exchangers and considerably higher than any liquid-to-liquid application reported for plastic heat exchangers. The theory describing heat transfer in PHFHEs will also be provided; due to the finite wall resistance of the polymeric hollow fibers it is somewhat different from that used for conventional metallic tube-based heat exchangers. It is also useful for the description of heat transfer during SHFCC.

A schematic showing the operating principle of a PHFHE is given in Figure 2.1. A PHFHE is essentially a shell-and-tube heat exchanger without baffles, fabricated by polymeric tubes of submillimeter diameter. The shell is preferably cylindrical; shells of different cross section, i.e., rectangular, are also a possibility. The feed stream is passed through the lumen side usually under laminar flow conditions. However, the stream velocities obtained are high, typical of the values used in conventional heat transfer equipment operated in the turbulent regime (Re ~ $7 \cdot 10^4 - 10^5$). A cooling/heating solution



Figure 2.1 Operating principle of a PHFHE.

is circulated through the shell side in parallel or cross flow. The creation of baffles is possible and has been performed for membrane contactors (Wang and Cussler, 1993).

Polymeric hollow fiber heat exchangers are somewhat identical to membrane contactors. Therefore, they offer extremely high surface area/volume ratios. Figure 2.2 shows this ratio for commercial metal heat exchangers and projected values for PHFHEs. Current commercial membrane contactors (Liqui-Cel[®] Extra-Flow 10x28, Celgard, Charlotte, NC) present a surface area/volume ratio based on total volume up to 3900 m²/m³. This value is slightly more than an order of magnitude higher than shell-and-tube or plate heat exchangers, higher than plate-fin heat exchangers and inferior only to periodic-flow (matrix surfaces) heat exchangers and rotary regenerators (London, 1983; Kays and London, 1984). It will be shown that, owing to this feature, the thermal performance of PHFHEs is superior on a volumetric basis compared to metal shell-and-tube or plate heat exchangers, making them an obvious choice for lower



Figure 2.2 Compactness of heat exchangers (based on London, 1983) and PHFHEs.

temperature and pressure applications. Additional advantages emanating from the similarity between PHFHEs and membrane contactors are the existence of well established fabrication techniques, a substantial operational experience with porous hollow fibers and the fact that they can easily be scaled up.

2.3 Heat Transfer in Hollow Fiber Devices - Theory

2.3.1 Problem Identification

In the analysis of conventional heat transfer equipment, a constant wall temperature or a constant wall heat flux boundary condition is usually assumed. In both cases, the wall resistance is not considered in the analysis since the thermal conductivity of metal tubes is so high, that the wall resistance accounts for less than 5% of the overall resistance. This is not correct however, when polymeric tubes are used. The thermal conductivity of polymers is low and the wall resistance will be substantial, even at thicknesses below 100 μ m, for which performance comparable to conventional heat transfer equipment can be claimed (Bandelier et al., 1992). Therefore, the wall resistance must be an integral part of the analysis.

Only laminar flow solutions will be considered here, since almost all of the heat transfer runs were performed in the laminar regime. There are two approaches used in the literature to solve laminar heat transfer problems with finite wall resistance: solve the problem as a conventional convection problem or as a conjugated problem (Shah and London, 1978). For the conventional convection problem, the wall resistance together with the outside convective resistance are treated as a lumped term and only the energy equation for the tube side liquid is solved. Usually, the T3 boundary condition (also known as the boundary condition of the third kind) is applied, which implies a convective boundary condition at the inside tube surface and a constant temperature for the medium surrounding the tube. On the basis of a constant outside convective resistance this is equivalent to a constant outside wall temperature. This treatment is directly analogous to

the classical Graetz problem and therefore this problem is often identified as the *extended Graetz problem*.

In the conjugated problem the energy equation for both the liquid and the solid wall, coupled by the boundary condition at the inner wall surface, are solved simultaneously. This approach, although more rigorous, presents a lot of mathematical difficulties and a relatively limited number of studies are available in the literature (Mori et al., 1974; Barozzi and Pagliarini, 1985; Bilir, 1995). These studies show that under certain conditions longitudinal wall conduction is important and the conventional convection problem formulation will not lead to accurate results. It remains to be examined in which category heat transfer in a PHFHE falls.

The difference between the conventional and the conjugated problem is the fact that axial conduction in the wall is not accounted for in the former. Mori and Tanimoto (1980) studied the conjugated problem for fully developed laminar flow in a flat duct with the boundary condition of the third kind prescribed at the outside wall surface in relation with the conventional concept of an overall heat transfer resistance, a central feature of this chapter. Although strictly valid for flat ducts, their results can serve as a comparison basis for the circular duct also. They showed that for values of the conductance ratio $k_ww/k_i\delta$ ($k_wr_i/k_i\delta$ for circular tubes) equal to 10 and 1000 the results of the conjugated approach are essentially the same with the ones obtained from the conjugated approach if $\delta/L < 0.05$ and $\delta/L < 0.01$ respectively. For hollow fiber diameters smaller than 0.5 mm this ratio will be about 1-2 orders of magnitude smaller, depending on the length of the fibers.

Polymeric materials have thermal conductivities between 0.1-0.4 Wm⁻¹K⁻¹ (Bandelier at al., 1992). Also, it was shown that as far as good heat transfer characteristics and mechanical strength are concerned, a r_i/δ ratio of 10 gives optimal results (Raman et al., 2000). Using the above values it was estimated that the conductance ratio for plastic tubes would reach a maximum value of 64-190 and 3-8 for air and water respectively as the tube side fluid. Accordingly, the conventional convection treatment will give reliable results for any plastic heat exchanger with tubes smaller than 1 inch and longer than 60-90 cm, dimensions that cover almost all practical applications including PHFHEs. The above arguments lead to the conclusion that heat transfer inside the polymeric wall of a hollow fiber is one-dimensional, longitudinal wall conduction is negligible in all cases and the conventional convection problem formulation will be applicable.

2.3.2 Laminar Flow Solutions for the T3 Boundary Condition

In this section solutions for both long (fully developed flow) and short (thermally developing flow) ducts will be presented. For fully developed flow, the limiting inside Nusselt number can be found from a relationship proposed by Hickman (1974):

$$Nu_{T3} = \frac{\frac{48}{11} + Nu_{w}}{1 + \frac{59}{220}Nu_{w}}$$
(2.1)

where

$$Nu_{w} = \frac{U_{w}D_{i}}{k_{i}}$$
(2.2)

$$\frac{1}{U_w} = \frac{D_i}{D_o h_o} + \frac{D_i}{2k_w} \ln\left(\frac{D_o}{D_i}\right)$$
(2.3)

Note that Equation (2.1) yields Nu_{T3} values that lie between 3.66 and 4.364, the limiting Nusselt numbers for the constant wall temperature ($Nu_w=\infty$) and the constant heat flux ($Nu_w=0$) boundary conditions respectively. This is in qualitative agreement with the numerical results of Mori et al. (1974) for the conjugated problem. In fact, the results of Equation (2.1) are higher than the ones obtained by the analytical solution described below, ranging from 0% for $Nu_w=0$ to 1.9% for $Nu_w=\infty$ (Shah and London, 1978). Note also that U_w in Equation (2.3) is based on the inside area and that a fouling coefficient for the outside stream can also be added. The overall Nusselt number is also based on the inside area and is given by

$$\frac{1}{Nu_{ov}} = \frac{k_i}{U_i D_i} = \frac{1}{Nu_{T3}} + \frac{1}{Nu_w}$$
(2.4)

where

$$\frac{1}{U_i} = \frac{A_i \Delta T_{lm}}{Q} = \frac{1}{h_i} + \frac{1}{U_w}$$
(2.5)

and h_i is calculated from Nu_{T3}. The above definitions are consistent with the fact that they are valid for a long duct, where a distinction between local and mean heat transfer coefficients and Nusselt numbers is meaningless. However, in the case of a short duct such a distinction is necessary. Inserting the expression for Nu_{T3} from Equation (2.1) into Equation (2.4) and after some manipulations the following second order algebric equation in terms of Nu_w results:

$$\left(1 - \frac{59}{220} N u_{ov}\right) N u_{w}^{2} + \left(\frac{48}{11} - 2N u_{ov}\right) N u_{w} - \frac{48}{11} N u_{ov} = 0$$
(2.6)

Equation (2.6) yields two roots, one negative with no physical significance and the other positive, which is the desired solution.

Equation (2.6) in combination with Equations (2.2), (2.3) and (2.5) can be used for the simultaneous determination of both the inside and outside heat transfer coefficients with the only required input being the overall heat transfer coefficient, which can be experimentally determined. This is of great interest in case parallel flow is used in the shell side of the PHFHE, a condition present in all experimental runs presented here. No reliable heat transfer correlation exists for the case of parallel flow along a bundle of randomly oriented cylinders (Kakac et al., 1987). Several mass transfer correlations (which could possibly be extended to heat transfer on the basis of heat and mass transfer analogy) for parallel flow in the shell side of membrane modules do exist; however, the results are scattered, error margins are rather large and channeling and bypassing reinforce the poor predictability of the process (Ho and Sirkar, 1992). Finally, Equations (2.1)-(2.6) are useful to obtain a first estimate of the inside and outside heat transfer coefficients in case the thermally developing flow problem, described in the next paragraph, is solved.

Various studies of the thermally developing T3 problem have been performed (Schenck and Dumore, 1951; Sideman et al., 1964), including a Leveque type solution (Rosen and Scott, 1961) and a solution including the effect of axial heat conduction (Hsu, 1968). The most complete solution of the problem, however, has been given by Hsu (1971), who solved it including a thermal energy source. The problem was formulated mathematically as follows:

$$\left(1-\xi^{2}\right)\frac{\partial\theta}{\partial z} = \frac{1}{r_{i}\operatorname{Re}\operatorname{Pr}}\left(\frac{\partial^{2}\theta}{\partial\xi^{2}} + \frac{1}{\xi}\frac{\partial\theta}{\partial\xi} + S^{*}\right)$$
(2.7)

with boundary conditions

$$At \ z = 0 \qquad \qquad \theta = 1 - \frac{T_a}{T_{in}} \tag{2.8}$$

for
$$z > 0$$
 at $\xi = 0$ $\frac{\partial \theta}{\partial \xi} = 0$ (2.9)

for
$$z > 0$$
 at $\xi = 1$ $-\frac{\partial \theta}{\partial \xi} = \frac{Nu_w}{2}\theta$ (2.10)

and

$$\xi = \frac{r}{r_i}, \ \theta = \frac{T - T_a}{T_{in}}, \ S^* = \frac{sr_i^2}{kT_{in}}$$

Note that, for $S^*=0$, Equation (2.7) is identical to the equation solved in the classical Graetz problem. The solution of the above equation yields the following relationships for the temperature as a function of radial and axial displacement and the wall heat flux and bulk mean temperature as a function of axial displacement only:

$$\theta(\xi, z) = \frac{T(\xi, z) - T_a}{T_{in}} = -\frac{S^* \xi^2}{4} + \frac{S^*}{2} \left(\frac{2}{Nu_w} + \frac{1}{2}\right) + \sum_{n=1}^{\infty} C_n Y_n \exp\left(-\frac{\lambda_n^2 z}{r_i \operatorname{Re} \operatorname{Pr}}\right) \quad (2.11)$$

$$q_{w} = U_{w}T_{in}\left(\frac{S^{*}}{Nu_{w}} + \sum_{n=1}^{\infty}C_{n}Y_{n}(1)\exp\left(-\frac{\lambda_{n}^{2}z}{r_{i}\operatorname{Re}\operatorname{Pr}}\right)\right)$$
(2.12)

$$\theta_{b} = \frac{T_{b} - T_{a}}{T_{in}} = 4 \left(\frac{S^{*}}{24} + \frac{S^{*}}{4Nu_{w}} + \frac{Nu_{w}}{2} \sum_{n=1}^{\infty} \frac{C_{n}Y_{n}(1)}{\lambda_{n}^{2}} \exp\left(-\frac{\lambda_{n}^{2}z}{r_{i}\operatorname{Re}\operatorname{Pr}}\right) \right)$$
(2.13)

Using the above expressions the local Nusselt number can be calculated as

$$Nu_{x,T3} = \frac{q_w}{T_b - T_w} \frac{2r_i}{k_i}$$
(2.14)

and from Equation (2.14) the mean inside Nusselt number is found by integration:

$$Nu_{m,T3} = \frac{1}{L} \int_{0}^{L} Nu_{x,T3} dz$$
 (2.15)

The eigenvalues λ_n and eigenfunctions Y_n are only functions of ξ and are calculated from the characteristic equation below,

$$\frac{d^2 Y_n}{d\xi^2} + \frac{1}{\xi} \frac{dY_n}{d\xi} + \lambda_n^2 (1 - \xi^2) Y_n = 0$$
(2.16)

which satisfies the following boundary conditions:

$$at \xi = 0 \qquad \frac{dY_n}{d\xi} = 0 \tag{2.17}$$

$$at \xi = 1 \qquad -\frac{dY_n}{d\xi} = \frac{Nu_w}{2}Y_n \qquad (2.18)$$

Finally, the coefficients in the series expansion are found from the set of equations given by:

$$C_n = \left(1 - \frac{T_a}{T_{in}}\right) I_n + S^* G_n \tag{2.19}$$

$$I_{n} = \frac{Nu_{w}}{2} \frac{Y_{n}(1)}{\lambda_{n}^{2} \int_{0}^{1} \xi(1-\xi^{2})Y_{n}^{2}d\xi}$$
(2.20)

$$G_{n} = \frac{-\int_{0}^{1} \xi Y_{n} d\xi}{\lambda_{n}^{2} \int_{0}^{1} \xi (1-\xi^{2}) Y_{n}^{2} d\xi}$$
(2.21)

From the above discussion, it follows that the problem of determining the temperature profile inside the PHFHE reduces to the problem of calculating the eigenvalues and eigenfunctions by solving the set of Equations and boundary conditions (2.16)-(2.18). The latter was solved as an initial value problem by integrating numerically Equation (2.16) with a fourth order Runge-Kutta method, combined with a secant method (Rice and Do, 1995) that utilizes the convective boundary condition, Equation (2.18).

Details of the solution procedure are given in Appendix A. The solution procedure was implemented in a computer program written in Microsoft Visual Basic for Applications, which can be used with the spreadsheet software Microsoft Excel. The full program is given in Appendix B. The exact analogous mass transfer problem was solved in a similar manner for membrane hollow fiber dialyzers by Davis and Parkinson (1970), who also included eigenvalues for values of the wall convective parameter appearing in Equations (2.10) and (2.18) smaller than 1.

2.3.3 Simplified Laminar Flow Solutions for the T3 Boundary Condition

In this section simplified laminar flow solutions for the T3 boundary condition are presented, which unlike Equation (2.1) are valid for both fully developed and thermally developing flow situations. Consequently, they can be used under most conditions in place of the tedious solution procedure described above for Equation (2.7). These solutions, based on the concept of the incremental heat transfer number (Shah and London, 1978), are presented for the first time and they can be useful for the design of PHFHEs as well as conventional plastic heat exchangers. Similar solutions, yielding the mean Nusselt number as a function of the dimensionless axial distance, have been obtained for the constant wall flux and the constant wall temperature boundary conditions. They follow a relationship of the form (Shah and London, 1978):

$$Nu_{m,bc} = Nu_{x,bc} + \frac{N_{H,bc}}{x^*} = Nu_{x,bc} + \frac{4N_{H,bc}}{\pi}Gz$$
(2.22)

Equation (2.22), which only requires the knowledge of the asymptotic or limiting Nusselt number and the incremental heat transfer number, is valid for $x^*>0.03$ and gives predictions within $\pm 3\%$ of the existing analytical solution for each of the boundary

conditions mentioned above. Note also that the upper error limit is obtained for the lower x^* values and that the error involving the use of Equation (2.22) in most practical applications will be less than $\pm 1\%$.

A simple formula similar to Equation (2.22) can be also derived for the T3 boundary condition. It can be written as follows:

$$Nu_{m,T3}(Nu_w) = Nu_{x,T3}(Nu_w) + \frac{N_{H,T3}(Nu_w)}{x^*} = Nu_{x,T3}(Nu_w) + \frac{4N_{H,T3}(Nu_w)}{\pi}Gz \quad (2.23)$$

It remains now to identify the functional dependencies for the asymptotic Nusselt number and the incremental heat transfer number. For the former, the asymptotic solution of Hickman (1974), Equation (2.1), can be used. The functional dependence of the incremental heat transfer on Nu_w can be found as in the case of the other boundary conditions, namely, by solving the energy equation for the fluid (Equation (2.7)) and then using the definition of the incremental heat transfer number, Equation (2.23):

$$N_{H,T3} = \left(Nu_{m,T3} - Nu_{x,T3}\right)x^*$$
(2.24)

Equation (2.24) requires the knowledge of the mean inside Nusselt number. The latter is related to the overall Nusselt number by a relationship similar to Equation (2.4):

$$\frac{1}{Nu_{m,ov}} = \frac{k_i}{U_i D_i} = \frac{1}{Nu_{m,T3}} + \frac{1}{Nu_w}$$
(2.25)

An expression for the overall mean Nusselt number is obtained from the following relationship, which is based on readily available design specifications and was also quoted by Hickman (1974) and Davis and Parkinson (1970):

$$Nu_{m,ov} = \frac{\ln(\frac{T_a - T_{in}}{T_a - T_b})}{4x^*}$$
(2.26)

Then, the mean Nusselt number for the tube side can be calculated from Equation (2.25).

Equation (2.7) was solved by using the first 150 eigenvalues and coefficients. The calculated local Nusselt numbers for $Nu_w = 0.01$ and $Nu_w = 10000$, values approaching respectively the constant wall flux and the constant wall temperature boundary condition, agree with the results of Shah and London (1978) within 0.006% (in absolute terms agreement at the second decimal place) down to $x^* = 0.00001$, the agreement being almost perfect at higher x^* .

Figure 2.3 shows the incremental heat transfer number obtained at $x^* = 0.2$ by the procedure described above. The curve presents two plateaus at low and high Nu_w numbers, while at intermediate Nu_w numbers (1-10) the dependence of the incremental heat transfer number on the former is almost linear. The two plateaus correspond to the two limiting cases of the T3 boundary condition, namely, the constant wall heat flux and the constant wall temperature. While the incremental heat transfer number at high Nu_w is practically the same with the value of 0.0499 found in the literature (Shah and London, 1978) for the Graetz problem, the same is not true for the other end.

At low Nu_w the incremental heat transfer number is equal to 0.0448, considerably less than the value of 0.0722 obtained for the constant wall heat flux boundary condition. Although at first sight this seems as a discrepancy, it should be pointed out that in the case Nu_w = 0 the constant wall flux condition although met, corresponds to the condition of a perfectly insulated body, namely, zero heat flux. In this special case, the heat transfer coefficient and consequently the Nusselt number will be zero along the whole length of the duct, a condition markedly different from the case when a nonzero amount of heat is transferred per unit area of the duct. Furthermore, the results presented here as Nu_w \rightarrow 0 are also corroborated by the results of Hickman (1974).



Figure 2.3 Incremental heat transfer number for the T3 boundary condition.

The data presented in Figure 2.3 were fitted with a Boltzmann sigmoidal function. The equation obtained was

$$N_{H,T3} = 0.0499 - \frac{0.06487}{1 + \exp\left(\frac{Nu_w + 5.37935}{2.17887}\right)}$$
(2.27)

and it represents the calculated incremental heat transfer numbers with a mean error of 0.04% and a standard deviation of 0.12%, while the % error ranges between -0.16 and 0.25%. Substitution of Equations (2.1) and (2.27) into Equation (2.23) yields the sought relationship:

$$Nu_{m,T3} = \frac{\frac{48}{11} + Nu_{w}}{1 + \frac{59}{220}Nu_{w}} + \left(0.0499 - \frac{0.06487}{1 + \exp\left(\frac{Nu_{w} + 5.37935}{2.17887}\right)}\right) \frac{4Gz}{\pi}$$
(2.28)

Equation (2.28) predicts the inside mean Nusselt number within -1.5 and 3.4% of the results obtained by the analytical solution for $Gz \le 26$. The mean prediction error for the whole Nu_w range shown in Figure 2.3 was 1.3% with a standard deviation of 0.86%. The above Gz range covers all applications of PHFHEs and most laminar flow applications for existing plastic heat exchangers. For higher Gz numbers it is imperative to use the analytical solution.

2.4 PHFHEs vs Metal Heat Exchangers – Comparison Criteria

In this section the way the experimental results were compared with existing metal heat exchangers is briefly described. All comparisons were made on a volumetric basis and the total volume of the heat exchanger was used. This should be emphasized, since in most of the heat transfer literature the surface area to volume ratio, β , based on one side

(cold or hot stream) is used. This parameter was not used, since it can give somewhat misleading results, i.e., in the case of plate heat exchangers it does not take into account the plate spacing. Two comparison criteria will be used. The first one is the overall conductance per unit volume, which is given by

$$CUV_{ov} = \alpha_i U_i = \alpha_o U_o \tag{2.29}$$

and expresses the total amount of heat transferred per unit time and unit volume. A higher CUV value simply indicates a more compact heat exchanger for the same thermal duty or a heat exchanger that transfers more heat for the same heat transfer equipment volume.

The second criterion is the volume goodness factor based on total volume (Shah, 1983a), which can be used to compare surfaces with different hydraulic diameters. The volume goodness factor was formulated based on β and not α and it refers to only one side of the heat exchanger. However, since for shell and tube heat exchangers $\alpha \approx \beta/2$ (Shah, 1981) and the surface to volume ratios are calculated in the exact same way for PHFHEs, it follows that the volume goodness factor can also be expressed in terms of α . Also, due to the similarity between shell and tube and PHFHEs it can be assumed, without introducing significant error in the calculations, that the shell side heat transfer and pressure drop characteristics will be similar for both types of exchangers. In this case, comparison of the conductance and frictional losses of only the tube side, gives a good estimate of the respective parameters for both sides. The volume goodness factor for a circular tube is expressed by a plot of the following two quantities (Shah, 1983a):

$$h\alpha = \alpha \frac{C_p \mu}{\Pr^{2/3}} \frac{1}{D} St \Pr^{2/3} \operatorname{Re} = \alpha N u \frac{k}{D}$$
(2.30)

$$E\alpha = \alpha \frac{1}{2} \frac{\mu^3}{\rho^2} \frac{1}{D^3} f \operatorname{Re}^3 = \alpha \frac{f \rho u^3}{2}$$
(2.31)

The surface that plots higher in a h α vs. E α plot is better and can transfer more heat per unit time per unit volume with the same frictional power loss per unit volume.

Equations (2.29)-(2.31) require the knowledge of the surface to volume ratio. The latter is found for a shell and tube heat exchanger or a PHFHE from the following relationship:

$$\alpha = \frac{4ND_o}{D_s^2} \tag{2.32}$$

The tube count can be approximated for shell and tube heat exchangers within $\pm 5\%$ by (Schlundler, 1983)

$$N \cong \frac{0.78(D_s - D_o)^2}{C_1 P_T^2}$$
(2.33)

For plate heat exchangers good estimates of the surface area to volume ratio can be obtained by

$$\alpha = \frac{N_p A_p}{V} = \frac{\frac{L}{t_p + b} W_p \times H}{W_p \times H \times L} \Longrightarrow \alpha = \frac{1}{t_p + b}$$
(2.34)

2.5 Experimental

2.5.1 Chemicals and Materials

Distilled water or denatured alcohol (Fisher Scientific, Pittsburgh, PA) was used as the tube side liquid. A 33% by volume aqueous ethylene glycol solution or tap water served as the cooling medium circulated in the shell side of the PHFHE. Polypropylene solid hollow fibers of 420/575 μ m ID/OD (Celgard Inc., Charlotte, NC) were used for the fabrication of three modules whose geometrical characteristics are shown in Table 2.2.

Module [*] #	N	Active length (cm)	Total length (cm)	φ	A_{frontal}	A _o (cm ²)	α (m^2/m^3)
1	35	21.9	28.0	0.200	0.107	138	1394
3	9	20.3	26.4	0.051	0.027	33	358
4	35	20.3	26.4	0.200	0.107	128	1394

Table 2.2 Geometrical Characteristics of Polymeric Hollow Fiber Heat Exchangers

* The shell inside diameter for all modules was 0.0076 m.

Two different lengths are quoted in Table 2.2: the active length used for the calculation of the heat transfer area and the total length used for pressure drop and friction factor calculations. The shell side in all cases was $\frac{3}{8}$ inch FEP tubing (Cole Parmer, Vernon Hills, IL). The modules were fabricated by connecting the FEP tubing with two polypropylene male run tees (Cole Parmer, Vernon Hills, IL). The fibers were available in the form of a net with threads every 1 cm of linear length. The thread was removed from the two ends (about 6-7 cm of linear length) to allow for fiber movement during the tube sheet formation. The fiber bundle was then loosely wrapped, tied with a thread at three points to preserve its cylindrical shape and inserted to the module. Figure 2.4 shows a picture of module # 3. The similarity with a shell-and-tube heat exchanger is readily apparent.

The tube sheet was formed by potting the two ends of the male run tees with an epoxy resin (C-4 resin with activator D from Armstrong, Easton, MA). The resin was left to cure for at least 24 hr. The outside fiber surfaces were treated with an aqueous potassium dichromate solution for 5-7 min. to enhance bonding with the epoxy. The



Figure 2.4 Photograph of module # 3.

solution was prepared by dissolving 5 g of potassium dichromate in 10 ml water and 80 ml of 95.7% sulfuric acid.

2.5.2 Apparatus and Procedure

In this section a description of the apparatus and the experimental procedures followed is given. Three different types of experiments are described, each one targeted to illuminate different aspects of the performance of PHFHEs. The first type of experiments was steady state measurements. These were useful to characterize the heat transfer performance of PHFHEs under various conditions and to test the validity of the theory presented in Section 2.3. The latter can be applied in the case PHFHEs are used as cooling crystallizers. The second type of experiments was transient measurements. It will be shown later, that these experiments provided sound justification of the experimental practices adopted, at first empirically, for SHFCC. Finally, the third set of experiments refers to pressure drop measurements. The latter are important in two ways. First, they provide necessary information on the pumping power expenditure of PHFHEs and facilitate comparisons with other types of heat exchangers based on the performance criteria presented in Section 2.4. Second, they show that the applicability of Hagen-Poiseuille theory for the prediction of friction factors for flow inside hollow fibers, an assumption dominant in the membrane literature, is not correct for the whole laminar regime.

The experimental setup used for heat transfer measurements is shown in Figure 2.5. The feed solution held to a constant temperature by means of a thermostatic bath (Haake A81), was circulated through the lumen side of the PHFHE by a diaphragm pump (Cole Parmer, Vernon Hills, IL). Before it entered the PHFHE, it went through an inline



Figure 2.5 Experimental setup for heat transfer measurements in polymeric hollow fiber heat exchangers.

filter (Whatman GF/B filter with a cutoff size of 2.7 μ m) to remove any particulate matter present. Tap water was passed through the shell side for the majority of the runs performed. However, for a significant number of runs, an aqueous cooling solution of 33% by volume ethylene glycol (EG) was circulated through the shell side by means of a Polystat[®] chiller (Cole Parmer, Vernon Hills, IL). In all runs the shell side fluid flowed along the fibers (parallel flow). The inlet and exit temperatures of the two streams were recorded with a four-channel temperature recorder (Sper Scientific, Scottsdale, AZ) with an accuracy of $\pm 0.2^{\circ}$ C. Flow rates were obtained at the two outlets of the PHFHE by measuring the time required to collect a certain volume of liquid.

The experimental procedure adopted was as follows. For each feed flow rate selected, 4-5 different shell side flow rates were employed, starting with the highest flowrate. Flow rates were measured at least twice during each run. Temperatures were recorded every 5-10 min until 2-4 subsequent readings did not differ by more than $\pm 0.1^{\circ}$ C. Most runs lasted between 30-40 min, although steady state conditions were attained much faster. The feed inlet temperature was varied between 40-75°C while the coolant inlet temperature was varied between -5 and 20°C.

A separate set of runs with water on both sides was also performed to extract information on the transient thermal response of solid hollow fiber devices. These experiments were performed to clearly show that the presence of a wall with a substantial thermal resistance would not introduce a prolonged response time for the PHFHE. Two sets of experimental runs were performed; one involved step changes in the flow rate of the lumen side (hot stream) and the other flow rate changes for the cold (shell side) stream. For each set, two runs were performed: one from a high to a low flow rate and
vice versa. For step flow rate changes in the lumen side, the flow rate in the shell side was taken approximately in the middle of the flow rate range used for the experiments described in the previous paragraph. For step flow rate changes in the shell side, the lumen side flow rate was set to a value close to the maximum that could be achieved in the current experimental setup. This was expected to result in a more pronounced transient behavior since the ratio of the mC_p product for the two streams was close to unity. Finally, the feed and coolant inlet temperatures were kept around 74 and 18° C respectively.

Pressure drop measurements were performed in a setup similar to the one depicted in Figure 2.5. The only difference was that all measurements were isothermal and no thermocouples were used. Distilled water was circulated only through the lumen side at a temperature of 21.2°C. A pressure gauge (Matheson, Montgomeryville, PA) with a 0.1 psi (0.69 kPa) subdivision was used to record the pressure head at the tube inlet of the PHFHE. The outlet of the PHFHE was kept at atmospheric pressure and the volumetric flow rate of the tube stream was determined by measuring the time required to collect a certain volume of water.

2.6 Results and Discussion

Table 2.3 gives the range of results obtained for the 143 heat transfer experiments performed with PHFHEs. Note that in Table 2.3 U_o is given, which is routinely used to compare different heat exchangers, while in Section 2.3 U_i was used for calculation purposes. In Table 2.4, representative heat transfer data, covering the whole range of operation tested in this thesis, are presented. These include the mass flow rate, inlet and

Tube	Shell	Module	Number	Re _t	Re _s	Q	\mathbf{U}_{o}
liquid	liquid	#	of runs			(W)	$(W m^{-2}K^{-1})$
Water	EG/Water	1*	48	63-860	150–930	120-501	320-800
Water	Water	3,4**	75	110-2537	758-5794	40-647	647-1314
Ethanol	Water	3**	20	197-1090	1471-5757	20-50	414-642

Table 2.3 Operational Range, Heat Transfer Rate and Overall Heat TransferCoefficient in Polymeric Hollow Fiber Heat Exchangers

* Vertical orientation of the PHFHE.

** Horizontal orientation of the PHFHE

outlet temperatures for each stream, the total rate of heat transfer, the overall heat transfer coefficient, the heat exchanger effectiveness, the number of transfer units (NTU) and the height of a transfer unit (HTU). The standard procedures used to obtain all these quantities from experimental data are briefly described in Appendix C. The physical properties required for the calculations were taken from the NIST Chemistry WebBook (<u>http://webbook.nist.gov/chemistry</u>) for water and the literature for aqueous ethylene glycol mixtures (Flick, 1998; Carrier Air Conditioning Co., 1965) and ethanol (Stephan and Hildwein, 1987; Perry and Green, 1999).

Table 2.3 shows that the heat transfer rate in a solid hollow fiber device can reach high values, up to 650W for a device that is essentially a piece of tubing, 9.5 mm in diameter and 20 cm long. The smaller numbers for ethanol-water runs are due to the fact that module #3, which has the smallest number of fibers, was used in these experiments. The overall heat transfer coefficients shown are the highest reported in the plastic heat exchanger literature for liquid-to-liquid applications and reasonably high compared to

Run	m_t	$\mathbf{T}_{t,in}$	T _{t,out}	\dot{m}_{s}	T _{s,in}	T _{s,out}	Q	Uo	3	NTU	HTU
	(g s ⁻¹)	(°C)	(°C)	(g s ⁻¹)	(°C)	(°C)	(W)	(Wm ⁻² K ⁻¹)			(cm)
Module #1 Water (tube) - Aqueous Ethylene Glycol (shell)											
4	2.3	59.8	24.1	42.2	1.1	3.5	351	682	0.618	0.975	22.5
21	6.4	63.4	44.0	30.7	0.8	5.3	501	720	0.302	0.375	58.3
25	1.0	59.8	11.0	39.0	1.1	2.7	214	575	0.854	1.861	11.8
42	6.0	39.5	36.2	10.1	20.2	22.6	85	375	0.176	0.206	106.2
Module #3 Water (tube) - Water (shell)											
10	1.3	44.9	31.7	59.6	15.3	15.6	69	945	0.446	0.594	34.2
13	2.2	46.0	38.6	25.5	16.4	17.1	69	826	0.250	0.291	69.7
16	4.0	47.2	41.2	59.9	16.5	16.9	100	1108	0.195	0.219	92.9
18	4.0	47.1	41.9	26.0	16.6	17.3	86	954	0.169	0.188	108.3
Module #3 Ethanol (tube) - Water (shell)											
1	0.6	40.2	26.3	15.1	17.9	18.2	19	414	0.623	0.984	20.6
4	0.6	40.3	25.1	39.2	17.3	17.4	21	456	0.660	1.082	18.8
17	2.4	46.2	38.8	40.1	17.9	18.2	47	584	0.261	0.305	66.6
20	2.5	46.5	40.3	14.7	18.3	19.0	41	507	0.222	0.254	80.0
Module #4 Water (tube) - Water (shell)											
8	1.6	44.8	29.1	27.5	23.2	24.1	103	686	0.729	1.340	14.1
17	3.9	45.5	32.9	42.2	23.0	24.1	205	1069	0.560	0.845	24.0
26	0.9	66.3	24.0	69.9	22.9	23.5	150	1029	0.975	3.714	5.5
46	5.1	74.2	44.2	71.0	18.1	20.3	647	1314	0.539	0.789	25.7

Table 2.4Sample Heat Transfer Data Obtained with Polymeric Hollow Fiber HeatExchangers

tubular metal heat exchangers. Design values of 1100-1400 and 300-850 $Wm^{-2}K^{-1}$ are quoted for the latter for water-water and organic solvent-water systems (Perry and Green, 1999). The above values include a total dirt factor of 0.00053 $m^{2}K W^{-1}$, which, if incorporated in the coefficients quoted in Table 2.3, would result in an upper limit of

about 800 and 500 Wm⁻²K⁻¹ for the water-water and ethanol-water runs respectively. However, the incorporation of the same fouling factor for polymer surfaces is questionable; limited experimental data (Githens et al., 1965) show that fouling in plastic tubes is considerably less than in metal tubes. Therefore, the difference in heat transfer performance between a PHFHE and conventional tubular heat exchangers is not as pronounced as one would initially think.

Note also, that all the runs for the water-EG/water system were performed in a vertical configuration with the hot stream traveling downwards. This configuration was primarily aimed at simulation and information gathering about the heat transfer conditions during crystallization in solid hollow fiber crystallizers. However, the results obtained illustrate the heat transfer performance of vertical PHFHEs. The latter, as the results of Table 2.3 suggest, is not significantly different from the performance in horizontal PHFHEs. This was confirmed by calculating the Rayleigh numbers for both the tube (53-545) and the shell side (776-2459); these values clearly show that superimposed natural convection effects are negligible if existent at all. The somewhat lower heat transfer coefficients obtained can be attributed to the fact that the shell side Re numbers fell in the laminar regime, below 1000 for flow parallel to bundles of cylindrical tubes spaced at least 0.2 diameters apart (Johannsen, 1983).

Table 2.4 indicates that high values of the heat exchanger effectiveness and the number of transfer units, up to 0.975 and 3.7 respectively, are attainable by PHFHEs. These values correspond to an extremely small HTU value of only 5.5 cm, which is also in agreement with HTUs obtained in microporous hollow fiber membrane-based separation processes like membrane solvent extraction (Prasad and Sirkar, 1988; 1990).

However, inspection of Table 2.4 also shows that considerably lower ε and NTU values and therefore higher HTUs were also obtained.

Hence, it is apparent that a PHFHE is intrinsically a very efficient heat exchanger and the accomplishment of an increased thermal performance is primarily a rating problem. This is clearly shown in Figures 2.6, 2.7 and 2.8, where the thermal effectiveness, the NTU and HTU respectively are plotted against the tube and shell side Reynolds numbers. It is evident from Figure 2.6 that a high effectiveness is achieved if the tube side Reynolds number is kept low, below about 500. However, the thermal effectiveness is also a function of the relative heat capacity rates of both streams as shown in Appendix C. Therefore, the general requirement for a high thermal effectiveness is the achievement of a high NTU number or a low HTU. Figure 2.7 shows that for about 40% of the runs performed, the number of transfer units achieved was higher than 1. It also shows that for PHFHEs, which operate primarily in the laminar regime, high NTUs are obtained at low tube side Re numbers. This is in agreement with the heat transfer literature (Schlundler, 1983). Another trend apparent in Figure 2.7 is a relatively moderate increase of the NTU with an increase of the shell side Re.

Figure 2.8 shows an even more interesting feature of the thermal performance of PHFHEs, namely, small HTUs. The height of a transfer unit is less than 30 cm (1 ft) for 56% of the runs performed with a minimum of 5.5 cm obtained from Table 2.4. If a PHFHE were constructed like a typical commercial membrane contactor (Liqui-Cel[®] Extra-Flow 10x28, Celgard, Charlotte, NC), these numbers would translate to a minimum of 2 and a maximum of 12 transfer units in a single device.



Figure 2.6 Effectiveness of polymeric hollow fiber heat exchangers as a function of tube and shell side Reynolds numbers.



Figure 2.7 Experimentally obtained NTUs in polymeric hollow fiber heat exchangers as a function of tube and shell side Reynolds numbers.



Figure 2.8 Experimentally obtained HTUs in polymeric hollow fiber heat exchangers as a function of tube and shell side Reynolds numbers.

Shell-and-tube heat exchangers are generally designed for 0.2-3 NTUs (Shah, 1983b) and have a typical length of 3.6 - 6.1 m (12-20 ft) (Perry and Green, 1999). Therefore, the lowest HTU obtained in a shell-and-tube heat exchanger is typically between 1-2 m, approaching only the high end of the results presented in this dissertation. Plate heat exchangers achieve 0.5-4 NTU with a channel length usually less than 2 m (Perry and Green, 1999). Consequently, the HTU for plate heat exchangers is estimated at around 40-50 cm. From the above discussion it follows that HTUs considerably smaller than those in shell-and-tube heat exchangers and comparable to or smaller than those in plate heat exchangers are obtained in PHFHEs. Figure 2.8 also indicates that, since small HTUs are obtained at low tube side flow rates, better thermal performance can be achieved if more frontal area is specified for the same packing fraction or a higher packing fraction is used for the same frontal area. It would then be possible to obtain high ϵ and NTU values with a smaller pressure drop, even for runs for which the C^* ratio is close to unity, i.e., run 42 for module #1 in Table 2.4.

At this point, the experimental results presented will be examined against the theory presented earlier. As mentioned in the experimental section, the flow in the shell side was parallel. Therefore, an independent estimate of the shell side heat transfer coefficient could not be obtained. However, as already explained, it is possible to determine simultaneously both the tube and shell side heat transfer coefficient based on experimental data only by the following iterative procedure:

1. Calculate Nu_w from Equation (2.6) based on the experimentally obtained U_i , which allows one to calculate Nu_{ov} from the first part of Equation (2.4). This is the Nu_w value that would be obtained if an infinitely long exchanger were used.

- 2. Based on the Nu_w obtained at the first step, solve Equation (2.7) as explained in the theory section and obtain $Nu_{m,T3}$ from Equation (2.15).
- 3. Obtain a new estimate of Nu_w from Equation (2.4) and repeat steps 2 and 3 until satisfactory convergence between successive Nu_w numbers is achieved.

In all calculations properties were evaluated at the average temperature between the inlet and the outlet. Figure 2.9 shows the prediction error for the tube outlet temperature obtained when the above iterative procedure was applied. The results presented here were calculated with only two iterations. The agreement between theory and experiment is excellent. The prediction error for 143 experimental runs ranged between -0.62 and 1.08 K. The mean error in the prediction of the tube outlet temperature was 0.17 K with a standard deviation of 0.29 K. Moreover, 85% of the data were predicted within ± 0.5 K as the dashed lines in Figure 2.9 indicate. Therefore, heat transfer in PHFHEs can be treated as a conventional convection problem with a convective boundary condition at the inside wall surface as Equations (2.7)-(2.10) describe, provided the shell side temperature does not vary substantially. This is in agreement with the results of Mori et al. (1974) for the conjugated problem in tubes, whose thickness is considerably smaller than their length, a condition valid for all PHFHEs used in this dissertation.

A similar, albeit simpler and easier to perform iterative procedure was also implemented based on the simplified formulae presented in Subsection 2.3.3. In this case the following steps were adopted:

- 1. Obtain a first estimate of Nu_w from Equation (2.6).
- 2. Based on the Nu_w obtained at the first step, obtain $Nu_{m,T3}$ from Equation (2.28).



Figure 2.9 Prediction error of Equation (2.7) for the tube exit temperature of a polymeric hollow fiber heat exchanger.

- 3. Obtain a new estimate of Nu_w from Equation (2.4) and repeat steps 2 and 3 until satisfactory convergence between successive Nu_w numbers is achieved.
- 4. The exit temperature is obtained from Equations (2.25) and (2.26) based on the Nu_w and Nu_{m,T3} values obtained during the last iteration.

In Figure 2.10 the results obtained with the above procedure are shown. The similarity with Figure 2.9 is apparent. The prediction error for the tube side outlet temperature is for all practical purposes exactly the same. In addition, the simple formulae of Subsection 2.3.3 give the designer the ability to perform easily hand calculations without a loss in accuracy and most important of all without the need to resort to any kind of sophisticated software.

The iterative procedure based on the solution of the energy Equation (2.7) also provided information on both the tube and shell side heat transfer coefficients, which were calculated based on the Nu_{m,T3} and Nu_w obtained. The shell side coefficient was estimated by Equations (2.2) and (2.3). The wall thermal conductivity needed for the calculations was taken equal to 0.17 Wm⁻¹K⁻¹ according to literature values (Mark, 1999). Table 2.5 provides the range of tube and shell side coefficients obtained for all systems tested. It is evident that the tube side coefficients achieved are very high for both water and ethanol. For water, they are about half of what can be achieved typically in a plate heat exchanger. The calculations performed show that similar coefficients can be achieved in ³/₄ inch tubes, the most commonly tubes used in shell-and-tube heat exchangers, at a velocity of about 2 m s⁻¹ or a Re of about 70,000. For ethanol, velocities in excess of 3 m s⁻¹ would be required in a ³/₄ inch tube to match the results presented here. It should also be noticed that higher tube coefficients were obtained for module #3, something that can be attributed to thermal entrance effects. The latter were more



Figure 2.10 Prediction error of simplified design formulae for the tube exit temperature of a polymeric hollow fiber heat exchanger.

Table 2.5Tube and Shell Side Heat Transfer Coefficients Obtained in PolymericHollow Fiber Heat Exchangers - Parallel Flow at the Shell Side

Module #	System	$\mathbf{h_t}^{\star}$	h _s *	
		$(Wm^{-2}K^{-1})$	$(Wm^{-2}K^{-1})$	
1	Water-EG/Water	6324-7052	409-1972	
3	Water-Water	6422-7818	1324-4189	
3	Ethanol-Water	1806-2223	886-2863	
4	Water-Water	6282-7070	1244-13335	

 ${}^{*}h_{t}$ is based on the inside fiber area, while h_{s} on the outside fiber area.

pronounced due to the smaller number of fibers used for about the same throughput.

Figure 2.11 shows a plot of the Colburn factor and friction factor for the tube side. The Colburn factor was calculated based on the calculated Nu_{m,T3}, while the friction factor was obtained from pressure drop measurements after appropriate corrections for inlet and exit losses and the hydrodynamic entrance effect. Details are given in Appendix C. The j_H factor obtained was higher than the one calculated from the Sieder-Tate correlation for the L/D ratio of the devices used for this thesis. This can be attributed to two reasons. First, the Sieder-Tate correlation is applicable only for RePr(D/L)>10. Below this limit, which was exceeded only during the ethanol-water runs, it considerably underpredicts the heat transfer coefficient (Bird et al., 1960). Therefore, even if a high Nu_w could be achieved (approaching the condition of constant wall temperature), the Sieder-Tate correlation would be a poor predictor of the tube side performance of a PHFHE for the whole laminar regime and especially for Re<1000. The second reason is the type of boundary condition applicable, namely, a convective boundary condition at the inside wall surface. Equation (2.1) shows that the Nusselt number approaches the value 4.36 for Nu_w $\rightarrow 0$ (constant heat flux $\rightarrow 0$) and the value 3.66 as Nu_w $\rightarrow \infty$ (constant wall temperature, $T_{w,i} \rightarrow T_{w,o}$). The highest Nu_w value achieved in the present setup was 3.62 revealing that the tube side Nusselt number would be closer to 4.36, much higher than the value for the constant wall temperature boundary condition.

Another interesting feature of the j_H vs. Re plot is its slope. As shown in Figure 2.11, the latter is equal to -0.926, a value between the theoretical prediction of -1 obtained for fully developed laminar flow (constant Nu) and -0.67 for thermally developing flow (Leveque type dependence of Nu). This fact simply suggests that in most



Figure 2.11 j_H and friction factors obtained in the tube side of polymeric hollow fiber heat exchangers.

cases the length of the PHFHEs used in this thesis is sufficiently larger than the thermal entry length but not large enough for the attainment of fully developed flow conditions.

This hypothesis was proved by correlating individually each data set for all systems presented in Table 2.5. The slope of the j_H vs. Re curve ranged from -0.85 for the ethanol-water runs with module #3 to - 0.93 for the water-water runs with module #4. Each data set had a correlation coefficient of 0.997 or better, indicative of the consistency of the results. Note also that the points looking as outliers in Figure 2.11 correspond to the ethanol-water runs, for which, the thermal entry length calculated for the prevailing hydrodynamic conditions, was comparable or even higher than the module length. As a result, a slope approaching the slope of the Sieder-Tate curve was obtained. From the above discussion it can be concluded that for longer modules a slope closer to the theoretical value of -1 will be obtained and that for viscous fluids a departure from fully developed flow conditions should be anticipated and incorporated in the design procedure of a PHFHE.

The friction factor curve shown in Figure 2.11 shows also a departure from conventional theory. The slope of the curve is -0.88 compared to the theoretical prediction of -1 for Hagen-Poiseuille flow, revealing that higher friction factors were obtained in the PP fibers used. The friction coefficients obtained were higher than theoretical predictions by 1-41% and increased as Re becomes larger. This contradicts previous studies with membrane hollow fibers (Goerke et al., 2002), where agreement with theory was claimed. However, no friction factor data were given and the analysis was based on the assumption that the Chilton-Colburn analogy holds for laminar flow, an assumption which is not valid. The friction factor plot shown in Figure 2.11 is in

accordance though with the results of Mala and Li (1999) for water flow inside stainless steel and fused silica microtubes.

The observation of considerably higher friction factors than theory for flow in microchannels has been a subject of debate lately and several explanations have been proposed as summarized by Guo and Li (2003a; 2003b). The most plausible for liquid systems seems to be surface roughness, which has often been neglected for laminar flow in conventional tubes. However, roughness elements of a few µm in a microchannel will correspond to high relative roughness values, which would lead to larger frictional losses and more flow disturbances, a cause for an early transition from laminar to turbulent flow. This is supported by the results of Mala and Li (1999), who reported a transitional regime between 500<Re<1500 and correlated well their results with a surface roughness-viscosity model. Additional material, supportive of the surface roughness hypothesis is given by Guo and Li (2003a; 2003b), who also quote the flow cross section variation as another factor causing higher frictional losses.

Similar behavior was also observed for macrosized (2 mm) Teflon tubes, for which, the transition from laminar to turbulent flow took place at Re around 1000 (Githens et al., 1965). The interesting feature of this study is that the friction factors in the turbulent regime were correlated well by a friction factor curve corresponding to tubes with a roughness of 0.006 diameters. This fact makes the surface roughness explanation even more credible. Therefore, surface roughness in combination with flow cross section variation, a known issue for membrane hollow fibers, are the factors explaining the experimental friction factors presented here. Finally, the similarity of the slopes for the $j_{\rm H}$ and f factor, although tempting to state that a relation similar to the

Colburn analogy holds, is misleading and incidental, since, as explained in the preceding paragraph, the j_H factor dependence on Re will change if a different length is used for the PHFHE.

Figure 2.12 shows the transient response of a PHFHE for step changes in the shell side flow rate. In Figure 2.12a, the response for a change from a high to a low flow rate is plotted, while the response for the exact opposite change is shown in Figure 2.12b. In both figures, the initial plateau corresponds to temperature measurements taken within 1 min. before the step change in shell side flow rate is implemented. Figure 2.12b is representative of what happens in a SHFCC run, for which, the feed is first introduced and then the coolant flow is switched on. It is evident that the feed outlet temperature reaches its steady state value in less than 2 min. The same is true for step changes in the lumen side flow rate, which are not presented here. On the contrary, Figure 2.12a shows that when a sudden and large decrease of the coolant flow rate occurs, the response of the SHFHE is slower; it takes about 10 min. to reach the new steady state. This indicates that a decrease in shell side flow rate is more difficult to control in accordance with the literature (Kays and London, 1984). Nonetheless, the limited transient data presented here clearly illustrate that the large surface area of PHFHEs, can quickly dampen any changes in upstream conditions and makes them ideal for temperature control.

Finally, a more comprehensive comparison of PHFHEs with metal shell-and-tube and plate heat exchangers will be attempted, based on the performance criteria presented in section 2.4. Table 2.6 summarizes the results obtained for the overall conductance per unit volume. Data for polymer heat exchangers taken from the literature and manufacturers are also included. Two cases are presented, namely, CUV values based on



Figure 2.12 Transient response of a PHFHE to a step change in coolant flow rate. Tube side flow rate = 4.54 cm^3 /s. Operating conditions: a) Step change in shell side flow rate from 69.2 to 10.1 cm³/s; b) Step change in shell side flow rate from 10.0 to 75.8 cm³/s.

Heat Exchanger	U _C	CUV _c	UD	CUV _D			
	$(Wm^{-2}K^{-1})$	$(Wm^{-3}K^{-1})$	$(Wm^{-2}K^{-1})$	$(Wm^{-3}K^{-1})$			
Water-Water							
PHFHE	647-1314	$9 10^5 - 1.8 10^6$	482-776	$6.7 10^5 - 1.1 10^6$			
Shell-and-tube ¹	2839-5678	$3 \ 10^5 - 6 \ 10^5$	1136-1420	$1.2 10^5 - 1.5 10^5$			
Plate ²	5700-7400	$2.4 \ 10^6 - 3.1 \ 10^6$					
Ametek fluoropolymer			567	3 10 ⁵			
heat exchangers ³							
George Fisher (PVDF,			341-454	$6\ 10^4$ -8 10^4			
$PP, PE)^4$							
HTN Shell-and-tube⁵	1100	6 10 ⁵	696	3.8 10 ⁵			
PEEK Plate heat	900	$1.03 \ 10^{6}$					
exchanger ⁶							
Water-Organic Solvent							
PHFHE	414-642	$5.8 \ 10^5 - 8.9 \ 10^5$	340-479	$4.7 10^5 - 6.7 10^5$			
Shell-and-tube ¹	334-1549	$3.5 \ 10^4 - 1.6 \ 10^5$	284-852	$3 \ 10^4 - 9 \ 10^4$			

Table 2.6Comparison of PHFHEs with Metal and Plastic Heat Exchangers: OverallConductance per Unit Volume

¹ ³/₄ tubes in a 1 in triangular pitch and a 30° layout. U data from Perry and Green (1999), $\alpha = 105 \text{ m}^2/\text{m}^3$ based on Equations (2.32)-(2.33) and shell diameters obtained from Schlundler (1983).

² Plates 0.4 mm thick, spaced 2 mm apart. U data from Perry and Green (1999).

³ Shell-and-tube heat exchangers with $\alpha = 123-541 \text{ m}^2/\text{m}^3$ and $U = 341-567 \text{ Wm}^2\text{K}^{-1}$. Data obtained from manufacturer brochures.

⁴ Tube plate heat exchangers with $\alpha = 341-454 \text{ m}^2/\text{m}^3$ and $U = 227-273 \text{ Wm}^2\text{K}^{-1}$. Data obtained from manufacturer brochures.

⁵ From Liu et al., (2000). U values are theoretical estimates based on the tube wall resistance.

⁶ From Jachuck and Ramsaw (1994). U values were estimated based on experimental heat transfer coefficients for one side and the assumption that both exchanger sides have approximately the same heat transfer coefficient.

clean and dirty respectively overall heat transfer coefficients. The design coefficients and dirt factors were obtained from the literature (Perry and Green, 1999) and clean coefficients were calculated based on these values. A common design of a shell-and-tube heat exchanger was chosen for comparison, while the data shown for plate heat exchangers represent an upper limit, in the sense that the smallest plate thickness and spacing were used to estimate α based on Equation (2.34). As already mentioned, the use of the same dirt factor for PHFHEs and shell-and-tube heat exchangers is questionable, since limited experimental data (Githens et al., 1965) show that fouling in plastic tubes is considerably less than in metal tubes.

Table 2.6 clearly shows that PHFHEs are superior to any commercial, under development or laboratory scale plastic heat exchanger as a result of higher heat transfer coefficients and higher surface area to volume ratio; the CUV achieved by PHFHEs is 2-20 times higher. Despite the fact that the above conclusions are based on results for water-water systems, they are expected to be also valid for water-organic solvent systems. Note also that the results presented for the HTN exchanger are estimates only and are not supported by any experimental results. In comparison to shell-and-tube heat exchangers, PHFHEs also show superior performance for both water-water and water-organic solvent systems, whether clean or dirty overall coefficients are used to calculate the overall conductance per unit volume. The latter was up to three times higher for clean coefficients and 5-8 times higher if dirty coefficients were used. These numbers show that the CUV of shell-and-tube heat exchangers will at best match the current results in the case $\frac{1}{4}$ inch tubes were used ($\alpha \sim 300 \text{ m}^2/\text{m}^3$) and that the influence of fouling in the performance of PHFHEs is of smaller magnitude. If fouling factors are introduced, then

PHFHEs are clearly a better choice, especially if one considers the fact that the packing fraction of the modules used here was only 5-20%. This is the main reason why the CUV of plate heat exchangers is 30-60 % higher than the results obtained with PHFHEs. However, as already mentioned, the values of Table 2.6 for plate heat exchangers represent an upper limit of current technology and packing fractions of 50% are common in membrane contactors (Ho and Sirkar, 1992). Therefore, more area can be packed in PHFHEs and this would simply be translated into a performance exceeding by at least 30-40% the thermal capabilities of plate heat exchangers.

Figure 2.13 shows a plot of the volume goodness factor for the tube side of PHFHEs and shell-and-tube heat exchangers for the water-water and the ethanol-water system. The plot was constructed based on Equations (2.30)-(2.31). Friction factors for the PHFHE were obtained based on the Equation shown in Figure 2.11. The data for shell-and-tube heat exchangers were calculated for $\frac{3}{4}$ inch tubes and fluid velocities between 1-5 m s⁻¹. Heat transfer coefficients and friction factors were calculated respectively by the Dittus-Boelter and the Blasius correlation (Perry and Green, 1999). The superiority of the PHFHE is evident in both Figures 2.13a and 2.13b: for the same frictional loss per unit volume, the overall conductance per unit volume for the PHFHE is higher than those of shell-and-tube heat exchangers by 5-20 times for the water-water and 12-20 times for the ethanol-water system.

Another interesting characteristic of the PHFHE curves in Figure 2.13 is that they are relatively flat; approximately the same h α is obtained regardless of the frictional loss. As a result, PHFHEs should be operated with low tube side velocities in order to achieve a combination of high thermal performance and low pressure drop. As already shown in



Figure 2.13 Comparison of PHFHEs with shell-and-tube heat exchangers based on the volume goodness factor. a) Water-water system and b) ethanol-water system.

Figures 2.6-2.8, the outcome of such an operation practice would be high effectiveness and NTU and extremely small HTU values. The same feature would also be a

Figure 2.14 shows the pressure drop needed to obtain one transfer unit as a function of tube side Re number. Note that, since the NTU achieved is also a function of the shell side fluid temperature and hydrodynamic conditions, a certain degree of scatter, increasing with tube side Re, will characterize the results. As shown in Figure 2.14, the pressure drop per NTU for PHFHEs is much smaller than 30 kPa, a commonly acceptable optimum value for plate heat exchangers (Raju and Bansal, 1983), if Ret is smaller than about 500. From a total of 79 runs at Re_t < 500, 72 have ΔP_t /NTU ratios smaller than 30 kPa/NTU. In fact, ΔP_t /NTU can routinely be as low as 1 kPa per NTU, an extremely small value. Therefore, similar or better thermal performance is achieved by PHFHEs compared to plate heat exchangers at a significantly lower pumping power cost. In fact, PHFHEs are useful if operated at low ΔP , preferably below 10 kPa; this is substantially below the commonly acceptable allowable ΔP limit of 66 kPa (~ 10 psi) for metal heat exchangers. Consequently, PHFHEs may be operated for substantial lengths of time without the type of performance deterioration observed in shell-and-tube heat exchangers.

tremendous advantage of PHFHEs over plate heat exchangers.



Figure 2.14 Pressure drop required to obtain one transfer unit in polymeric hollow fiber heat exchangers.

2.7 Conclusions

A theoretical framework for the description and design of PHFHEs, which is based on a convective boundary condition at the inside wall of the hollow fibers was provided. It includes equations for both short (thermally developing flow) and long (fully developed flow) devices. In addition, accurate, simple and easy to use design formulae were presented for the first time. The theory, quite different from conventional heat exchanger theory, was tested against extensive experimental data and was established as a good predictor of PHFHEs performance. It can therefore be directly used for design purposes, i.e., in the case of SHFCC, which is the subject of Chapter 3. Moreover, the experimental pressure drop measurements presented in this Chapter provide tube side friction factors that can be used for the whole laminar regime.

The experimental results presented, clearly illustrate that the overall heat transfer coefficients routinely realized in PHFHEs, are larger than any values ever reported for liquid-liquid applications in plastic heat exchangers of commercial or laboratory scale. They are also comparable to the ones obtained in metal shell-and-tube heat exchangers and only inferior to the values obtained in plate heat exchangers.

The large surface area/volume ratio of PHFHEs makes them extremely efficient heat exchangers. The transient experiments performed, indicated a fast response of PHFHEs to flow rate step changes introduced at either side of the exchanger. This behavior reveals that any changes in upstream conditions can quickly be dampened and PHFHEs are ideal for temperature control. In addition, efficiencies up to 97.5% were obtained and more than one transfer unit was routinely achieved for Re_t<500 in devices less than 30 cm long. The height of a transfer unit was as low as 5 cm, 20 times less than the lower limit for shell-and-tube heat exchangers and about 10 times less than typical values for plate heat exchangers. The above results suggest that PHFHEs, if properly rated and if designed like commercially available membrane contactors, can easily achieve 2-12 NTU in a single device.

The moderately packed hollow fiber modules used in this dissertation clearly show, based on overall conductance per unit volume, superior thermal performance compared to any commercial, under development or laboratory scale plastic heat exchanger. It was also demonstrated that PHFHEs can transfer up to one order of magnitude more heat per unit time per unit volume than metal shell-and-tube heat exchangers and comparable quantities to plate heat exchangers. These numbers can increase 2-3 times if PHFHEs were designed for the same packing fraction as commercial membrane contactors. Further, this performance level can be obtained with an extremely small pumping power expenditure. At the same pumping power expenditure, PHFHEs can transfer 5-20 times more heat per unit time per unit volume than typical shell-and-tube heat exchangers. Moreover, very low pressure drops, as low as 1 kPa, are required to obtain one transfer unit compared to a requirement of 30 kPa for metal heat exchangers.

Significant performance improvements are anticipated if cross flow were used in the shell side of PHFHEs. Also, if hollow fibers made of materials like PTFE, PEEK or HTN having thermal conductivity higher than PP were used, then the overall coefficients obtained would be up to 40% higher for water-water and 25-30% higher for organics-water systems. This improvement would be simultaneously accompanied by better chemical resistance, considerably larger mechanical strength and an extended operational temperature range. Fiber reinforced polymers, yet another choice, could also offer even higher thermal performance and better mechanical strength at the expense of higher cost.

Apart from the superior thermal performance of PHFHEs, which can readily be ameliorated, their low weight and the lower cost of polymeric materials, would make them an attractive choice over metal heat exchangers as far as construction, transportation and installation costs are concerned. To put things into perspective, it can be easily shown that the weight of 0.6 m long PP fibers similar to the ones used in this study needed to obtain an outside surface area of 1000 m², is only 61 kg! If ¾ inch steel tubes, 20 BWG gauge and 4.88 m (16 ft) long were used, the same area would be obtained at a weight of 6684 kg, a 100-fold difference. In addition, by proper rating, PHFHEs are characterized by a considerably lower pumping cost, which will also reflect in lower operational cost. In conclusion, the results shown here strongly manifest that PHFHEs are very efficient heat exchangers and should be seriously considered as substitutes for metal shell-and-tube or plate heat exchangers at lower temperatures (up to 150-200°C) and low pressures, both on grounds of heat transfer performance and economic considerations.

CHAPTER 3

SOLID HOLLOW FIBER COOLING CRYSTALLIZATION

It was shown in Chapter 2 that PHFHEs are more efficient heat transfer devices than existing conventional heat exchangers, metal or plastic. The same devices can be used also for heat transfer with phase change, namely, crystallization. The objective of this Chapter is to clearly illustrate that the characteristics of solid hollow fiber devices make them ideal for crystal size distribution control of both aqueous or organic solutions. Results for different operation modes and a broad range of supersaturations will be presented and compared to existing literature data for MSMPR crystallizers. A total of three systems, both readily and sparingly soluble, were tested including an inorganic, an organic and a pharmaceutical molecule.

3.1 Operating Principle

An illustration of the proposed technique is provided in Figure 3.1. The solution to be crystallized is fed through the lumen side of a Solid Hollow Fiber Crystallizer (SHFC), which essentially is a heat exchanger identical to the polymeric hollow fiber heat exchangers described in Chapter 2. A suitable cooling solution is circulated in countercurrent, cocurrent or crossflow mode through the shell side of the device. In such an arrangement, the feed solution, subdivided into numerous fluid packets, travels through each hollow fiber with the same velocity and under the same cooling conditions. If cooling proceeds below the feed saturation temperature, crystallization will take place in each fiber under the same conditions leading to a narrow CSD.



Figure 3.1 Solid Hollow Fiber Cooling Crystallization: Operating principle.

Solid Hollow Fiber Crystallizers differ from conventional cooling crystallization equipment at several levels. First, the flow inside the hollow fibers will be in most practical cases laminar. According to residence time distribution theory this means that the mixing conditions inside the hollow fibers are between plug flow and complete mixing (Smith, 1981), which is usually assumed in stirred crystallizers. In principle, the transitional and tubular regimes are also an option and would lead closer to a true plug flow situation. On the other hand, the friction factor measurements presented in Figure 2.11 combined with the small fiber diameter lead to a very high pressure drop and consequently a high pumping cost and a limited operational regime for SHFCs.

Second, flow and residence time can be accurately controlled in SHFCs. Their scale up is not anticipated to be a problem in contrast to stirred crystallizers, for which, poorer mixing accompanied by better slurry suspension is a known scale up issue (Mersmann, 2001). The theory presented for laminar flow in polymeric hollow fibers in Chapter 2, shows that the temperature profiles obtained along the fiber depend primarily on three factors: the flow rate through each fiber, the polymeric wall material and the temperature and hydrodynamic conditions of the shell side fluid. Of the above factors, the first two will be exactly the same upon scale up and the same will also be true for the shell side fluid temperature. Hence, the main source of uncertainty remaining is the hydrodynamic conditions on the shell side. The latter are a known source of variability for membrane contactors, especially if parallel flow is used at the shell side (Ho and Sirkar, 1992). However, as already mentioned in Chapter 2, cross flow configurations can improve the situation and have already been applied in commercial membrane contactors.

Third, the polymeric nature of the hollow fibers makes them ideal to control the temperature of the inside wall, which is the cooling surface exposed to the crystallizing solution. By varying the thermal conductivity of the wall by choosing different construction materials and/or varying the wall thickness, one obtains different external resistance values. The heat transfer theory presented in Chapter 2 predicts that the result of these actions will be a different inside wall temperature. It will be shown in this Chapter that the difference between the inside wall and the crystallizing solution temperatures can be kept as low as 1-2°C in SHFC devices. As a result, supersaturation creation at each fiber cross section is relatively uniform.

Such a control capability is very important and absent in the case of conventional cooling crystallizers, for which, due to the negligible heat transfer resistance of the metal wall, the inside wall temperature is equal to the coolant temperature. In addition, the temperature difference between the coolant and the crystallizing solution has to be maintained high during scale up of jacketed crystallizers in order to compensate for the surface area/volume loss accompanying the larger vessel diameter. This leads to severe incrustation problems (Price, 1997). The same temperature difference is also relatively high, about 5-10°C, in shell and tube heat exchangers used in forced circulation crystallizers and can lead to uncontrolled nucleation (Myerson, 2002). From the above discussion it is apparent that solid hollow fiber devices offer the ability to decouple to a certain degree the choice of the coolant temperature from the crystallization kinetics, as expressed by the metastable zone width. The same will also be possible in the case of evaporation crystallization, where excessive nucleation and/or product disintegration near

the cooling/heating surfaces are known problems that can lead to CSD broadening or poorer product quality (Paul, 1997).

Further, since the polymeric fibers are nonporous and have a relatively smooth surface, the possibility of fiber rupture by crystals is minimized. Due to the low energy surface of polymers, fouling is less than in metal tubes. This is supported on a short-term basis by the data shown in Figure 3.2. The stability plastic tubes offer, as well as the steep reduction in thermal performance for metal tubes, are apparent. Moreover, in most cases, the scale formed on the fiber wall will probably have a higher or comparable thermal conductivity with the wall material, limiting the significance of fouling. In contrast, the large difference between the tube wall and the foulant thermal conductivity in metal tubes, is simply reflected in the large difference between clean and dirty overall design heat transfer coefficients (Perry and Green, 1999). The inertness of polymeric materials towards aqueous and many organic solvents, apart from making SHFCs suitable for both kinds of feed, allows also aggressive cleaning to be performed. The latter has been practiced repeatedly during this study without any significant loss in heat transfer performance. Two modules have been used for over 40 crystallization runs of 20-30 min. duration. The same modules were also used for heat transfer studies with tap or deionized water for over 50 hours.

The most distinctive characteristic of SHFCs, however, is the small diameter of the hollow fibers, typically in the sub-millimeter range. The small diameter corresponds to an also small wall thickness and, as already shown in Chapter 2, is responsible for the good heat transfer performance of hollow fiber devices. It also leads to high values of surface area/volume ratio, up to $4000 \text{ m}^2/\text{m}^3$. According to Figure 2.2 these values are at



Figure 3.2 Comparison of fouling in plastic and metal tubes (reproduced based on data from Githens et al., 1965).

least one order of magnitude higher than shell-and-tube heat exchangers typically used in forced circulation cooling or evaporating crystallizers. For conventional cooling coils, ypically used in batch or continuous stirred tanks, the same ratio is $314 \text{ m}^2/\text{m}^3$ for a coil of $\frac{1}{2}$ inch diameter and if only the pipe volume is considered. However, in a real arrangement, the total volume occupied by the coil depends also on its width; hence, the above value should be divided by a factor of at least 3-5. For jacketed vessels the comparison is even more favorable, since for a vessel of 60 cm diameter the surface to volume ratio is only 7 m²/m³. The thermal performance of SHFCs can be improved if fibers were packed in a helical manner. This will lead to the formation of Dean vortices which can improve the overall device performance in two ways: increasing the heat transfer performance and reducing fouling by sweeping newly formed crystals near the wall. A similar increase in mass transfer performance was reported for removal of volatile organic components from water by pervaporation (Schnabel et al., 1998).

The large surface/volume ratio that hollow fiber devices offer can have an impact on the overall device performance at several levels. First, it can improve heat transfer and can be used for a precise and close control of the temperature profile of the crystallizing solution. The results presented in Chapter 2 for single-phase heat transfer show that the hollow fiber devices used in this study can transfer 3-10 times more heat on a volumetric basis than conventional shell-and-tube heat exchangers for both aqueous or organic streams. These numbers will be similar for cooling coils and an order of magnitude higher for jacketed vessels. Second, process performance dependence on fouling of the heat transfer area is appreciably reduced since there is a large amount of area available to compensate for any local losses. Finally, the very large surface area available can lead to higher nucleation rates compared to conventional crystallizers of the same volume and operated under the same supersaturation conditions.

As far as crystallization kinetics are concerned, solid hollow fiber crystallizers offer yet another, more fundamental advantage over conventional cooling crystallizers stemming from the small diameter of the hollow fibers used. It is the possibility to control the nucleation rate by varying the diameter of the fiber. This can be explained as follows. Schubert and Mersmann (1996) carried out precipitation experiments with Ba(OH)₂ and H₂SO₄ in the presence of nanoparticles of SiO₂, Al₂O₃ and TiO₂. They found that the rate of heterogeneous nucleation was proportional to the volumetric surface α_{for} of foreign particles present in the solution in the range 5 x $10^3 - 2.5 \times 10^5 \text{ m}^2/\text{m}^3$. On the other hand, the inside surface of the hollow fiber can be considered as foreign surface available for heterogeneous nucleation. The volumetric surface area for a hollow fiber or in general a tube based on the inside area (the area available for nucleation) can be calculated by

$$a_{for,l} = \frac{\pi D_{i}L}{\pi \frac{D_{i}^{2}}{4}L} = \frac{4}{D_{i}}$$
(3.1)

Figure 3.3 is a plot of Equation (3.1). It indicates that values inside the range quoted by Schubert and Mersmann (1996) can be obtained if hollow fibers with diameter between 100-800 μ m were used. As a result, it can be expected that higher nucleation rates will be achieved by using fibers of decreasing diameter. Figure 3.3 also explains why such an issue does not arise in conventional cooling crystallizers; the volumetric surface of conventional tubes is very low and heterogeneous nucleation can occur only due to suspended solids inside the crystallizing solution. The role of suspended particles will also be important for hollow fiber devices. However, unless a certain concentration


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Figure 3.3 Volumetric surface area of tubes and hollow fibers as a function of their inside diameter.

of foreign solids in the crystallizing solution is exceeded, the volumetric surface of the fiber will be equally contributing or the controlling factor of heterogeneous nucleation

3.2 Experimental

3.2.1 Chemicals and Materials

Aqueous potassium nitrate solutions were prepared by dissolving potassium nitrate (>99%, Sigma Aldrich, St Louis, MO) in deionized water. Denatured alcohol (Fisher Scientific, Pittsburgh, PA) was used in KNO₃ crystal sizing by laser diffraction measurements. Solutions of salicylic acid (Fisher Scientific., Pittsburgh, PA) were prepared by dissolving salicylic acid in 99.9% ethanol (Sigma Aldrich, St Louis, MO). N-Hexane (95% pure, Acros Organics., NJ) was used as the suspension medium for salicylic acid crystal sizing by laser diffraction measurements. Paracetamol (4-acetamidophenol, 98%, Fisher Scientific) solutions were prepared by dissolving the compound in deionized water. Modules 1 and 4 were the SHFCs used throughout this study. Their geometrical characteristics have already been presented in Table 2.2.

3.2.2 Apparatus and Procedure

A schematic and a photograph of the experimental setup used are shown in Figures 3.4 and 3.5 respectively. Figure 3.4 illustrates the various operating schemes implemented for Solid Hollow Fiber Cooling Crystallization. The feed solution held to a constant temperature by means of a thermostatic bath (Haake A81), is circulated through the lumen side of the SHFC by a diaphragm or peristaltic pump (Cole Parmer, Vernon Hills, IL). An aqueous cooling solution of 33% by volume ethylene glycol is circulated through



Figure 3.4 Solid Hollow Fiber Cooling Crystallization experimental setup.



Figure 3.5 Solid Hollow Fiber Cooling Crystallization – Photograph of the experimental setup.

the shell side by a Polystat[®] chiller (Cole Parmer, Vernon Hills, IL). The inlet and exit temperatures of the two streams were recorded with a four-channel temperature recorder (Sper Scientific, Scottsdale, AZ) with an accuracy of $\pm 0.2^{\circ}$ C and at time intervals varying between 5-20 seconds. Flow rates were measured by flowmeters (Cole Parmer) and confirmed by measuring the time required to collect a certain volume of liquid.

There are several choices at the exit of the SHFC, which dictate the operating mode used. The simplest one is to immediately direct the crystallizing solution to the filters obtaining the <u>once through mode of operation</u>. Operating in this manner, the solid hollow fiber module acts as a crystallizer. Another choice is to recycle the feed for a certain amount of time and then direct it to the filters. This is the <u>feed recycling mode of operation</u> and it can be useful in the case of slow nucleation kinetics for seeding purposes or if lower levels of supersaturation are desired. Here, the solid hollow fiber module acts first as a nuclei generator and when the nuclei are formed as a crystallizer. A third choice is to direct the supersaturated solution to a completely stirred tank (CST) and then to the filters. This is the <u>SHFC-CST in series mode of operation</u>, where the solid hollow fiber module acts primarily as a supersaturation generator. However, crystal nucleation and growth inside the device cannot be ruled out and the device acts simultaneously as a crystallizer. The completely stirred tank can be operated in semi-batch or continuous mode. An in-line static mixer (Cole Parmer) was also used instead of the CST.

Crystals obtained on the filters were thoroughly dried and then weighed. The volume of filtrate collected was also measured to obtain the magma density of the suspension exiting the experimental setup. Two kinds of filters were used throughout this

study: glass fiber filters (Whatman 934-AH) with a cutoff size of 1.5 μ m and hydrophilized PVDF membranes (Pall Corp., NY) with a cutoff size of 0.2 μ m.

The way the experimental runs were carried out for KNO₃ crystallization is briefly described below, since all operating modes were tested for KNO₃. Salicylic acid and paracetamol runs were performed respectively with the SHFC-CST and the SHFCstatic mixer in series mode of operation only. For once through mode runs, the feed was passed through the lumen side of the SHFC and after 1-2 min. the coolant flow was switched on. The coolant flow rate was set in such a way as to obtain a value suitable to bring down the feed exit temperature to about 2.5-4°C below the saturation temperature, close to the metastable zone width reported for aqueous KNO₃ solutions at room temperature (Nyvlt et al., 1970; Nyvlt, 1993; Mersmann and Bartosch, 1998). The feed was collected in a separate beaker for 10-15 min. and then the flow was switched for 1-2 min. to the filters to separate the generated crystals. Feed recycling mode runs were performed in the same way, the only differences being the lower undercooling used (0.6–1.3°C) and the fact that initially the exiting feed stream was recycled for 15-20 min.

The SHFC-CST in series runs were also of once through nature. The difference was that samples were collected and simultaneously stirred for 1-2 min. in separate vessels and then the suspension was filtered. Note, that operated in this way, the CST is in semi-batch mode. In the case the CST was operated continuously, a peristaltic pump (Cole Parmer) was used for slurry removal towards the filters. The undercooling used in SHFC-CST in series experiments was dictated solely by the SHFC and varied between the values used for the other two operating modes, namely, between 1.5-3.5°C. The same

undercooling was maintained inside the CST. Samples were taken at least 10 min. after the coolant flow was switched on.

The selection of a time interval of at least 10 min for sampling to begin was based initially on the fact that the feed exit temperature attained a steady value quickly. Later, single-phase transient heat transfer experiments performed and already presented in Figure 2.12, showed that, for the conditions present during the crystallization runs, namely, coolant flow rates at least 10 times higher than feed flow rates, a steady state value after a step change in coolant flow rate can be achieved in only 2-3 min. Therefore, if the feed flow rate is kept stable, steady state conditions will be attained or be closely approximated before sampling commences.

3.2.3 Analytical Methods

Feed concentration determination for KNO₃ solutions was performed using three methods. For fresh feed batches, it was done gravimetrically. In all other cases, it was performed with UV analysis (Hitachi U-2000 spectrophotometer) and/or density measurements. The nitrate ion absorbs weakly ($\epsilon = 7.73$ L mole⁻¹cm⁻¹, standard error 0.8%) at 300.6 nm. The density measurements were performed with an Anton-Paar DMA-46 (Anton Paar, Graz, Austria) density meter at 25°C. The calibration curve used was found to agree within ±0.1% with available literature data (Isono, 1984; Daniel and Albright, 1993). Salicylic acid concentration was determined either gravimetrically or by density measurements at 25°C. Paracetamol concentration was determined based on a UV method or gravimetrically. Sample calibration curves are given in Appendix D.

Crystal sizing was performed with a Coulter LS-230 laser diffraction instrument. In all measurements an optical model based on the complete Mie theory was used. The refractive index of the suspension medium was measured between 20-28°C with an Abbe-3L refractometer having a precision of 0.0001 refractive index units. The suspension medium used for crystal sizing was denatured alcohol for KNO₃ and n-hexane for salicylic acid. The refractive indices of potassium nitrate (Lide and Frederikse, 1994) and salicylic acid (Thomas, 1997) were taken from the literature and their values were also confirmed to the third decimal place by the method of oblique illumination (Phillips, 1971). The latter is described in more detail in Appendix D. The shape factor of KNO₃ crystals was taken equal to 1 in accordance with literature values (Miller, 1993; Shor and Larson, 1971). The shape factor of salicylic acid was determined experimentally by sizing 750 crystals with an optical microscope. The crystals were assumed to be square base parallelepipeds with sides β_1 and β_2 ($\beta_1 > \beta_2$) and the shape factor was calculated as 5.03 ± 3.22 according to procedures described in the literature (Myerson, 2002).

An additional technique used for crystal sizing, but also to obtain information about the crystal morphology, was optical microscopy. Paracetamol crystals were sized with this method, since they are known to agglomerate heavily (Fujiwara et al., 2002). An optical microscope (Swift Instruments International, M4000-D) equipped with a digital camera and a stage micrometer was used to obtain sample pictures. Crystal sizing was performed with available free imaging software (Image Tool version 3, Univ. of Texas Health Science Center in San Antonio, TX) either automatically or manually. When sizing is performed automatically, the software measures the area of the crystal/particle and assigns it to an ellipse. Therefore, the crystal size computed this way is based on area and not on volume as in the case of laser diffraction.

3.3 Theory

In this section the way the experimental data were compared with existing literature data obtained in MSMPR crystallizers will be briefly discussed, together with necessary references to crystallization theory. All comparisons between SHFCs and MSMPR crystallizers were made on the basis of the same relative supersaturation. The latter is given by (Myerson, 2002)

$$\sigma = \frac{C - C^*}{C^*} \tag{3.2}$$

The quantities compared include the mean crystal size L_{mean} , its standard deviation (SD), the coefficient of variation (CV), the mode size and the d_{10} , d_{50} and d_{90} sizes, which are the sizes corresponding to the 10^{th} , 50^{th} and 90^{th} percentiles respectively of the undersize volume cumulative crystal size distribution. The use of all these parameters ensures that the comparison is as complete as possible and yields meaningful results. The mean size, the SD and the CV of the CSD are given from the following relationships based on population density values (Randolph and Larson, 1988):

$$L_{mean} = \frac{\int_{L_1}^{L_2} L^4 n(L) dL}{\int_{L_1}^{L_2} L^3 n(L) dL}$$
(3.3)

$$SD = \sqrt{\frac{\int_{L_1}^{L_2} (L - L_{mean})^2 L^3 n(L) dL}{\int_{L_1}^{L_2} L^3 n(L) dL}}$$
(3.4)

$$CV = \frac{SD}{L_{mean}} 100\%$$
(3.5)

Finally, the number of crystals produced per unit volume, indicative of the nucleation rate achieved, can be found by numerical integration of the population density curve with respect to crystal size:

$$N_{c} = \int_{L_{1}}^{L_{2}} n(L) dL$$
 (3.6)

Integration was performed in all cases by using the composite trapezoidal rule.

For the SHFC runs, C in Equation (3.2) is equal to the feed concentration C_f while C* is equal to the saturation concentration of the feed solution $C_{f,out}^*$ at its exit temperature. The saturation concentration was calculated from solubility data available for potassium nitrate (Rolfs et al., 1997; Perry and Green, 1999), salicylic acid (Stephen and Stephen, 1963) and paracetamol (Granberg and Rasmuson, 1999; Grant et al., 1984). The experimentally obtained magma density was found from filtration data by (Myerson, 2002)

$$M_T = \frac{m_c}{V_{fil}} \tag{3.7}$$

The magma density can also be calculated based on a solute mass balance around the crystallizer and the solubility curve:

$$M_T = \frac{\dot{m}_c}{\dot{V}_f} = \frac{C_{f,in} - C_{f,out}^*}{\dot{V}_f} \dot{m}_{solv}$$
(3.8)

Population densities for the SHFC runs were obtained from the following relationship:

$$n_i(L_i) = \frac{x_{w,i}M_T}{k_v \rho_c L_i^3 \Delta L_i}$$
(3.9)

Equation (3.9) is based on the assumption that the weight fraction of crystals of size L_i is the same as the volume fraction found from the laser diffraction measurements. Note also that the experimentally obtained magma density (Equation 3.7) was used in all cases for the calculation of the population density.

For the literature MSMPR data, relative supersaturations were calculated from Equation (3.2) based on the inlet and operating temperatures of the MSMPR crystallizer. Magma densities were used as quoted in the respective references, while crystal sizing was performed by sieving. The CSD characteristics were given in the form of the population density curve. The latter was obtained primarily from MSMPR kinetic expressions (Myerson, 2002)

$$n_i(L_i) = n^o \exp(-\frac{L_i}{G\tau})$$
(3.10)

and on a secondary basis from diagrams read with digital imaging software (Image Tool version 3, Univ. of Texas Health Science Center in San Antonio, TX) with an accuracy of 1-2%. Mean size, SD and CV were calculated from Equations (3.3)-(3.5) with numerical integration between the lower and upper sieve sizes reported. The % weight crystal size distributions, which are directly comparable to the % volume crystal size distributions measured by laser diffraction, were generated based on the following relationships:

$$W_i(L_i) = n_i(L_i)k_v \rho_c L_i^3 \Delta L_i$$
(3.11)

$$x_{w,i} = \frac{W_i(L_i)}{\sum_i W_i(L_i)}$$
(3.12)

The % weight cumulative curve was then constructed and used to find the d_{10} , d_{50} and d_{90} sizes with interpolation.

Heat transfer calculations inside the SHFC were performed based on the theory presented in Chapter 2. Two cases were examined: single-phase heat transfer and heat transfer with change of phase. The former will be valid if the SHFC were operated as a nuclei generator while the latter corresponds to a situation where the SHFC acts as a crystallizer. In this case, an expression for the source term in Equation (2.7) is needed. The latter is given by

$$S^* = \frac{sr_i^2}{kT_{in}} \tag{3.13}$$

where the dimensional source term is expressed in Wm⁻³. For a flowing crystallization system, it is calculated as

$$s = \frac{\dot{m_c} \Delta H_c}{V} \tag{3.14}$$

The volume of a SHFC available for crystallization corresponds to the volume of the fibers based on the inside diameter:

$$V = N\pi \frac{D_i^2}{4} L = N\pi r_i^2 L$$
 (3.15)

Combining Equations (3.13)-(3.15) one obtains the following expression for the dimensionless source term:

$$S^* = \frac{m_c \,\Delta H_c}{N\pi L k T_{in}} \tag{3.16}$$

3.4 Results and Discussion

In this section the results for each compound tested will be presented separately. Most of the results were obtained for the aqueous potassium nitrate system, a common inorganic chemical for the following reason: enough literature data were available to compare SHFCC with conventional MSMPR crystallizers. Salicylic acid in ethanol and paracetamol in water are typical examples of readily and sparingly soluble organic and pharmaceutical molecules respectively.

3.4.1 Potassium Nitrate Crystallization

The potassium nitrate system is one of the most studied systems in cooling crystallization. Therefore, a comparison with conventional cooling crystallizers can be made. The latter is based on existing literature data (Helt and Larson, 1977; Juzaszek and Larson, 1977). Primarily the results for the SHFC-CST in series and the once through operation modes will be reported here. The results for the once through and the feed recycling operation mode are similar and the trends or conclusions reported for the former also hold for the latter.

Figure 3.6 shows the operational conditions during the experimental runs in a concentration-temperature plot. The coordinates for each point are the temperature at the outlet of the SHFC and the starting feed concentration C_f . Also plotted is the metastability curve based on literature data (Nyvlt et al., 1970; Nyvlt, 1993; Mersmann and Bartosch, 1998). The latter is rather approximate since the data available are scattered and also depend on the cooling rate applied during the metastable zone width determination as well as the method of determination (Myerson, 2002). Figure 3.6 shows that almost all SHFC-CST in series runs fall inside the metastable zone. The contrary is



Figure 3.6 Operating conditions during the KNO₃ SHFCC runs.

true for the SHFC once through mode runs, which were performed very close to or crossed the metastable zone limit. A significant amount of runs was also attempted well below the metastable zone limit; however, the large amount of crystals generated due to spontaneous primary nucleation led to fiber clogging. Therefore, for a readily soluble system like KNO₃, the metastable zone width seems to be the operational limit for SHFC devices. Feed recycling runs were operated at much lower supersaturation levels and are closer to the solubility curve.

In Figure 3.7, typical % volume differential crystal size distributions are given for the SHFC-CST in series operation mode together with the operating conditions during the runs. The Re numbers quoted, are somewhat uncertain, since the literature viscosity data (Isono, 1984) were obtained for slightly more dilute solutions (concentration up to 0.3 g/g). For comparison purposes, a similar CSD obtained from an MSMPR crystallizer (Juzaszek and Larson, 1977) is also given. Note that all runs were performed under the same relative supersaturation conditions and therefore can be directly compared, despite the fact that small operating temperature differences do exist. From Figure 3.7 it is immediately apparent that the reproducibility obtained with the experimental SHFCC apparatus is reasonably good. Also, it is obvious that under the same relative supersaturation conditions, the SHFC-CST in series arrangement produces crystals considerably smaller than MSMPR crystallizers. This is more evident in Figure 3.8 where the % volume cumulative undersize CSD is plotted for the three runs presented in Figure 3.7. For both runs performed in the SHFCC experimental setup, 90-95% of the crystals produced are smaller than 300 μ m. This size compares favorably with the MSMPR run, for which, 90% of the crystals produced are smaller than 500-550 μ m.



Figure 3.7 KNO₃ crystallization from aqueous solutions: % Volume differential CSD for the SHFC-CST in series operation mode. Operating conditions: a) Run 10: $C_f = 0.382$ g/g, $T_{f,in} = 27.3^{\circ}$ C, $T_{f,out} = 22.3^{\circ}$ C, $T^* = 24.6^{\circ}$ C, $\text{Re}_f = 140$, $\tau_{\text{CST}} = 120$ s; b) Run 12: $C_f = 0.382$ g/g, $T_{f,in} = 28.4^{\circ}$ C, $T_{f,out} = 22.3^{\circ}$ C, $T^* = 24.6^{\circ}$ C, $\text{Re}_f = 143$, $\tau_{\text{CST}} = 120$ s.



Figure 3.8 KNO₃ crystallization from aqueous solutions: % Volume cumulative undersize CSD for the SHFC-CST in series operation mode. Operating conditions as in Figure 3.7.

The situation is somewhat different for the once through operation mode. Figure 3.9 shows the % volume differential CSDs for two once through runs and a MSMPR run (Juzaszek and Larson, 1977) performed under the same relative supersaturation conditions. Also included are the operating conditions used during these two runs. Figure 3.10 illustrates the % volume undersize cumulative curves for the same runs.

One can immediately recognize some differences, but also a few similarities, between the curves in Figures 3.7 and 3.9. In the once through mode of operation the reproducibility between different runs is lower than in the case of the SHFC-CST in series runs. Also, the CSDs obtained are broader and overlap with the MSMPR curve for a significant size range, something not observed in Figure 3.7. However, the mode of the CSD curves in Figures 3.7 and 3.9 falls in the same range, between 100-200 µm. This reveals that, in both operation modes, the SHFC is producing primarily small crystals, something also shown in Figure 3.10 for Run 2; the resemblance with Figure 3.8 is evident. The difference in the once through operation mode is that CSD broadening can occur at larger sizes. The two SHFCC curves in Figure 3.9 have approximately the same shape until a crystal size of about 300 µm, the only difference being the smaller % volume values for Run 8, which, however, can be attributed to the presence of a significant amount of larger crystals. This is also apparent in Figure 3.10 where significant departure of the two curves is observed for sizes above 300 µm.

The % volume differential CSDs for two feed recycling runs and an MSMPR run at the same relative supersaturation are given in Figure 3.11. The resemblance with Figure 3.9 is apparent. The mode size of the distribution is between 100-200 μ m. However, for the feed recycling runs reproducibility is even poorer. Also the CSDs



Figure 3.9 KNO₃ crystallization from aqueous solutions: % Volume differential CSD for the SHFC once through operation mode. Operating conditions: a) Run 2: $C_f = 0.363$ g/g, $T_{f,in} = 27.3^{\circ}$ C, $T_{f,out} = 20.3^{\circ}$ C, $T^* = 23.3^{\circ}$ C, $\text{Re}_f = 55$; b) Run 8: $C_f = 0.370$ g/g, $T_{f,in} = 28.6^{\circ}$ C, $T_{f,out} = 20.7^{\circ}$ C, $T^* = 23.8^{\circ}$ C, $\text{Re}_f = 147$.



Figure 3.10 KNO₃ crystallization from aqueous solutions: % Volume cumulative undersize CSD for the SHFC once through operation mode. Operating conditions: same as in Figure 3.9.



Figure 3.11. KNO₃ crystallization from aqueous solutions: % Volume differential CSD for the SHFC feed recycling operation mode. Operating conditions: a) Run 2: $C_f = 0.372 \text{ g/g}$, $T_{f,in} = 28.7^{\circ}\text{C}$, $T_{f,out} = 23.5 \text{ }^{\circ}\text{C}$, $T^* = 23.9^{\circ}\text{C}$, $\text{Re}_f = 145$; b) Run 8: $C_f = 0.350 \text{ g/g}$, $T_{f,in} = 28.1^{\circ}\text{C}$, $T_{f,out} = 21.5^{\circ}\text{C}$, $T^* = 22.3^{\circ}\text{C}$, $\text{Re}_f = 147$.

obtained are much broader. It follows then that the feed recycling and the once through operation modes will show similar performance trends with the situation being somewhat better for the latter.

The population density curves for the runs depicted in Figures 3.7 and 3.9 are given in Figures 3.12a and 3.12b, respectively. In Figure 3.12b, only data for run 8 (Figure 3.9) is included; the magma density was not determined experimentally for run 2. Figure 3.12a clearly shows that SHFC-CST in series arrangements produce a higher number of smaller crystals compared to MSMPR crystallizers. Also, the slope of the curve is much larger, revealing that the CSD can be confined to small sizes and the number of larger crystals produced will be small. Moreover, the two curves obtained in the SHFCC setup show good reproducibility, which starts to break down at a size near 300 µm. The latter, as shown in Figure 3.8, corresponds roughly to the 90th percentile of the % volume undersize cumulative CSD, showing that variability of the present results is significant only for larger crystal sizes, namely, at the high end of the CSD.

Figure 3.12a shows also that the nucleation rate in SHFC-CST in series arrangements is at least 1-2 orders of magnitude higher than the respective value for the MSMPR crystallizers. This estimate was obtained by extrapolating the linear part of the curves between 35-300 μ m. On a rigorous basis, this is incorrect, since the kinetics described by Equation (3.10) are not valid for semi-batch operation. However, for the last measured class size for the MSMPR run, which corresponds to a US No. 200 sieve or 82.5 μ m average size, the population density for the SHFC-CST in series runs is already seven times larger. This difference will be amplified at smaller sizes due to the larger slope of the SHFC-CST in series curves.



Figure 3.12 KNO₃ crystallization from aqueous solutions. Population density curves obtained with solid hollow fiber cooling crystallization: (a) SHFC-CST in series; (b) SHFC once through operation mode.

The situation is quite different for the SHFC once through run shown in Figure 3.12b. In this case, the population density curve of the SHFC is below the respective curve of the MSMPR run, for the whole size range measured for the MSMPR run (80-1000 μ m). At 82.5 μ m, the population density for the latter is twice that of the SHFC once through run. Therefore, following the arguments described above, it can be stated that, the apparent nucleation rate achieved by the once through mode of operation seems lower than the respective value for the SHFC-CST in series runs and comparable with the MSMPR values.

More insight on the magnitude of the nucleation rate can be obtained from Figure 3.13, which shows a plot of the generated crystals per unit volume with respect to relative supersaturation for the SHFCC setup and the MSMPR data set (Helt and Larson, 1977; Juzaszek and Larson; 1977). Calculations were performed based on Equation (3.6). Note that not all once through runs are shown in Figure 3.13, since for some of them the magma density was not determined. Figure 3.13 clearly illustrates that under the same relative supersaturation conditions, the SHFC-CST in series arrangement produces 2-3 orders of magnitude more crystals than MSMPR crystallizers. The results are more scattered and this can be partially attributed to the semi-batch operation of the CST. A larger amount of crystals, about 2 orders of magnitude, is also produced in the once through mode of operation. However, this amount is smaller than the respective number for the SHFC-CST in series runs. This is somewhat surprising, since the once through runs were performed at a higher level of supersaturation and hence nucleation would be more favored than growth.



Figure 3.13 Number of KNO_3 crystals generated per unit volume: Solid hollow fiber cooling crystallization vs. MSMPR data.

Additional information on the crystallization kinetics in the experimental apparatus can be obtained by the magma density values. Ideally, this should be the same as the value calculated by Equation (3.8). The latter is the value obtained in MSMPR crystallizers, where all supersaturation created is depleted. The experimentally obtained magma densities for both operation modes examined are shown in Figure 3.14, where they are compared with the calculated values. Immediately, one recognizes that in the majority of the runs performed, the magma density values obtained are much smaller than the calculated ones. This simply means that all of the supersaturation created in the SHFCC setup is not depleted. The situation is better for the SHFC-CST in series runs for which values close to the thermodynamic limit predicted by Equation (3.8) were obtained for about 45% of the runs performed. The variability in the results can, up to a certain extent, be attributed to the semi-batch operation of the CST and its small retention time of two minutes or less. The same variability is observed in MSMPR crystallizers during startup.

More information however, on the condition of the crystallizing solution exiting the SHFC can be obtained by examining the heat transfer inside the device. Two cases can be distinguished based on Equation (2.7). If the solution is in a metastable condition, then heat transfer can be best described as single-phase and the source term given by Equation (3.16) can be neglected. The theory of Chapter 2 including the simple formulae presented can be used for design purposes. The SHFC functions in this case solely as a nuclei generator or a device creating uniform supersaturation. On the other hand, if all or most of the created supersaturation is depleted, then heat transfer includes change of



Figure 3.14 KNO₃ crystallization from aqueous solutions: Comparison of experimental and magma density values calculated by Equation (3.8).

phase, Equation (2.7) must be solved using the source term and the SHFC will act as a crystallizer.

Calculations were performed for all SHFC-CST in series runs, for which the magma density and hence the crystal rate production were determined experimentally. As already mentioned, magma density was determined experimentally for only a smallfraction of the once through runs. Figure 3.15 shows the prediction error in the lumen side exit temperature obtained by solving equation (2.7) for single-phase heat transfer and with a source term representing the heat of crystallization released.

As shown in Figures 3.15a and 3.15b, single-phase calculations generally underpredict the feed side exit temperature, since the heat of crystallization is neglected. The opposite is true for the case where the source term is included. The latter is applied for the whole crystallizer length. In reality, the feed enters the SHFC at a temperature higher than its saturation temperature and crystallization takes place at a distance downstream of the crystallizer entrance. Therefore, the feed exit temperature will be overpredicted in this case, exactly the trend shown in Figure 3.15. Regardless of these trends however, it is apparent that both approaches yield the same level of accuracy. This fact in combination with the much lower than anticipated magma densities, leads to the conclusion that the SHFC acts primarily as a nuclei and supersaturation generator; a considerable amount of the generated supersaturation is not depleted as confirmed numerous times by the appearance of crystals in the filtrate and the SHFC can be considered as a class I system (Randolph and Larson, 1988).



Figure 3.15 KNO_3 crystallization. Prediction error in the calculated feed exit temperature for the a) SHFC-CST in series and b) the once through operation modes.

Two factors can contribute to the observed metastability of the system. The first one is the fact that the solution is cooled very quickly by the SHFC to its final temperature, typically in 1-3 seconds. It is known that the metastable zone width increases with the cooling rate (Mersmann, 2001; Myerson, 2002). Despite the fact that a cooling rate in a continuous device like the SHFC cannot be defined in the same way as in a typical batch experiment for the determination of the metastable zone width, theeffective cooling rate in a SHFC (2-3 K/s) is considerably higher than 20 K/hr, the maximum cooling rate for which the metastable zone curve depicted in Figure 3.6 is based.

The high cooling rates achieved in SHFCs can be effectively utilized to decouple nucleation and growth, a topic further discussed for the system paracetamol-water in Subsection 3.4.3. This is not possible in conventional cooling crystallization equipment where both events are taking place simultaneously in the same vessel. A similar decoupling has been achieved only in impinging jet precipitation or static mixer precipitation (Rivera and Randolph, 1978; Raphael and Rohani, 1999). However, the ability to operate the SHFC considerably below the metastable zone will also depend on the system crystallized; it will be more feasible with sparingly soluble organic systems. Several experimental attempts to crystallize potassium nitrate under high supersaturation conditions failed due to fiber clogging.

To a certain extent this can possibly be attributed to the fact that cooling in multitube laminar flow is unstable (Mueller, 1986). Flow maldistribution or fiber cross section variation, a known issue in membrane contactor technology, can lead to a situation where some fibers are running at a low while others at a higher temperature. Pressure drop inside the cold fibers is higher due to the high viscosity; as a result the velocity inside the cold fibers will decrease approximately according to Hagen-Poiseuille law and the temperature will further drop. For a crystallizing system this simply leads eventually to fiber blockage. For the same volumetric flow rate, the rest of the fibers will run at a higher velocity and the tube side exit temperature will increase. This was observed experimentally several times, with and without fiber blockage. However, the contribution of the small number of fibers (35) of the SHFCs used in this dissertation is rather decisive. At an industrial scale, any instability due to flow maldistribution will probably be dampened by the extremely large number of fibers used. The same would be true if some of the fibers were blocked; the performance of the device would be minimally affected.

High cooling rates can potentially be exploited for crystal morphology control. Am Ende and Brenek (2004) have shown that the cooling rates obtained in double-pipe heat exchangers can be used to achieve the preferential formation of a polymorph. This is not possible in batch or continuous stirred vessels, in which the cooling rate is low. Considering the superior thermal performance of PHFHEs over metal heat transfer equipment, already shown in Chapter 2, it should be anticipated that SHFCs can further facilitate selective polymorph crystallization.

The second reason for the metastability observed is the mixing conditions prevailing inside the SHFC. Flow inside the device is fully laminar, although characterized by velocities that are more typical of turbulent flow inside larger tubes. As a result, the crystallizing solution is at best mildly mixed. This is apparent in Figure 3.16, which shows the dispersion number inside a hollow fiber vs. the Reynolds number. The



Figure 3.16 Mixing conditions inside a SHFC. Dispersion number as a function of Reynolds number.

dispersion number was calculated based on the Aris-Taylor dispersion coefficient for laminar flow

$$D^* = D_{AB} + \frac{U^2 R^2}{48 D_{AB}}$$
(3.17)

The diffusion coefficient for aqueous potassium nitrate solutions was obtained from the literature (Daniel and Albright, 1991). As already shown in Figures 3.7, 3.9 and 3.11, all SHFCC runs were performed at Reynolds numbers between 50-150. For the lower limit, the dispersion number is around 0.4, closer to the plug flow than the completely mixed case; for the former complete segregation is assumed. Figure 3.16 shows that as the Reynolds number increases, the dispersion number attains higher values and starts approaching the completely stirred flow limit, for which perfect mixing is assumed. However, at Re = 150 mixing is still very mild; the crystallizing solution is essentially unmixed and this simply translates to considerably higher metastable zone widths than the ones quoted in the literature and obtained in stirred vessels.

From the above discussion it is apparent that mixing downstream of the SHFC is of paramount importance for the success of the proposed technique. An arrangement where the mixing device (a CST or a static mixer) is operated continuously would be advantageous in two ways, provided the mixing device has a residence time that is close to the residence time of the SHFC. First, it would be possible to improve CSD reproducibility, which already is reasonably good. Second, magma densities along the solid line shown in Figure 3.14 could be systematically obtained and all supersaturation created could be exploited. As a result, the difference in the n(L) values between SHFC-CST in series arrangements and MSMPR crystallizers would further increase. This is exactly what Figure 3.17 illustrates for one of the SHFC-CST in series runs for which the M_T reached its limiting value, in comparison to an MSNPR run. Evidently, the difference in population density values is much larger than the one in Figure 3.12a: at 82.5 µm, the n(L) value for the SHFC-CST in series experiment is 40 times higher than the respective value for the MSMPR run. This fact clearly shows that substantially higher nucleation rates are achievable in the SHFCC experimental setup. Note also that the maximum in the population density curve at low sizes can be attributed to segregation effect caused by the SHFC (Tavare, 1986; 1989).

This concept was tested experimentally with a continuously operated CST. As already mentioned in the experimental section, a peristaltic pump was used for slurry removal. The latter however, proved inadequate for this cause. The same was true for a gear pump tested. Slurry removal decreased with time as experienced by a rise of the liquid level inside the CST. As a result, growth of existing crystals was favored over nucleation, a fact reflected in Figure 3.18 that shows the population density obtained in one run, during which the CST was operated continuously. The difference with Figures 3.12 and 3.17 is apparent. A shift towards higher sizes can be observed together with a decrease in the number of crystals produced. This run ended with clogging of the slurry removal line. The same phenomenon was observed numerous times. The inability of the pumps used to remove slurry at a constant rate proved an insurmountable obstacle in the effort to obtain reliable and reproducible results.

The higher nucleation rates obtained in the SHFCC setup are resulting from two factors. The first one is the high surface area/volume ratio of hollow fiber devices, which facilitates heat transfer, the driving force for supersaturation creation and also increases



Figure 3.17 KNO₃ crystallization from aqueous solutions: Population density plot for a SHFC-CST in series run, for which the experimental magma density is in agreement with the value calculated by Equation (3.8).



Figure 3.18 KNO₃ crystallization from aqueous solutions: Population density plot for a SHFC-CST in series run, during which the CST was operated continuously.
the volume of solution processed for a given equipment volume. In addition, the fiber inside area facilitates heterogeneous nucleation (Schubert and Mersmann, 1996). Order of magnitude calculations based on the procedures described in the literature (Mersmann, 1996) for the determination of heterogeneous nucleation rates were performed for both SHFCC operating modes. Details can be found in Appendix E. These calculations confirm that heterogeneous nucleation is the controlling mechanism; for all runs the heterogeneous nucleation rate calculated based on the tube side exit temperature is at least an order of magnitude higher than the values reported in Figure 3.13. The difference is attributed to the approximate nature of these calculatons and the fact that the nucleation rate upstream of the SHFC exit will be smaller.

The second one is the difference between bulk and wall temperature, also observed in membrane distillation-crystallization (Tomaszewska, 1993). According to heat transfer calculations performed, this difference is between 1-2°C for the majority of the runs performed and will become higher if higher feed velocities are used; however, it is much lower than the corresponding temperature difference in metal heat exchangers. Consequently, the nucleation rate near the wall is higher than what is dictated by the bulk temperature, which is experimentally obtained. If one considers that nucleation is activated (heterogeneous), it follows that this small difference in temperature translates to orders of magnitude differences in nucleation rate. Therefore, nucleation is favored over growth in the vicinity of the wall. A similar analysis for much higher temperature differences explained the experimental data for para-xylene crystallization in completely stirred scraped-surface crystallizers (Patience et al., 2001).

The difference in mixing conditions between the once through and the SHFC-CST in series operation modes introduced by the presence of the mixing device can explain the higher number of crystals obtained in the latter as well as the crystal morphology. When operating in the SHFC-CST in series mode, all but a small percentage of the nuclei/crystals coming out of the SHFC at the end of the sampling period have the chance to grow inside the CST to a size ensuring their retention on the filter. On the other hand, this is not the case for the once through runs. The presence of a maximum in the population density plot (see Figure 3.12) within 1.5 μ m from the filter. This was verified experimentally numerous times by the appearance of crystals in the filtrate. Therefore, nuclei loss through the filter caused by absence of mixing is the primary factor causing the differences in the number of crystals generated per unit volume, shown in Figure 3.13.

The same argument can explain the much longer filtration times observed for the once through mode compared with the SHFC-CST in series operation mode. For slightly smaller suspension amounts filtered, the filtration time for the former was between 2-5 min. compared to an average of 10-20 s for the latter. The very large variability in filtration time for the once through runs can be explained by the presence of a substantial amount of fines, which can block the filter and reduce the cake permeability significantly. During these runs, blocking was routinely observed after a short period of time, about 10-30 s, when a sharp decrease of the filtration rate was realized and the level of mother liquor on the filter increased substantially. Mota et al. (2003) showed that the presence of a substantial amount of fines (about 10% by volume) in combination with the presence of



Figure 3.19 Crystal morphology obtained during KNO_3 solid hollow fiber cooling crystallization: (a) SHFC-CST in series operation mode; (b) SHFC once through operation mode.

a much smaller number of larger crystals results in a minimum value for the cake porosity. This is exactly what Figure 3.12b shows: a large number of fines with sizes up to about 60 μ m accompanied by smaller numbers of larger crystals. Note also that from Figure 3.10 a volume fraction of about 5-6% for crystals up to 60 μ m large is obtained. This shows that the fines fraction obtained in the SHFCC experimental setup corresponds to cake porosities in the vicinity of the minimum.

The slow filtration rate described above together with the conditions of minimal mixing on the filter can lead to differences in crystal morphology. This is shown in Figure 3.19, where one microscope picture is given for each operation mode. Figure 3.19a shows that the crystals obtained with the SHFC-CST in series operation mode are well formed, rounded and of relatively uniform size. Their morphology is such that it allows fast filtration, as observed in practice. Mixing in the CST plays an important role in crystal morphology. On the contrary, the crystals obtained with the once through operation mode are needle-like with very large aspect ratios. This is a result of slow filtration in combination with minimal mixing conditions. Such a combination allows localized growth on the filter under high supersaturation conditions, resulting in broad CSDs similar to the ones shown in Figure 3.9.

An assessment of the performance of the SHFCC experimental setup and its various operating schemes against MSMPR crystallizers can be made by comparing several characteristics of the CSD curves obtained. This comparison can give a more complete picture of the trends and possible advantages or disadvantages of the different SHFCC operating schemes implemented. All MSMPR data used for the comparison were obtained from the literature (Helt and Larson, 1977; Juzaszek and Larson, 1977).

Figure 3.20 shows a plot of the mean crystal size obtained with respect to relative supersaturation. The mean size obtained for the SHFC-CST in series runs ranges between 95-170 μ m, 3-4 times lower than the MSMPR values, which range between 350-450 μ m. For the once through mode runs the situation is different, since for half of the runs performed, the mean size obtained is between 200-300 μ m while for the other half it is almost constant at a value of 450 μ m. It is apparent that for the SHFC-CST in series arrangement the variation of the mean crystal size is slightly lower than the MSMPR data, while the mean crystal size for the once through mode runs varies considerably

However, of special interest in Figure 3.19 are the two points corresponding to Run 14 from Juzaszek and Larson (1977); the CSD for this run has already been presented in Figure 1.1 The one with the lower mean size corresponds to the samples obtained from the crystallizer from the usual sampling point, while the other corresponds to a sample taken from a dead zone inside the crystallizer, where mixing is poor. The difference between the two values is evident (about 25%) and shows that significant CSD broadening can occur in MSMPR crystallizers due to poor mixing. It is also indicative of the performance limitations inherent in MSMPR crystallizers. The MSMPR data presented here were taken in a small crystallizer with a volume of only 10 liters; upon scale up, one would anticipate poorer control of mixing intensity and a CSD much broader and shifted towards larger sizes. No such behavior is expected in a SHFC, regardless of the device size.

In Figure 3.21 the SD of the mean crystal size is plotted with respect to relative supersaturation, while Figure 3.22 shows the respective plot for the CV of the crystal size distribution. From Figure 3.21, it can be seen that, the SD is lower (between 43-115 μ m)



Figure 3.20 KNO₃ mean crystal size: Solid hollow fiber cooling crystallization vs. MSMPR data.



Figure 3.21 Standard deviation (SD) of the mean crystal size of KNO₃: Solid hollow fiber cooling crystallization vs. MSMPR data.



Figure 3.22 Coefficient of variation (CV) of KNO₃ crystal size distributions: Solid hollow fiber cooling crystallization vs. MSMPR data.

in absolute terms for the SHFC-CST in series arrangement than the respective values (140-185 μ m) for the MSMPR data set. However, the SD for the dead zone point is about 265 μ m, markedly higher than the rest of the MSMPR data set. The SD for the once through mode runs ranged between 140-420 μ m, revealing broad CSDs and low reproducibility for the reasons analyzed above, namely, slow filtration and localized growth on the filter. This is also apparent in Figure 3.22, from which, a CV value of about 80% for the majority of the once through mode runs can be obtained. The CV values for the SHFC-CST in series runs ranged between 45-70%, which are higher than the respective values for the MSMPR data set, primarily due to the semi-batch operation mode of the CST. In semi-batch crystallizers the generated supersaturation and hence nucleation and growth go through a maximum before they attain a relatively stable value (Myerson, 2002). This can lead to variations in the CST.

Figure 3.23 shows a plot of the mode size of the distribution with respect to relative supersaturation. The mode size for the SHFC-CST in series runs ranged between 88-154 μ m, 3-4 times less than the respective range of 328-550 μ m for the MSMPR data. Again, the point corresponding to the dead zone is an outlier for the MSMPR data set with a mode size of 780 μ m. From the above discussion it is concluded that reproducibility of the mode size is good, especially if one considers that for 56% of the SHFC-CST in series runs performed, the mode size ranged between 127-140 μ m, a rather narrow range. The mode size for the once through runs ranged between 154-429 μ m, values obviously higher than the SHFC-CST in series operation mode but certainly lower than the MSMPR data set. However, this range is confined between 154-245 μ m for 65%



Figure 3.23 KNO $_3$ mode size: Solid hollow fiber cooling crystallization vs. MSMPR data.

of the once through runs performed, which is close to the respective range for the SHFC-CST in series operation mode. This shows that the SHFC is primarily producing small crystals.

Figure 3.24 shows that the d_{10} size is very reproducible for the SHFC-CST in series runs, between 40-65 µm. Slightly lower reproducibility is obtained for the once through runs, for which the d_{10} size ranged between 72-107 µm. Both operation modes yielded lower d_{10} sizes than the MSMPR crystallizer, for which the results are considerably more scattered. Figure 3.25 shows a plot of the d_{50} size with respect to relative supersaturation. The same trend is evident for the SHFC-CST in series operation mode: the d_{50} size is reproducible for a wide supersaturation range and considerably smaller than the respective CSD characteristic of the MSMPR runs. The situation is different for the once through mode runs. Reproducibility is already lost at the d_{50} size as evident from the scatter of the results. Above this size, one should anticipate significant CSD broadening, as already shown in Figure 3.9.

Figure 3.26 shows the d_{90} size as a function of relative supersaturation. For the once through runs the scatter of the results and the CSD broadening are apparent. A considerable scatter is also evident in the case of the SHFC-CST in series runs. This shows that loss of reproducibility and broadening occurs at the high end of the CSD. However, the significance of the presence of a small number of larger crystals in the case of the SHFC-CST in series runs is larger due to the fact that the CSD is confined to small sizes. The presence of a small number of large crystals can skew significantly the distribution towards the larger sizes end. Finally, it should be mentioned that, for half of the SHFC-CST in series runs performed, the d_{90} size falls between 200-250 µm, a narrow



Figure 3.24 KNO₃ d_{10} size: Solid hollow fiber cooling crystallization vs. MSMPR data.



Figure 3.25 KNO₃ d₅₀ size: Solid hollow fiber cooling crystallization vs. MSMPR data.



Figure 3.26 KNO₃ d₉₀ size: Solid hollow fiber cooling crystallization vs. MSMPR data.

range and that for all runs 90% of the crystals produced is smaller than 370 μ m. This is indicative of the fact that SHFC-CST in series arrangements can be used for the production of small crystals.

3.4.2 Salicylic Acid Crystallization

Salicylic acid in ethanol was chosen as an example of a readily soluble organic system. Salicylic acid is obtained in a crystalline form by precipitation processes and various studies are available in the literature (Tavare and Gaikar, 1991; Nallet et al., 1998; Blandin et al., 2001) providing information on the CSDs obtained. However, no cooling crystallization data are available to the author's knowledge. Therefore, a direct comparison of solid hollow fiber cooling crystallization with literature data cannot yield meaningful results on a rigorous basis, since the mechanism of supersaturation creation and the levels of supersaturation involved in the process are completely different. The main purpose of the limited number of experiments performed with the SHFC-CST in series operation mode and presented below, is to clearly illustrate that, unlike the other membrane based crystallization techniques, SHFCC can be also applied to organic systems without any differences or additional difficulties compared to aqueous solutions.

Figure 3.27 shows typical % volume differential CSDs for salicylic acid crystallization from its ethanol solutions. Also included are the operating conditions during these runs. One can immediately notice the similarity with Figure 3.7. The CSD is confined to relatively small sizes, up to about 400 μ m. Reproducibility is also good. This is more apparent in Figure 3.28, where the % volume undersize cumulative curves are given for the same runs. The two curves are almost overlapping up to a size of 200 μ m,



Figure 3.27 Salicylic acid crystallization from ethanol solutions: % Volume differential CSD for the SHFC-CST in series operation mode. Operating conditions: a) Run 2: $C_f = 0.534$ g/g, $T_{f,in} = 24.5^{\circ}$ C, $T_{f,out} = 16.0 \ ^{\circ}$ C, $T^* = 20.4^{\circ}$ C, $\tau_{CST} = 120$ s; b) Run 4: $C_f = 0.536$ g/g, $T_{f,in} = 24.8^{\circ}$ C, $T_{f,out} = 15.9 \ ^{\circ}$ C, $T^* = 20.7^{\circ}$ C, $\tau_{CST} = 120$ s.



Figure 3.28 Salicylic acid crystallization from ethanol solutions: % Volume undersize cumulative CSD for the SHFC-CST in series operation mode. Operating conditions as in Figure 3.27.

where deviations start to appear. Figure 3.28 also shows that the d₉₀ size takes values of 300 µm and lower. Typical population density curves are given in Figure 3.29. The population density values shown in Figure 3.29 are comparable or higher than the respective values for batch precipitation in stirred vessels (Tavare and Gaikar, 1991). This means that higher nucleation rates can be achieved in the SHFCC apparatus, despite the much lower supersaturations used in the experiments reported here. The population density curves show the same characteristics with the ones in Figure 3.12a, namely, high values of population density at small sizes followed by a steep decrease at higher sizes, due to the large slope of the curve. However, there is a difference between the two curves in Figure 3.29, despite the fact that the % volume undersize cumulative curves shown in Figure 3.28 overlap. This simply means that the magma density values in the two runs were quite different for the same reasons explained in Subsection 3.4.1 for the KNO₃ runs. From the above discussion, it follows that the SHFCC experimental apparatus shows the same performance trends, regardless of the nature of the crystallizing system, aqueous or organic. Differences can arise only due to system specific characteristics, such as crystallization kinetics.

Table 3.1 summarizes the characteristics of the crystal size distributions obtained from the four salicylic acid runs performed. These results are far from optimal, however, they are indicative of the performance that can be achieved in a SHFC-CST in series arrangement. The mean size obtained is small and reproducible. Moreover, it compares well with mean sizes of 75-102 μ m obtained by precipitation in batch stirred crystallizers (Blandin et al., 2001). The latter were based on a number distribution and therefore will generally tend to be smaller than the volume average found by ensemble techniques such



Figure 3.29 Salicylic acid crystallization from ethanol solutions: Population density curves. Operating conditions as in Figure 3.27.

CSD characteristic	Range
Mean Size (µm)	120-139
SD (µm)	84-108
CV (%)	60 - 83
Mode size (µm)	128-223
d ₁₀ size (μm)	29-35
d ₅₀ size (μm)	92-128
d ₉₀ size (μm)	243-283

Table 3.1Salicylic Acid Crystallization from Ethanol Solutions: CSD Characteristicsfor the SHFC-CST in Series Operation Mode

as laser diffraction. Also, supersaturation ratios between 2.7-3.4 were used in the batch crystallizer compared to 1.02-1.08 in the SHFCC apparatus. The SD of the mean crystal size, although low in absolute terms, is high compared to the mean size resulting therefore in high CV values. However, as shown in Table 1 the d_{10} , d_{50} and d_{90} sizes are reproducible. Therefore, the high CV values and the CSD broadening are caused by the presence of a small number of large crystals, which are probably produced due to solvent evaporation in the CST or the exit of the line connecting the SHFC and the CST.

3.4.3 Paracetamol Crystallization

Paracetamol (4-acetamidophenol, acetaminophen) crystallization from its aqueous solutions is an example of an organic system with low solubility. Paracetamol is also known as an over-the-counter analgesic; it is a system representative of crystallization in the pharmaceutical industry. Several studies of paracetamol crystallization exist. These

include cooling crystallization from aqueous (Fujiwara et al., 2002; Nagy et al., 2003) or ethanol (Worlitschek and Mazotti, 2004) solutions as well as cooling crystallization of the orthorhombic form from ethanol solutions (Al-Zoubi et al., 2002). In addition, Granberg et al. (1999; 2001) have also described batch antisolvent crystallization of paracetamol from acetone-water mixtures. However, no quantitative data are given in these studies to allow an elaborate comparison similar to the one performed for the KNO₃ runs. The experiments presented below had two goals. The first one was to illustrate the performance of SHFCC at considerably higher supersaturation levels, for which the contribution of homogeneous nucleation to the overall nucleation rate is either significant or dominant. This was not possible during the potassium nitrate and salicylic acid runs, which were operated close to or below the metastable zone boundary. The second goal was to clearly show that SHFCC can be used to effectively decouple nucleation and growth, the former being performed by the SHFC and the latter by a mixing device (CST or static mixer) downstream.

All experiments were performed with an in-line static mixer downstream of the SHFC to avoid the problems encountered with the CST operation described in Subsection 3.4.1. Two samples were obtained during each run: one was mixed magnetically for 15-30 seconds and then filtered while the other was filtered immediately as it was coming out of the static mixer. The difference between the two samples can be used to further illustrate the effect of mixing in the SHFCC device. The operating conditions during the runs performed, are shown in Figure 3.30, which is a concentration-temperature diagram similar to Figure 3.6. The metastable zone was based on data from the



Figure 3.30. Operating conditions during the paracetamol runs in the SHFCC device.

literature (Fujiwara et al., 2002). The latter were available up to 45°C; the rest of the curve was estimated based on the assumption that as the solution concentration increases, the metastable zone width decreases (Mersmann, 2001). Figure 3.30 shows that in the case of a system with a relatively low solubility it is possible to operate the SHFC deep inside the labile zone, as low as 40°C below the solubility curve. Consequently, high nucleation rates, typical of primary nucleation, can be achieved.

The crystal size distributions obtained for the 4 runs performed are shown in Figures 3.31 and 3.32, respectively, for the magnetically mixed and the unmixed samples respectively. These are based on microscope measurements. The latter were chosen over laser diffraction measurements due to the fact that paracetamol crystals are known to agglomerate heavily (Fujiwara et al., 2002); only in-line measurements such as FBRM can overcome this problem. Crystal agglomeration was confirmed by measuring the mixed sample from Run 1 with laser diffraction; the mode of the distribution occurred at a size of about 400 μ m. As shown in Figure 3.31, no crystal was measured larger than 150 μ m. The crystal size presented in Figures 3.31 and 3.32 corresponds to the circle equivalent diameter (CED), namely, the diameter of a circle having the same area as the measured crystal. For each run at least 650 crystals were measured.

Figure 3.31 shows that for all runs except run 4 the number distributions obtained were very similar. The CSD is practically confined between 3-150 μ m. These numbers compare well with the results of Nagy et al. (2003) and Fujiwara et al. (2002), who reported sizes as large as 400-600 μ m for crystallization from aqueous solutions. However, no quantitative comparison can be made with the results of this dissertation due to the fact that special algorithms have to be employed to obtain the true CSD from the



Figure 3.31 Paracetamol crystallization from aqueous solutions. % number differential CSD of mixed samples for the SHFC-in-line static mixer in series operation.



Figure 3.32 Paracetamol crystallization from aqueous solutions. % number differential CSD of unmixed samples for the SHFC-in-line static mixer in series operation.

chord length distributions obtained by FBRM measurements (Worlitschek and Mazzotti, 2004). Figure 3.32 shows similar trends; reproducibility between runs is good and the CSD is confined below 200 μ m. However, for the unmixed samples the tail of the distribution at sizes higher than 100 μ m is significant. It also reminds, albeit to a lesser extent, the tail of the curves shown in Figure 3.9 for the potassium nitrate runs.

The tail in the CSDs in Figure 3.32 and its absence in Figure 3.31 reveals different degrees of mixing between the two samples obtained during each run. The same conclusion can be drawn from Figure 3.33, which shows a plot of the experimentally obtained magma densities together with the thermodynamic limits calculated from Equation (3.8). Figure 3.33 shows similar trends with Figure 3.14, namely, magma densities smaller than anticipated. Therefore, the SHFCC apparatus can still be considered a class I system, in which not all supersaturation created is relieved. However, it is also apparent that the magma densities of the unmixed samples are higher compared to the values for the once through operation mode shown in Figure 3.14. Consequently, the presence of the in-line static mixer serves the purpose of supersaturation depletion. A longer and narrower static mixer would perform better and would be able to induce the necessary degree of mixing.

It should be noted here that the SHFCs used in this study were small compared to the in-line static mixer, which had an inside diameter of around 9 mm. Ideally, the static mixer would be chosen in such a way that its cross section were at least 4-5 times smaller than the cross section of the fibers used in the SHFC. Translating this requirement to the experimental setup of this dissertation, the diameter of the static mixer to be used would have to be smaller than 1 mm. Consequently, the CSDs of Figure 3.32 and the results of



Figure 3.33 Paracetamol crystallization from aqueous solutions: Comparison of experimental and magma density values calculated by Equation (3.8).

Figure 3.33 cannot be considered optimal. Rather, they are indicative of the potential of SHFCC if operated at a different scale.

Figures 3.34 and 3.35 illustrate the % number cumulative undersize CSDs obtained for the mixed and unmixed samples respectively. Figure 3.34 shows that, for all runs, 90% of the crystals produced are smaller than 50 μ m; further, the CSD for all purposes can be considered confined below 100 μ m. The d₉₀ size obtained from Figure 3.35 is higher, about 70 μ m and indicates local supersaturation depletion. However, the supersaturations involved in the paracetamol experiments are considerably higher compared to the potassium nitrate runs. As a result, a much larger number of nuclei are present, which can grow in a more uniform way. The same argument explains the larger sizes compared to Figure 3.34 at the high end of the CSD.

Another observation that can be made from Figures 3.34 and 3.35 is that the crystal sizes obtained for run 1 are markedly smaller than the rest of the runs. This can be explained on the basis of the much higher supersaturation used during this run. Hence, higher nucleation rates were obtained, with the contribution of homogeneous nucleation being more significant.

The above argument becomes clear by inspecting Figure 3.36. The latter shows a plot of the nucleation rate with respect to the inverse of the square of the logarithm of the supersaturation ratio, the functional dependence valid for primary nucleation rate as shown in Appendix E. The nucleation rates shown in Figure 3.36 are approximate; they were estimated based on the number CSD by dividing the crystal production rate obtained experimentally with the calculated mass of the crystals sized. The point that corresponds to run 1 is an obvious outlier compared to the rest of the runs; it corresponds



Figure 3.34 Paracetamol crystallization from aqueous solutions. % number cumulative undersize CSD of mixed samples for the SHFC-in-line static mixer in series operation.



Figure 3.35 Paracetamol crystallization from aqueous solutions. % number cumulative undersize CSD of unmixed samples for the SHFC-in-line static mixer in series operation.



Figure 3.36 Experimentally obtained nucleation rates during paracetamol solid hollow fiber cooling crystallization from aqueous solutions.

to an order of magnitude higher nucleation rate, a fact indicating that the nucleation mechanism is possibly different for this run. This was confirmed by the calculations presented in Appendix E. These calculations show that, for run 1, the contribution of homogeneous nucleation starts to become appreciable. They also show that the calculated values are close to the experimental ones. Therefore, a combination of homogeneous and heterogenous nucleation is more possible for high supersaturations. As a final remark it is noted that the nucleation rates quoted in Figure 3.36 are very high; to the author's knowledge similar values are obtained only during antisolvent or precipitation crystallization.

Finally, a plot of the mean crystal size vs. the coolant temperature used is presented in Figure 3.37. The obtained mean crystal size is proportional to the coolant temperature; the lower the value of the latter, the smaller the size of the crystals produced due to the higher nucleation rates involved. Consequently, controlling the coolant temperature is a simple means to control the mean crystal size, a trend also reported in the literature (Am Ende and Brenek, 2004). However, this dependence will be observed primarily in the case of systems with low solubility, for which operation in the labile zone is possible, as shown in this subsection. For soluble systems like potassium nitrate, such a trend was not observed.



Figure 3.37 Paracetamol solid hollow fiber cooling crystallization from aqueous solutions. Dependence of mean crystal size on coolant temperature.

3.5 Conclusions

Solid hollow fiber cooling crystallization is a new promising crystallization technique that can be used for both aqueous and organic systems including pharmaceutical molecules. Solid hollow fiber crystallizers are compact devices that can be operated from bench to industrial scale and can be easily scaled up. They provide extremely high surface area/volume ratio that facilitates accurate control of the temperature difference between the crystallizing solution and the coolant. Therefore, they can be used to control the rate at which supersaturation is generated and to produce narrow and reproducible crystal size distributions. Due to the nature of the surface of the fibers, they also promote heterogeneous nucleation, which can lead to higher nucleation rates and smaller crystal sizes.

Solid hollow fiber crystallizers were tested in several operating modes. For low supersaturations they were operated in the feed recycling mode; they were used first as seed/nuclei generators and then as standalone crystallizers. If the crystallization kinetics of the solute to be crystallized permit it, solid hollow fiber devices can be used as standalone crystallizers in the once through operation mode or as supersaturation generation devices in combination with completely stirred tank crystallizers in the SHFC-CST in series operation mode or with in-line static mixers.

It was found that in all operation modes the SHFC acts primarily as a nuclei or supersaturation generator and it can be considered a class I system with considerable unrelieved supersaturation. This was attributed to two factors: the high cooling rates realized in SHFCs, which are orders of magnitude higher than conventional cooling equipment and the lack of mixing inside the SHFC. The latter is the dominant factor; paracetamol cooling crystallization runs clearly showed that the SHFC can be operated deep inside the labile zone without bulk crystallization taking place.

Comparison with MSMPR data from the potassium nitrate crystallization literature showed that in the feed recycling and the once through operation mode, the performance of solid hollow fiber crystallizers is characterized by broader crystal size distributions and lower reproducibility. However, this was attributed primarily to the metastability of the system described in the preceeding paragraph and the production of a large amount of fines, which block the filters resulting in slow filtration rates, localized growth on the filter and a needle-like crystal morphology. The number of crystals generated during the once through runs was about two orders of magnitude higher than the respective value for MSMPR crystallizers but lower than the SHFC-CST in series results. This fact was attributed to the lack of mixing present during the once through operation and the corresponding metastability of the system.

The SHFC-CST in series operation mode yielded excellent results. Compared to the data for potassium nitrate crystallization in MSMPR crystallizers, SHFC-CST in series arrangements yielded narrow and reproducible CSDs with mean sizes between 100-150 µm and 90% of the crystals produced in all runs performed being smaller than 370 µm. The crystals obtained were well formed and rounded presenting good filterability characteristics. Moreover, the number of crystals generated in SHFC-CST in series arrangements, is at least 2-3 orders of magnitude higher than the respective number for the MSMPR crystallizers, despite the fact that the magma density values obtained experimentally were lower than their thermodynamic limit. This, together with the small performance variations observed, was attributed to the semi-batch operation of the completely stirred tank in the SHFC-CST assembly and its small retention time. Significant performance improvements are anticipated if the CST is operated in a continuous mode or if preferably a suitably sized in-line static mixer is used downstream the SHFC. The SHFC-CST in series runs with salicylic acid clearly showed that, unlike other membrane hollow fiber based techniques studied earlier, solid hollow fiber cooling crystallization does not suffer any performance losses or additional operating difficulties if organic solvent-solute systems are used. Performance is similar to the potassium nitrate system.

The paracetamol experiments illuminated a different operating regime for SHFCC, characterized by high supersaturations and primary nucleation. This regime is important for pharmaceutical molecules or fine chemicals production. It was shown that the mixing conditions inside the SHFC can be used to carry out operation at very high supersaturation levels and essentially decouple the nucleation step from crystal growth. Such a capability does not exist in conventional cooling crystallizers. In stirred vessels, continuous, batch or semi-batch, nucleation and growth occur in the same device. High supersaturations cannot be used due to severe incrustation of the cooling surfaces and a corresponding loss in performance.

The high supersaturations applied during the paracetamol runs offer two advantages. First, the nucleation rates achieved are extremely high, considerably higher than the ones obtained in stirred cooling crystallizers. They are also 2-4 orders of magnitude higher than the results presented for potassium nitrate and salicylic acid. Consequently, the mean crystal size obtained is decreased substantially. Second, a high yield can be obtained while operating continuously and for a shorter period of time. High
yields accompanied by a controlled crystal size distribution are achievable only in batch crystallizers operated with an optimized cooling program and over a significant period of time.

The paracetamol experiments also showed that the mean crystal size can be effectively controlled by manipulating the temperature of the coolant circulated through the shell side. This was not apparent from the potassium nitrate and salicylic acid runs owing to the considerably smaller supersaturations applied. The same control capability can be potentially used for crystal morphology control and preferential unseeded polymorph crystallization.

The above conclusions are based on short-term operation of the SHFCC setup. Future investigations should clearly show the long-term characteristics of cooling crystallization in SHFCs. The experiments presented in this dissertation were all performed at Reynolds numbers between 50-300. The whole laminar regime should be investigated to see if any operational advantages stem from higher flow rates, i.e., the ability to remove more easily crystals from the fiber interior and avoid blockage. This would be useful in the case of soluble systems for which the solids loading is high and could possibly extend the operational range of SHFCs inside the labile zone in a manner similar to the paracetamol experiments. It should be kept in mind, however, that the results of Chapter 2 show that hollow fiber devices show a better thermal performance for Reynolds numbers below 500.

Scaling up is another issue that should be addressed during future studies. However, it is the author's opinion that operation at a larger scale would be less troublesome and more indicative of the advantages SHFCC offers. This is justified at several levels. First, scale-up can be performed easily by maintaining constant the ratio of the feed volumetric flow rate and the fiber cross sectional area. This would introduce minor performance variations in the shell side. Second, the presence of more fibers will make operation more stable; non-uniform local cooling and the associated generated flow disturbances, can be compensated by the large amount of fibers used. Thirdly, properly sized in-line static mixers can be used to deplete the supersaturation created from the SHFC. As already stated, the diameter of the in-line static mixer used in the experiments presented here was far from optimal. This did not allow the achievement of a high degree of mixing downstream the SHFC and the exploitation of all supersaturation generated. For a larger operational scale, such a problem would be easily overcome and the full potential of SHFCC could be realized.

CHAPTER 4

POROUS HOLLOW FIBER ANTISOLVENT CRYSTALLIZATION

In this chapter a drowning out crystallization technique based on porous hollow fiber devices is described. Miscible solvent-antisolvent pairs are considered here; immiscible systems will be presented in Chapter 5. The technique relies on the permeation of the antisolvent through a membrane to the crystallizing solution and vice versa. The ability of the membrane device to permeate the necessary amount of antisolvent or crystallizing solution is of paramount importance. Therefore, mixing experiments with the solvent-antisolvent pair were performed first to determine the maximum supersaturation that can be achieved in the lumen side of porous hollow fiber devices. Based on these experiments, the conditions during the crystallization runs were chosen. The system studied was of biological importance: an aqueous solution of an amino acid, L-asparagine monohydrate, with 2-propanol serving as the antisolvent.

4.1 Background

Antisolvent crystallization is similar to precipitation; high supersaturations are usually employed that result in primary nucleation and mixing of the crystallizing solution and the antisolvent influences heavily the final product CSD and yield. It is not a surprise then that they are often treated simultaneously in the crystallization literature and that the same operation practices are adopted. The only difference between the two techniques is the reaction constant in precipitation and its magnitude with respect to other time scales of the system. Since mixing has a predominant effect in product quality it will be briefly considered below.

The product CSD in industrial stirred crystallizers, including antisolvent addition devices, is affected by the levels of micromixing and macromixing present in the crystallizer. Two extremes of micromixing can be distinguished according to chemical reaction theory. The first one (Model I) is maximum mixedness: all fluid elements in the vessel have the same residual lifetime and mixing in the molecular scale is complete. The second (Model II) is complete segregation. In this case each fluid element behaves like a batch crystallizer that does not interact with its surrounding elements; mixing is perfect at a macroscopic scale but not existent in the molecular scale. It also occurs at the exit of the crystallizer, namely, as late as possible.

Garside and Tavare (1985) have shown that the state of micromixing can exert a dramatic influence on the crystal size distribution of an MSMPR crystallizer. The population density plot for Model II passes through a maximum and reduces to zero at a certain cut-off size, which depends on the nucleation and growth kinetics of the crystallizing system. Such a behavior with the exception that a sharp cut-off size was not observed, has already been discussed in a solid hollow fiber crystallizer for the aqueous potassium nitrate system in Figure 3.17 and is in contrast with the straight line obtained for a Model I MSMPR crystallizer. In addition, Garside and Tavare (1985) showed that complete segregation yields smaller mean size and coefficient of variation, narrower CSDs and considerably larger nucleation rates in the case where nucleation strongly depends on supersaturation, i.e., primary nucleation.

Tavare (1989) has extended this analysis to the other level of mixing, namely, macromixing. Two extremes are also distinguished here: complete mixing, which corresponds to a completely stirred tank crystallizer and complete segregation, which corresponds to a plug flow crystallizer. It was shown that for a constant supersaturation generation rate the plug flow crystallizer produces CSDs with 2-5 times lower mean size and smaller coefficient of variation. Similar conclusions have also been reported by Winter and Georgi (1985). However, at higher supersaturation generation rates, typical of primary nucleation, the plug flow crystallizer performs slightly worse than a Model II MSMPR crystallizer in terms of mean size. Therefore, at high supersaturation levels micromixing is more important than macromixing.

The above discussion sheds some light as to why industrial antisolvent crystallizers often perform poorly when a small crystal size and a narrow CSD are desirable. In this case, good micromixing should be ensured by adding the antisolvent or the crystallizing solution close to the stirrer discharge area, where, the mean specific power input ε is maximum (Baldyga and Bourne, 1999). However, in this area the fluctuations of the mean specific power input are also high and strongly dependent on the distance from the impeller (Mersmann, 2001). Consequently, the micromixing time will vary locally and this variability will also translate into supersaturation fluctuations. On the other hand, primary nucleation, which is usually obtained in antisolvent crystallization, depends strongly on the supersaturation created. Therefore, orders of magnitude fluctuations in the nucleation rate can be observed, which accordingly lead to locally different median crystal sizes and a broad CSD. If in addition macromixing is

poor, then fast local growth under high supersaturation conditions is another factor facilitating a broad CSD.

Additional complications may arise from the fact that the antisolvent and the solution have different viscosities. In the more common case where the antisolvent is added to the crystallizing solution and the antisolvent has a higher viscosity, i.e., adding an alcohol to an aqueous solution, micromixing by engulfment can be delayed significantly due to encapsulation of the antisolvent in the crystallizing solution as if both fluids were immiscible (Choplin and Villermaux, 1994). Similar complications can arise in impinging jet antisolvent crystallization and precipitation (Kirwan et al., 2003) and is probably the main obstacle to widespread usage of an otherwise successful, scaleable and robust technology.

4.2 **Operating Principle**

An illustration of the proposed technique is shown in Figure 4.1. Two variations of the technique are shown. Figure 4.1a depicts the addition of antisolvent to a crystallizing solution flowing in the lumen side of a microporous hollow fiber membrane. The antisolvent and the solution are miscible. The shell side pressure is kept higher and at a level that facilitates the appropriate antisolvent permeation rate. Note also that the exact opposite scheme, namely addition of the crystallizing solution to the antisolvent flowing in the lumen side can also be employed. Supersaturation is created locally at the mouth of a very large number of pores; the antisolvent is distributed evenly and mixing with the crystallizing solution is further facilitated by the small fiber diameter. A similar approach has recently been proposed for precipitation reactions (Zhiqian and Zhongzhou, 2002).



Figure 4.1 Porous hollow fiber antisolvent crystallization (PHFAC) operating principle: a) Permeation from shell to lumen side and b) permeation from lumen to shell side.

Figure 4.1b shows another operating scheme that can be employed in porous hollow fiber devices, namely, permeation of the tube side fluid to the shell side of the membrane device by keeping the lumen side pressure higher. The variation shown in Figure 4.1b is proposed for the first time. It presents certain advantages compared to tube side permeation. First, it is much easier to pressurize the tube side from an operational point of view. Second, permeation to the shell side does not include an appreciable pressure drop due to the additional volumetric flow rate of permeate, since in general the shell side cross sectional area is larger compared to the tube side cross sectional area. The opposite is true for permeation to the lumen side; the additional flow will result in a higher tube side pressure head for a fixed outlet pressure according to Hagen-Poiseuille law and accordingly lower transmembrane pressure along the device, which is the driving force for permeation. Thirdly, crystals formed on the outside surface of the fibers will be more easily swept away by the shell side fluid, which can also be circulated in turbulent flow. A disadvantage of the configuration shown in Figure 4.1b is the fact that only solution addition to the antisolvent is applicable. The opposite configuration would simply result in a low final superaturation due to the smaller volume of the lumen side compared to that of the shell side.

Porous hollow fiber antisolvent crystallization (PHFAC) has several advantages compared to industrial antisolvent crystallizers. The first one is related to the micromixing efficiency of porous hollow fiber devices. Due to the small diameter of the pores, typically in the submicron or the nanometer range, it is expected that permeation of the antisolvent/crystallizing solution will take place in the form of unstable droplets or jets in the micron range. Therefore, a large interfacial area between the two initially segregated fluids is generated, which is exactly the objective of mixing (Ottino and Wiggins, 2004). This has already been proved a successful method to produce fine emulsions (Joscelyne and Trägård, 2000) and will be further discussed in Chapter 5. Even in the case where non-optimal conditions are used, the droplet or jet diameter will rarely exceed 50-100 μ m. These sizes are close to or below the Kolmogorov scale, especially for viscous fluids.

To put things into perspective, the Kolmogorov scale for some common solvents is given in Table 4.1 for two different values of the mean specific power input, 1 W/kg and 10 W/kg, the latter representing an approximate upper limit for stirred crystallizers (Bourne, 2003). It is apparent that, even for low viscosity solvents, the Kolmogorov scale will be at least 10-20 μ m and in most cases about 40-50 μ m. For more viscous solvents like t-butanol the Kolmogorov scale can often exceed 100 μ m. It follows then that porous

Solvent	$\varepsilon = 1 $ W/kg	$\varepsilon = 10 \text{ W/kg}$	
Solvent	λ _K (μm)		
Water	28	16	
Ethanol	40	23	
2-Propanol	64	36	
t-Butanol	116	65	
n-Hexane	80	45	
Toluene	22	12	
Ethyl Acetate	18	10	

Table 4.1Kolmogorov Scale Achieved in Stirred Crystallizers for Some CommonSolvents at 25°C

hollow fiber devices can disperse a fluid into fine elements, whose size permits micromixing by molecular diffusion, bypassing this way the necessity of mechanical mixing. The latter is necessary to bring the feed stream down to the Kolmogorov scale. This inherent capability of porous hollow fiber devices will be more pronounced in the case of viscous systems and can also result in a significant energy consumption reduction. It can also be used to overcome the limitations of impinging jet mixers when mixing viscous fluids.

Another inherent advantage of porous hollow fiber devices is the extremely large number of feed introduction points, namely, the membrane pores. It is known that the performance of chemical reactors is improved by increasing the number of feed points (Bourne, 2003; Sirkar et al., 1999). Drawing the analogy for antisolvent crystallization, one would anticipate that the introduction of the antisolvent/crystallizing solution through an extremely large number of pores would simply result in a more uniform supersaturation generation and better performance compared to single feed points used in stirred tanks. It should also be emphasized that practical construction difficulties preclude the use of more than 3-4 feed addition points in stirred tanks (Bourne, 2003).

The addition of the antisolvent through the pores in a direction perpendicular to the main flow and in a random manner both in time and space can yet serve another purpose: the disruption of the boundary layer near the wall. In this way, three-dimensional fluctuations of the velocity field are introduced, which are characteristic of turbulent flow and mixing can become more efficient. A similar mixing improvement was also observed during experiments in microconduits, where up to three side channels were used to impose cross flows to the main velocity field (Bottausci et al., 2004; Tabeling et al., 2004). The cross flow also promotes mixing in the radial direction, which is absent in the case of laminar flow inside ducts. It will be later shown that the velocity of the liquid permeated through the pores can be as high as 100-500 μ m/s, which compares well to the fiber radii used in this dissertation; the time necessary for convection in the radial direction can be comparable to the residence time of the liquid inside the fibers. Such a condition, however, will not be present when the tube side fluid is dispersed in the shell side of porous hollow fiber devices.

Additional advantages of porous hollow fiber devices are similar to the ones reported in Chapters 2 and 3 for polymeric hollow fiber heat exchangers and solid hollow fiber crystallizers respectively. These include a high surface area/volume ratio, which can be potentially utilized to increase the amount of feed processed and therefore maximize the product yield on a volumetric equipment basis. Further, control of flow conditions and residence time is easy to achieve, if the operating scheme shown in Figure 4.1a is used. These parameters together with the shell side pressure determine completely the supersaturation generation inside the membrane hollow fibers. Upon scale up all three parameters can be maintained the same, a simplicity not encountered in stirred crystallizers or impinging jet mixers. Performance will be the same whether operating at bench or industrial scale. The same will be also true for the operating scheme shown in Figure 4.1b with the exception that shell side flow maldistribution, channeling and bypassing can cause variations in performance (Ho and Sirkar, 1992). The latter however can be minimized if cross flow configurations are used.

4.3 Experimental

4.3.1 Chemicals and Materials

Deionized water was used as the tube side liquid for the mixing experiments. Nearly saturated solutions (concentration of about 25 g/L) of L-asparagine monohydrate (99%, Fisher Scientific, Pittsburgh, PA) in deionized water were used during the crystallization experiments. The antisolvent circulated in the shell side of the Membrane Hollow Fiber Crystallizer (MHFC) was 2-propanol (IPA, 99%, Fisher Scientific, Pittsburgh, PA); IPA was also used as the suspension medium for the size determination of L-asparagine crystals by laser diffraction.

Porous polypropylene hollow fibers (Celgard X-20) of $350/400\mu m$ ID/OD (Celgard Inc., Charlotte, NC) were used for the fabrication of five modules whose geometrical characteristics are shown in Table 4.2. Celgard X-20 fibers have a pore size of 0.03 μm , a porosity ε_m of 0.4 and a tortuosity τ_m of 2.4 (Prasad and Sirkar, 1988). The shell side in all cases was made of FEP tubing. Module fabrication procedures are similar

Module #	N	Active length (cm)	Total length (cm)	D _s (cm)	A_o (cm ²)
X-20 #1	23	19.1	23.5	0.48	55
X-20 #2	23	30.0	34.0	0.48	87
X-20 #3	23	19.0	22.9	0.76	55
X-20 #4	23	29.5	33.5	0.76	85
X-20 #5	11	29.2	33.2	0.76	40

Table 4.2 Geometrical Characteristics of Membrane Hollow Fiber Crystallizers

to the ones already described in Chapter 2 for PHFHEs.

4.3.2 Apparatus and Procedure

Figure 4.2 illustrates the experimental setup used for PHFAC when permeation of the shell side fluid was performed. A drawing of the apparatus is given in Figure 4.2a, while a photograph of the experimental setup is shown in Figure 4.2b. The same setup was used for the mixing experiments. Therefore, the description that follows is also applicable in this case with the difference that instead of a crystallizing solution, deionized water was used and no filtration or additional mixing steps were taken.

The feed solution was pumped to the lumen side of the MHFC by means of a peristaltic pump (Cole Parmer, Vernon Hills, IL). Its flow rate was measured with a flow meter (Cole Parmer, Vernon Hills, IL). A check valve (V1) was placed right before the entrance of the MHFC, to prevent antisolvent leakage in the connecting tubing. The MHFC was positioned in a vertical manner to facilitate crystal removal from the hollow fibers. The antisolvent was circulated countercurrently in the shell side by means of a peristaltic pump (Cole Parmer, Vernon Hills, IL). Check valve V2 (Crum & Company, Mountainside, NJ), adjustable in the range between 3-50 psig, was used to maintain the shell side pressure at appropriate levels. A peristaltic pump was used instead of a nitrogen cylinder to induce pulsations in the shell side pressure and consequently in the permeant flow. These pulsations are known to improve mixing (Ottino and Wiggins, 2004). More importantly, they can also serve as a means to push newly formed crystals away from the inside surface of the hollow fibers. Two pressure gauges were used in the tube and shell side inlets to record the pressure head. Pressure in the shell side can be





Figure 4.2 Experimental setup for porous hollow fiber antisolvent crystallization – Permeation to the tube side: a) Drawing of the apparatus and b) photograph of the apparatus.

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considered constant and equal to the inlet value because the pressure drop is very small. The tube side exit pressure was in all cases 1 bar.

Each crystallization run was performed as follows. First, the tube side flow was switched on and the flow rate and inlet head were measured without any antisolvent being circulated at the shell side. Initially, deionized water was circulated to avoid crystallization in the small space between the inlet of the MHFC and check valve V1. After 5-10 min the antisolvent flow was initiated in the shell side of the MHFC and permeation of the antisolvent under a transmembrane pressure difference started. The flow rate of the tube side exit stream was measured at appropriate time intervals and samples were obtained and analyzed for concentration determination. After 30-35 min. steady state permeation conditions were established inside the MHFC. At that time, the feed flow was switched to the crystallizing solution. Sampling and flow rate measurements were continued to determine any possible changes in antisolvent flux and in the composition of the stream exiting the lumen side of the MHFC.

Periodically, the feed exit stream from the MHFC was treated in a manner similar to the one described in Chapter 3 for solid hollow fiber cooling crystallization. Directing the feed outlet stream immediately to the filters one obtains the MHFC once through mode of operation. Alternatively, the solution exiting the MHFC can be collected in a CST, where it is stirred for a predetermined amount of time (1-2 min.) and then filtered. This is the MHFC-CST in series operation mode. During all runs performed in this dissertation the CST was operated in a semi-batch mode. Note also, that other mixing devices, i.e., static mixers, can be also used. Crystals obtained on the filters were thoroughly dried and then weighed. The volume of filtrate collected was also measured to obtain the magma density of the suspension exiting the experimental setup. Two kinds of filters were used throughout this study: glass fiber filters (Whatman 934-AH) with a cutoff size of 1.5 μ m and hydrophilized PVDF membranes (Pall Corp., NY) with a cutoff size of 0.2 μ m.

Figures 4.3a and 4.3b show a drawing and a photograph respectively of the experimental setup used for PHFAC by permeation of the crystallizing solution to the shell side. The apparatus shown in Figure 4.3 is similar to the one described in Figure 4.2. The major difference is that in the present configuration the lumen side of the MHFC is pressurized by means of check valve V1. Also, an additional pressure gauge was placed in the tube side exit of the MHFC and the crystallizing solution was recycled to the feed tank. Finally, the antisolvent was circulated co-currently to the crystallizing solution. Such an arrangement simply facilitates the removal of newly formed crystals.

The experimental procedure adopted is described below. First, the tube side solution was pressurized, the solution was left to permeate to the shell side for about 5 min. and the flow rate of the permeate was measured. Then, the antisolvent pump was turned on at a high speed to ensure quick removal of the solution already filling the shell side. Subsequently, the antisolvent flow rate was adjusted at appropriate operating levels. The latter were about 10 times higher than the permeate flow rate. Such difference was necessitated solely by the geometrical design of the male run tees used in the manufacturing of the MHFCs, which promotes blocking phenomena at the shell side exit. This issue will be further addressed in the discussion of the results obtained. The shell side exit stream was treated again in two ways; either directed immediately to the filters





(b)

Figure 4.3 Experimental setup for porous hollow fiber antisolvent crystallization, permeation to the shell side: a) Drawing of the apparatus and b) photograph of the apparatus.

in an once through mode or collected in a semibatch CST, stirred and then filtered. The filters used were the same reported for the experimental setup shown in Figure 4.2.

4.3.3 Analytical Methods

The feed concentration of L-asparagine monohydrate aqueous solutions was determined gravimetrically for all runs. The concentration of 2-propanol was determined based on two methods. The first was based on density measurements. The latter were performed with an Anton-Paar DMA-46 (Anton Paar, Graz, Austria) density meter at 25°C. This technique was used to obtain the % weight concentration of IPA in the feed exit stream, while the experimental runs were being performed; however, it was applied in an off-line manner. The dependence of the % weight IPA concentration of aqueous IPA solutions on density was obtained from the literature (Perry and Green, 1999). The second technique used was gas chromatography. Analysis was performed in an HP 6890 series gas chromatography system equipped with a HP 7694 automated headspace sampler (Agilent Technologies, Palo Alto, CA). A polar column 30 m x 0.0530 mm x 1.0 μ m film thickness was used for the analysis and a sample calibration curve are given in Appendix D.

Crystal sizing was performed with a Coulter LS-230 laser diffraction instrument. In all measurements an optical model based on the complete Mie theory was used. The refractive index of the suspension medium was measured between 20-28°C with an Abbe-3L refractometer with a precision of 0.0001 refractive index units. The suspension medium used for crystal sizing was isopropanol. The refractive index of L-asparagine monohydrate was determined to the third decimal place by the method of oblique illumination (Phillips, 1971). The latter is described in more detail in Appendix D. The shape factor of L-asparagine monohydrate crystals was taken equal to 1.09 in accordance with literature values (Mahajan et al., 1991). L-asparagine monohydrate crystals were found to form loose agglomerates. The latter were destroyed by mild sonication prior to measurement.

4.4 **Results and Discussion**

4.4.1 Mixing Experiments

Mixing experiments during which isopropanol was permeated from the shell to the tube side of porous hollow fiber devices, where deionized water was circulated, were performed with two goals. The first one was to determine the maximum amount of supersaturation that can be achieved by a MHFC based on the final IPA concentration and the solubility curve of L-asparagine monohydrate in aqueous isopropanol solutions. (Orella and Kirwan, 1989; 1991). The second goal was to determine the dependence of the final IPA concentration obtained, on the main operating parameters, namely, the tube side flow rate and the transmembrane pressure. The latter was calculated as the average of the pressure difference at the inlet and the outlet of the MHFC:

$$\Delta P_m = \frac{\left(P_{s,in} - P_{t,in}\right) + \left(P_{s,out} - P_{t,out}\right)}{2} \tag{4.1}$$

Figures 4.4 and 4.5 show respectively the IPA weight fraction in the tube side outlet stream and the individual and total tube side flow rates as a function of time. Figure 4.4 shows that, immediately after the shell side stream is brought into the MHFC,



Figure 4.4 Tube side exit weight fraction of IPA as a function of time. Mixing experiments, run 1, module X-20 #2.



Figure 4.5 Total and individual flow rates inside the MHFC as a function of time. Mixing experiments, run 1, module X-20 #2.

isopropanol displaces the water completely out of the membrane hollow fibers. For the first 2-3 min. almost pure isopropanol exits the tube side of the MHFC. This is also apparent in Figure 4.5; the IPA flow rate goes through a maximum in the first few minutes of operation while the opposite is true for the deionized water flow rate. The complete displacement of water from IPA during startup was also confirmed experimentally by observing a momentary interruption of the tube side flow. Figures 4.4 and 4.5 also show that gradually the water flow increased with a corresponding decrease of the IPA concentration in the tube side outlet stream. Inspection of Figures 4.4 and 4.5 also reveals that steady state conditions were approached after about 10 min. of operation.

The phenomena mentioned above dictated the practice described in Section 4.3 of initiating the crystallization experiments by first circulating pure solvent and then the crystallization solution. Adopting this operating practice, stable operation is facilitated in two ways. First, crystallization of the solute right before the entrance of the MHFC and a consequent blockage of the membrane hollow fibers is avoided. Second, by allowing the system to run for some time before the crystallizing solution is introduced in the tube side of the MHFC, one obtains a stable flow of antisolvent, which can potentially sweep away crystals formed near the wall and prevent pore blockage.

Figure 4.6 illustrates the pressure head profiles in both sides of the MHFC as well as the total head difference at the inlet of the MHFC as a function of time. In accordance with Figures 4.4 and 4.5, Figure 4.6 shows that steady state values are obtained quickly. It also shows an increase in the tube side pressure head, which is more than 10 times the value before IPA permeation started. This difference cannot be explained only on the



Figure 4.6 Pressure head profiles in a MHFC as a function of time. Mixing experiments, run 1, module X-20 #2.

basis of the additional flow induced by the permeation of IPA. Inspection of Figure 4.5 shows that the latter is only about 50% of the initial water flow rate. Another reason for increased pressure drop in the tube side is the higher viscosity of aqueous IPA solutions compared to pure water. For the IPA weight fraction obtained in the run shown in Figure 4.4, the viscosity of the final mixture is about 3 times higher than water (Tanaka et al., 1987). The pressure drop according to Hagen-Poiseuille law is given by

$$\frac{\Delta P}{L} = \frac{128\mu V}{\pi D^4} \tag{4.2}$$

Equation (4.2) shows that the increased viscosity and flow rate due to IPA permeation have a synergistic effect. However, this could increase the total head by a factor of 4 or 5, which is still lower compared to what was observed in practice. The additional pressure drop observed is possibly caused by the flow of IPA perpendicular to the direction of the main flow. This cross flow distorts the laminar velocity profile assumed in the derivation of Hagen-Poiseuille's law and does not allow for its complete development. The relationships presented in Appendix C for the calculation of the friction factor in the hydrodynamic entrance regime show that higher pressure drops are obtained for developing flow. In addition, the cross flow creates three-dimensional fluctuations of the velocity field, which are characteristic of turbulent flow and could possibly cause an earlier transition to turbulence; the latter phenomenon has already been claimed as a source of higher friction factors in microchannels without any cross flows entering the system (Mala and Li, 1999; Guo and Li, 2003a; 2003b).

Figure 4.7 shows a plot of the IPA flux vs. the transmembrane pressure. The flux was calculated based on the measured IPA concentration, the outside fiber diameter and other experimentally obtained parameters from the following relationship:

$$J_{AS} = \frac{C_{AS}}{1 + C_{AS}} \frac{m_{tot}}{\rho_{AS}} \frac{1}{N\pi D_o L}$$
(4.3)

A linear relationship is obtained between the antisolvent flux and the transmembrane pressure, as anticipated. Consequently, raising the shell side pressure when performing PHFAC, will result in a higher mean supersaturation.

Figure 4.8 shows a plot of the weight fraction of IPA in the tube exit stream as a function of the velocity of water after IPA was introduced through the shell side. All three runs presented in Figure 4.8 were performed at the same shell side pressure. It is apparent that the net result of keeping the shell side pressure constant and increasing the water flow rate is to reduce the IPA concentration in the exit stream. Therefore, if crystallization experiments were performed, high supersaturations would be obtained only when the crystallizing solution flow rate is kept low.

Figure 4.9 illustrates the cross flow permeation velocity of IPA achieved in the mixing experiments described in this section. The cross flow velocity of the permeate can be calculated from the following relationship:

$$u_{AS,cr} = 4J_{AS} \frac{D_o}{\left(D_o + D_i\right)} \frac{\tau_m}{\varepsilon_m}$$
(4.4)

Equation (4.4) is based on the assumption of pores of a circular cross section without any constriction or enlargement, which however can be tortuous. Despite the fact that such pore morphology is idealized, it is closer to reality; the pore volume depends more on the



Figure 4.7 IPA flux as a function of transmembrane pressure.



Figure 4.8 Weight fraction of IPA in the tube side exit stream as a function of water flow rate.



Figure 4.9 Cross flow permeation velocity in porous hollow fiber devices as a function of transmembrane pressure.

membrane tortuosity compared to its local diameter. Details for the derivation of Equation (4.4) are given in Appendix F.

It is evident from Figure 4.9 that the cross flow velocity of the permeate is appreciable, especially if one considers the diameter of the fibers used. Therefore, the cross flow of the permeate distorts the parabolic velocity profile of the main tube side stream, creates three-dimensional velocity fluctuations and enhances radial mixing.

The cross flow velocities shown in Figure 4.9 permit radial mixing on a time scale that is comparable to the mean residence time of the tube side fluid inside the MHFC. Figure 4.10 shows a plot of the time required for the permeate to be convectively transported to the hollow fiber centerline with respect to the mean residence time. The former is simply found from

$$t_{cen} = \frac{D_i}{2} \frac{1}{u_{AS,cr}} \tag{4.5}$$

For most of the runs performed, this time is 1-2 times smaller than the mean residence time inside the device. This further proves that radial mixing in porous hollow fiber devices is significant. It can also be improved by using higher transmembrane pressures, longer devices and/or lower tube side velocities. In this aspect, the radial mixing problem in porous hollow fiber devices is similar to the heat transfer rating problem for polymeric hollow fiber heat exchangers (PHFHEs), already discussed in Chapter 2; the analogy between the transmembrane pressure and the temperature difference is straightforward.



Figure 4.10 Radial mixing time scale vs. mean residence time inside a MHFC.

4.4.2 Crystallization of L-Asparagine Monohydrate

In this section the results of the crystallization runs of L-asparagine monohydrate from aqueous solutions will be presented. This system has already been studied in the literature (Mahajan et al. 1991) for relatively moderate supersaturations. Therefore, a first comparison of PHFAC with antisolvent stirred crystallizers will be attempted. First, the results obtained with permeation of the antisolvent to the tube side will be presented. The opposite operation mode, namely, permeation of the crystallizing solution from the tube side to the antisolvent flowing in the shell side is described next.

Figure 4.11 shows a % volume differential curve obtained for one run performed with antisolvent permeating to the tube side and the MHFC-CST in series operation mode. The sample was obtained 10 min. after the flow at the tube side was switched from water to the L-asparagine solution. The operating conditions during the run are also shown, as well as one run obtained in a batch stirred crystallizer (Mahajan et al., 1991). The latter was obtained at approximately the same IPA concentration but at a lower L-asparagine concentration in the aqueous solution. Therefore, the supersaturations involved in the two runs were quite different and the comparison can only be qualitative.

Figure 4.11 shows first that the shape of the CSD is reasonably symmetric with the exception of a small peak at around 15 μ m. This was also confirmed by a relatively low coefficient of variation of 46%. Second, most crystals produced are below 100 μ m and the whole CSD is confined below 200 μ m. Consequently, PHFAC can offer good CSD control. Comparing the curve obtained in the PHFAC setup to that in a batch stirred vessel, it is apparent that the former is shifted towards smaller sizes. This shows the potential of porous hollow fiber devices to produce small crystals especially if one



Figure 4.11 % Volume differential crystal size distribution for antisolvent crystallization of L-asparagine monohydrate in porous hollow fiber devices – Permeation of antisolvent to the tube side. Operating conditions: module Celgard X-20 #2, $u_t = 0.3 \text{ m s}^{-1}$, $\Delta C = 0.019 \text{ g/g}$.

considers that 10 times higher supersaturation was used in the PHFAC run. This fact is also indicative of higher nucleation rates. For the same nucleation rate, higher supersaturation would simply translate to higher crystal growth rates and correspondingly larger crystals.

Despite these encouraging results, a decrease in the rate at which IPA permeated to the tube side, shown in Figure 4.12, was experienced shortly after the crystallizing solution was circulated through the tube side. Also shown for comparison purposes is the permeation rate of IPA in the case of a mixing experiment, during which no solute was present. The two runs were performed under slightly different shell side pressures; however, a direct comparison of the shape of the curves is pertinent. It is apparent from Figure 4.12 that the presence of the solute results in a sharp decrease of the antisolvent permeation rate in a rather short time after the introduction of the crystallizing solution. Such a decrease was not experienced during the mixing experiment; the permeation rate remained steady for the whole run duration after the initial transitional stage. The same behavior was observed for two additional runs performed.

The decrease of the antisolvent permeation rate leads to a situation where the supersaturation generated decreases with time. Clearly, this phenomenon is undesirable and is also one of the weaknesses of other membrane based crystallization techniques, namely, reverse osmosis (Azoury et al., 1986a), membrane distillation (Curcio et al., 2001) and precipitation in membrane reactors (Zhiqian and Zongzou, 2002). Pore blockage by crystals formed near the wall seems to be the most plausible explanation for the experimental behavior observed.



Figure 4.12 Comparison of IPA flow rate as a function of time for a crystallization and a mixing experiment.

However, more insight on the mechanism that leads to antisolvent flux decline can be gained from Figure 4.13, which shows the pressure head profiles obtained during the crystallization run presented in Figures 4.11 and 4.12. Comparing Figures 4.12 and 4.13 it is evident that the antisolvent permeation rate decrease is accompanied by a corresponding decrease in the transmembrane pressure and an increase of the tube side pressure head. These trends cannot be explained in terms of pore blockage only. They cannot also be rationalized in terms of the explanations given in Subsection 4.4.1 for the corresponding increase of the tube side pressure head during the mixing experiments. In the crystallization run, the viscosity of the final solution decreases with time due to the lower IPA concentration and the total flow rate also decreases with time due to the decreased IPA permeation rate. Consequently, according to Equation (4.2) the pressure drop inside the fibers and hence the pressure head should decrease, unless there is a considerable rise in the solution viscosity due to precipitation. The only other mechanism to explain the increased resistance to flow observed is gradual fiber blockage. A similar phenomenon was also observed in the case of crystallization by reverse osmosis (Azoury et al., 1986a) and it limits the applicability of PHFAC by permeation of the antisolvent to the tube side.

Figures 4.14 and 4.15 show typical % volume differential and % volume cumulative undersize CSDs respectively for PHFAC runs with permeation of the crystallizing solution to the antisolvent flowing in the shell side. Two curves are shown: one for the MHFC-CST in series and one for the once through operation mode. Also included is a curve for a run performed in a batch stirred crystallizer obtained from the literature (Mahajan et al., 1991). The comparison between PHFAC and the literature data



Figure 4.13 Antisolvent crystallization of L-asparagine monohydrate in porous hollow fiber devices, permeation of antisolvent to the tube side. Pressure head profiles as a function of time. Operating conditions as in Figure 4.11.


Figure 4.14 Typical % volume differential crystal size distributions for antisolvent crystallization of L-asparagine monohydrate in porous hollow fiber devices – Permeation of crystallizing solution to the shell side.



Figure 4.15 Typical % volume cumulative undersize crystal size distributions for antisolvent crystallization of L-asparagine monohydrate in porous hollow fiber devices – Permeation of crystallizing solution to the shell side.

can only be qualitative due to the different levels of supersaturation included. Nonetheless, it is indicative of the differences between the two techniques.

Note also that despite the fact that the crystallizing solution is fed to an antisolvent environment, the final supersaturation is relatively low. This can be attributed to the high antisolvent circulation rate used. The latter was necessary to avoid clogging of the shell side exit: the male run tees used for the MHFC fabrication have openings that are much narrower than the nominal shell side diameter. If different fittings or a different shell side configuration were used, the antisolvent flow rate could be adjusted appropriately and higher supersaturations and higher yields could be obtained. These issues will be further discussed below.

Figure 4.14 shows that in once through operation the mode of the distribution is smaller compared to the MHFC-CST in series run. However, the CSD is broader as evident from its tail at larger sizes. Figure 4.15 further supports these observations; smaller crystal sizes are obtained up to the 70th percentile with considerable broadening occurring at the high end of the CSD due to localized growth. This is in accordance with the theoretical results of Garside and Tavare (1985) and Tavare (1989). In once through operation, the MHFC is more closely approximated by plug flow, while in the MHFC-CST in series operation mode the PHFAC experimental assembly can be considered as a partially segregated MSMPR crystallizer. For the low levels of supersaturation involved during the runs shown in Figures 4.14 and 4.15, this simply means that one should anticipate smaller median and consequently smaller mode sizes in once through operation. The opposite would be true for higher supersaturations. In

addition, the presence of the CST increases the overall residence time of the crystals inside the apparatus and correspondingly their size.

Figures 4.14 and 4.15 also show that the CSDs obtained by PHFAC are shifted towards smaller sizes compared to batch stirred vessels. The median size obtained in the PHFAC setup is 37 μ m compared to 126 μ m for the stirred crystallizer, a three-fold difference. This can be attributed to the segregation effects induced by the MHFC. Tavare (1989) has shown that such effects are responsible for lower median sizes at a constant supersaturation generation rate. In addition, Figure 4.15 illustrates that the CSDs obtained can be confined below 100 μ m, a range especially useful for crystalline pharmaceutical products for which bioavailability often dictates the desired CSD.

The segregation effect introduced by the MHFC is clearly shown in Figure 4.16, where the population density curves for the runs of Figures 4.14 and 4.15 are presented. There is a characteristic maximum in both curves. This has been observed numerous times for products obtained in industrial stirred crystallizers (Tavare, 1989) and has been modeled and explained as the effect of a plug flow zone inside the crystallizer. The same behavior, albeit less pronounced, has also been observed in Figure 3.17 for solid hollow fiber cooling crystallization. Compared to the batch stirred vessel both PHFAC runs produced a higher number of smaller crystals as the population density plot of Figure 4.16 reveals. However, this fact can also be attributed to the higher supersaturation levels during the PHFAC runs and the correspondingly higher nucleation rates.

Next, a more comprehensive examination of the CSD characteristics obtained during the PHFAC runs with permeation of the crystallizing solution to the antisolvent will be attempted. This is similar to the one already presented in Chapter 3 for the



Figure 4.16 Typical population density plots for antisolvent crystallization of L-asparagine monohydrate in porous hollow fiber devices – Permeation of crystallizing solution to the shell side.

potassium nitrate runs. However, it should be mentioned that only a limited number of runs were performed and the results presented here are qualitative. The reason was that the geometry of the MHFCs used was not optimal. As already stated, the male run tees used to fabricate the MHFCs had openings that were much smaller than the nominal diameter of the shell side. These points were susceptible to fouling and necessitated the use of high antisolvent flow rates to prolong operational time. In addition, the ability to pack a large number of fibers in the shell side, beneficial for heat transfer and cooling crystallization, is not optimal for the configuration described here. A more open arrangement is needed. A MHFC with a shell of rectangular cross-section, a staggeredfiber arrangement in the form of flat nets spaced a few fiber diameters apart and cross flow of the antisolvent would be a better albeit considerably more challenging configuration to implement and test. Moreover, special consideration should be given in the design of the shell side inlet and outlet.

Figures 4.17 and 4.18 show respectively plots of the mean crystal size and its standard deviation vs. supersaturation. It is evident from both Figures that the presence of a mixing device downstream the MHFC is beneficial; the mean size obtained in the MHFC-CST in series runs is confined between 33 and 40 µm compared to a range of 34-86 µm for once through operation. Moreover, there seems to be a linear dependence of the mean crystal size on the supersaturation applied, although the limited number of data points does not allow generalizations. However, it should be noticed that this linear dependence would still hold if the run presented in Figure 4.11, which was performed at much higher supersaturation levels, was also included. The increase of the mean size with supersaturation can be explained in terms of two factors that act in a synergistic way. The



Figure 4.17 Mean crystal size obtained during antisolvent crystallization of L-asparagine monohydrate in porous hollow fiber devices – Permeation of crystallizing solution to the shell side.



Figure 4.18 SD of the mean crystal size obtained during antisolvent crystallization of L-asparagine monohydrate in porous hollow fiber devices – Permeation of crystallizing solution to the shell side.

first one is the relatively flat nucleation rates due to the low supersaturations involved. The second one is the increase of the crystal growth rate with supersaturation. It should also be noted that a similar shift towards larger sizes with an increase in supersaturation was also observed by Mahajan et al. (1991) for lower supersaturations.

The same clear dependence of mean size on supersaturation is not apparent in Figure 4.17 for the once through runs. The results are clearly more scattered and less reproducible. This can be attributed to local supersaturation generation and depletion. The former is responsible for nucleation; once the nuclei are formed, supersaturation is quickly depleted by growth. However, these phenomena are local due to the absence of substantial mixing and when averaged for the whole device variability in the results is obtained. As a result, much higher CV values are obtained as shown in Figure 4.19 compared to the MHFC-CST in series runs. For the latter, the CV is always lower than the theoretical limit of 50% for MSMPR crystallizers.

Figure 4.20 shows a plot of the median crystal size with respect to supersaturation. An almost linear increase is observed for the MHFC-CST in series runs, while the results are scattered for the once through operation mode. The linear increase of the median crystal size observed is in accordance with the theoretical predictions of Tavare (1989) for segregated MSMPR crystallizers, in which the supersaturation generation rate is low. In the present configuration, the segregation effect is caused by the MHFC; its influence was already illustrated in the population density plots of Figure 4.16. However, it is noted that at high supersaturations the theoretical model predicted the existence of a maximum and a subsequent decrease of median size with supersaturation.



Figure 4.19 Crystal size distribution CV obtained during antisolvent crystallization of L-asparagine monohydrate in porous hollow fiber devices – Permeation of crystallizing solution to the shell side.



Figure 4.20 Median crystal size obtained during antisolvent crystallization of L-asparagine monohydrate in porous hollow fiber devices – Permeation of crystallizing solution to the shell side.

Figure 4.21 illustrates a plot of the d_{90} size obtained during the PHFAC runs. Again, a linear dependence is observed for the MHFC-CST in series runs and less reproducible results for once through operation. More important however, is the fact that a combination of a MHFC and a mixing device can yield distributions for which 90% of the crystals are smaller than 70 µm. If one considers that the MHFCs used in this dissertation are not optimally designed, these sizes are very low. Confining the CSD close or below this limit would be sufficient for most pharmaceutical applications. The same conclusion applies to a lesser extent for the once through runs. The CSD can be confined at sizes close or below 150 µm. These numbers compare favorably with existing literature data for L-asparagine antisolvent crystallization. The maximum size reported in MSMPR crystallizers is 300 µm, while for batch crystallization the respective number is 200 µm (Mahajan et al., 1991).

Figure 4.22 shows a plot of the nucleation rates obtained. Nucleation rates were calculated by the following relationship, which also utilizes Equation (3.6):

$$B_o = \frac{\int_{l_1}^{l_2} n(L) dL}{t_{samp}}$$
(4.6)

It is evident in Figure 4.22 that a linear increase between the nucleation rate and supersaturation exists for the once through runs. This is expected in terms of primary nucleation theory: a small change in supersaturation results in a large difference in nucleation rate. The same behavior is not observed for the MHFC-CST in series runs. However, the limited number of runs precludes any definite conclusions. Finally, a comparison of the nucleation rates shown in Figure 4.22 with literature data will be



Figure 4.21 The value of the d_{90} size obtained during antisolvent crystallization of L-asparagine monohydrate in porous hollow fiber devices – Permeation of crystallizing solution to the shell side.



Figure 4.22 Nucleation rates obtained during antisolvent crystallization of L-asparagine in porous hollow fiber devices – Permeation of crystallizing solution to the shell side.

attempted. The nucleation rates observed in batch stirred crystallizers (Mahajan et al., 1991) were between 10^5 and 10^7 no/m³ s for supersaturations ranging from 0.001 to 0.002 g/g. Inspection of Figure 4.22 reveals that the nucleation rates obtained in the PHFAC apparatus for the same supersaturations are 1-5 orders of magnitude higher. The superior performance in terms of nucleation rate observed for solid hollow fiber cooling crystallization is also characteristic of porous hollow fiber antisolvent crystallization.

4.5 Conclusions

Porous hollow fiber devices offer the same flexibility and characteristics observed in polymeric hollow fiber heat exchangers and solid hollow fiber crystallizers. They are easy to design and control and their scale up is straightforward. Used as mixing devices they offer various advantages compared to traditional mixing equipment. For a given design of the porous hollow fiber device, one can accurately control the final concentration of the added component in the exit stream, by simply manipulating only two operating parameters, the shell side pressure and the tube side flow rate. In addition, by packing more or less fibers at a given shell, one can increase or decrease respectively the final concentration of the added component for the same feed volumetric throughput.

For the experiments presented here, final concentrations of up to 30% weight were achieved; higher values are also possible by further raising the shell side pressure and/or lowering the tube side velocity. These concentrations are considerably higher compared to what has been practiced until now in membrane reactors, especially for liquid phase reactions (Sirkar et al., 1999). They also point to the possibility of carrying out liquid phase reactions in a 1:1 stoichiometric ratio, a task that has not been performed until now in membrane reactors.

The operating conditions for achieving this goal are favorable. Higher concentrations of the added component are obtained at low tube side velocities, which in turn allow for larger residence times inside the reactor. Therefore, more time is available for the reaction to occur. Also, mixing in the radial direction will be considerably enhanced; the results presented in this dissertation show that the permeate flow can reach the centerline of the fibers very quickly. Further improvement can also be obtained by using smaller fiber diameters.

Future investigations should address in more detail the issue of mixing achieved in porous hollow fiber devices. Macromixing can be examined by residence time distribution studies. An in-line device for concentration measurement would be particularly useful for this purpose. Micromixing issues can be examined by carrying out a set of suitable reactions, i.e., competitive-consecutive reactions (Baldyga and Bourne, 1999; Bourne, 2003). Such studies could possibly elucidate the micromixing efficiency of porous hollow fiber devices and lead to a new method of mixing characterized by low energy input and the absence of mechanical components inside the mixing device, i.e., stirrers and motors.

The crystallization runs with permeation of the antisolvent to the tube side encountered difficulties. Despite the fact that crystal samples, whose crystal size distribution was shifted to smaller sizes compared to literature data obtained in batch stirred crystallizers, were obtained, the operation of the MHFCs was characterized by a decrease of the permeation rate of the antisolvent and consequently the supersaturation generated with time. Clearly, such an effect is undesirable and leads to a situation where crystallization cannot be continued for a prolonged period of time. This decrease in antisolvent flux is in accordance with previous crystallization and precipitation studies in membrane hollow fiber devices. It was attributed primarily to pore blockage combined with fiber blockage by newly formed crystals.

The crystallization runs with permeation of the crystallizing solution to the antisolvent flowing at the shell side can be considered successful. They prove the applicability of PHFAC and also show promising results. Two operating modes were implemented for the system L-asparagine in water and IPA (antisolvent), which were similar to the ones used for solid hollow fiber cooling crystallization: the MHFC-CST in series and the once through mode of operation.

The crystal size distributions obtained for both operating modes were shifted to smaller sizes compared to literature data obtained in batch stirred vessels obtained approximately under the same supersaturation conditions. About 90% percent of the crystals produced were smaller than 70 μ m for the MHFC-CST in series runs, while the respective value for the once through operation mode was around 150 μ m. These numbers compare favorably to 200 μ m and 300 μ m obtained respectively in batch stirred vessels and MSMPR crystallizers. They are also sufficient for most crystalline pharmaceutical products, for which bioavailability and/or formulation concerns dictate the desired CSD.

Mean crystal sizes ranging between 33-40 μ m and 34-86 μ m were obtained for the MHFC-CST in series and the once through operation mode respectively. The latter was characterized by broader distributions compared to the MHFC-CST in series runs, as indicated by the SD of the mean crystal size and the CV of the CSD, due to local supersaturation generation and depletion. In addition, the mean, the median and the d₉₀ sizes for the MHFC-CST in series runs showed a linear and consequently predictable dependence on supersaturation, which was not found for the once through runs. Therefore, the combination of a MHFC with a downstream mixing device is more advantageous. Static mixers could also offer an alternative to stirred tanks. Finally, in agreement with the results of Chapter 3, porous hollow fiber devices present superior nucleation performance compared to stirred vessels; the nucleation rates obtained in the PHFAC experimental setup were 1-5 orders of magnitude higher than the ones achieved in batch stirred vessels.

The CSD characteristics of MHFCs presented above can be considerably improved. The design of the devices used in this dissertation was far from optimal. Future studies should address this issue in more detail. The cylindrical geometry used, useful in heat transfer and cooling crystallization applications, results in close packing of the fibers in a cylindrical shell, whose diameter is primarily dictated by the smallest opening of the male run tees used for the fabrication of the MHFCs. This can promote crystal entrapment in the intrafiber space and subsequent gradual blockage. Although this phenomenon was not observed for the larger part of the crystallizer, it took place at the shell side outlet and necessitated the use of high antisolvent circulation rates.

Better performance can be achieved by implementing a more open geometry. A shell of rectangular cross section would be very useful. In such an arrangement the fibers can be placed in a layered structure with a suitable spacing and a staggered fiber arrangement. Moreover, cross flow of the antisolvent can be easily applied. This would help to sweep newly formed crystals from the fiber surface and improve mixing in the shell side of the device. Finally, the shell side inlet and outlet should be carefully designed to promote crystal removal from the MHFC interior. Computational fluid dynamics could be used as a guide for the selection and implementation of the appropriate shape for the shell inlet and outlet ports.

CHAPTER 5

POROUS HOLLOW FIBER EMULSION CRYSTALLIZATION

In this chapter a crystallization technique for immiscible solvent-antisolvent pairs is described. Crystallization is based on the formation of a fine emulsion of the crystallizing solution in a continuous phase comprising of the antisolvent by means of porous hollow fiber devices. The ability of the membrane hollow fibers to provide an emulsion with a small droplet diameter and a narrow droplet size distribution is of paramount importance for the successful implementation of porous hollow fiber emulsion crystallization (PHFEC). As a result, a brief review of membrane emulsification is given in this Chapter as well as an assessment of the performance of the hollow fiber devices used in this dissertation in terms of droplet size distribution. Next, the attempts to crystallize salicylic acid by dispersing solutions of salicylic acid in 1-octanol in water are described.

5.1 Membrane Emulsification - Background

Membrane emulsification is a relatively new technique used to prepare emulsions based on the use of microporous membranes with a relatively narrow pore size distribution. The technique relies on the permeation under pressure of the dispersed phase into an immiscible phase, which is called the continuous phase. Membrane emulsification is advantageous compared to conventional emulsification equipment due to its low energy input requirement and its ability for the production of nearly monodisperse emulsions with micron or submicron sizes (Gijsbertsen-Abrahamse et al., 2004). Note also that the low energy input requirement for membrane emulsification is similar to the one claimed in Chapter 4 for PHFAC and stems from the lack of a necessity for intensive mixing.

Membrane emulsification has found various applications; the reader can find interesting reviews in the literature (Joscelyne and Trägård, 2000; Nakashima et al., 2000; Gijsbertsen-Abrahamse et al., 2004). Membrane emulsification is used for the preparation of a low fat spread on a commercial scale (Katoh et al., 1996), in drug delivery systems (Higashi and Setoguchi, 2000), for preparation of core particles for toner application (Ha et al., 1999) and preparation of polymer paricles (Yuyama et al., 2000).

The majority of the membrane emulsification literature involves the preparation of oil-in-water emulsions using the SPG membrane (Shirasu Porous Glass) membrane, which was the first membrane to be used for this purpose (Kandori et al., 1991; Katoh et al., 1996; Ha et al., 1999; Higashi and Setoguchi, 2000; Yuyama et al., 2000). Other types of membranes used for the preparation of oil-in-water emulsions include ceramic membranes (Schröder and Schubert, 1999), polyamide (Giorno et al., 2003) and polycarbonate (Kobayashi et al., 2002b). Water-in-oil emulsions were studied in polypropylene membranes (Vladisavljević et al., 2002) or in oil pretreated SPG membranes (Mine et al., 1996; Sotoyama et al., 1999). The preparation of oil-in-water emulsions in hydrophilized PTFE membranes has also been reported (Yamazaki et al., 2002). However, when the membrane is rendered hydrophobic or hydrophilic by pretreatment, the droplet size distribution is broader and shifted towards larger sizes. This can be easily explained by the fact that the dispersed phase gradually displaces the continuous phase present in the pores due to the pretreatment of the membrane. When this happens, the requirement for the production of uniform and small droplets that the dispersed phase does not wet the membrane surface (Joscelyne and Trägård, 2000) is no longer met.

Various factors affect the preparation of an emulsion with a small droplet size and a narrow droplet size distribution. First, a membrane with a sufficiently small pore size and a narrow pore size distribution must be available. Second, the dispersed phase must not wet the membrane. Microscope pictures taken on the surface of a polycarbonate membrane showed that wetting makes the dispersed phase spread smoothly over the pores, which subsequently do not participate in droplet formation (Kobayashi et al, 2002b). In addition, Christov et al. (2002) have shown that two emulsification regimes are observed depending on the wetting conditions in the pore mouth. If the continuous phase is completely displaced from the pore, then droplets with diameters larger than four times the pore diameter are obtained. In the case the continuous phase wets the inner wall of the pore near its mouth, a stable droplet size of about 3 pore diameters is achieved, which leads to predictable performance and narrow droplet size distributions.

Another major factor is the dynamic interfacial tension between the forming droplet and the continuous phase, which was studied by Schröder et al. (1998). It was shown that the faster the dynamic interfacial tension is reduced to its final value, the smaller the droplet size obtained. This requirement also dictates the type and concentration of emulsifier used, which should adsorb on the droplet surface as fast as possible. It was also proven that fast emulsifier adsorption activates more pores and as a result increases the dispersed phase flux through the membrane. The equilibrium interfacial tension between the droplets and the continuous phase should also be as low as possible. Yuyama et al. (2000) correlated the obtained droplet size with an equation used for perforated plates. The agreement was good and showed a linear dependence of the droplet size on the interfacial tension.

The continuous phase velocity, which directly influences the wall shear stress, is another critical operating parameter. Microscope observations have confirmed that the shearing action of the continuous phase is responsible for droplet detachment from the pore mouth (Kobayashi et al, 2002b). The droplet size was found to decrease by an increase in the continuous phase velocity (Joscelyne and Trägård, 1999; Kobayashi et al., 2002b).

Other parameters influencing the droplet size distribution are the transmembrane pressure, the membrane surface porosity and the shape of the pore opening. Increased transmembrane pressures can lead to the formation of jets in the pore mouth and very large droplets (Joscelyne and Trägård, 1999). The membrane surface porosity should have an optimum value. If too low, the dispersed phase flux is insufficient for production purposes; in the opposite case it can lead to droplet coalescence and larger droplets (Gijsbertsen-Abrahamse et al., 2004). Finally, the shape of the pore mouth can be critical. Kobayashi et al. (2002a) found that oblong pores lead to a droplet size roughly twice the equivalent pore diameter. For the same operating parameters and circular pores the droplets obtained were much larger, in excess of ten pore diameters.

5.2 Operating Principle

An illustration of the proposed technique is shown in Figure 5.1. Figure 5.1a illustrates the configuration used for crystallization of a saturated aqueous solution by using an organic antisolvent. The aqueous solution is fed to the shell side of the membrane hollow fiber crystallizer, while the antisolvent is circulated through the lumen side of the device. Hydrophobic fibers are used to avoid wetting phenomena. Note that the exact opposite configuration of feeding the dispersed phase through the lumen side is also possible. The shell side is kept at a pressure higher than the tube side and the breakthrough pressure of the crystallizing solution through the membrane pores. Under the applied transmembrane pressure, droplet formation is initiated and an emulsion of aqueous droplets in the organic antisolvent is created. Figure 5.1b shows a similar configuration for the crystallization of organic solutes by using water or an aqueous solution as the antisolvent. In this case hydrophilic gel membranes are used, which are not wetted by apolar organic compounds. In both cases crystallization can start at the interface between the droplet and the antisolvent. Once the first crystals or nuclei are formed, crystallization can continue by a heterogeneous nucleation mechanism.

Polymeric hollow fiber emulsion crystallization presents the same advantages as membrane emulsification. The most important is the ability to accurately control crystal size. By using membranes of appropriately small pore size and narrow pore size distribution and further controlling the operating parameters presented in Section 5.1, one can obtain an emulsion of droplets in the micron or submicron level. The final crystal size distribution will also be of the same magnitude and width, since crystallization is constrained inside the droplets. By also controlling the residence time of the solution



Figure 5.1 Operation principle of porous hollow fiber emulsion crystallization (PHFEC): a) Crystallization of aqueous solutions and b) crystallization of organic solutions.

inside the membrane hollow fiber crystallizer, the time that is available for crystal growth can also be controlled. An additional advantage is the low energy requirement for the production of the emulsion and hence the crystal suspension. Intensive mixing is required for commercial or literature-based emulsion crystallization applications (Shiloh et al., 1975; Sun, 1978; Reuter, 1998; Marie et al., 2003; Taden and Landfester, 2003), which in most situations must be applied for a time period of several hours. Finally, like the other hollow fiber based crystallization techniques already presented, PHFEC can be easily scaled up and controlled by manipulating simple operating parameters such as the velocity of the continuous phase and the transmembrane pressure.

5.3 Experimental

5.3.1 Chemicals and Materials

Deionized water was used as the continuous phase circulated through the tube side. Sodium dodecyl sulphate (Fisher Scientific, Pittsburgh, PA) was the surfactant used in % weight concentrations around 1%. Saturated solutions (concentration of 290 g/kg solvent, De Fina et al., 1999) of salicylic acid (Fisher Scientific, Pittsburgh, PA) were prepared by dissolving an excess amount of salicylic acid in 99% 1-octanol (Fisher Scientific, Pittsburgh, PA). The solutions were stirred vigorously for at least 18 hr and then filtered by using glass fiber filters (Whatman 934-AH) with a cutoff size of 1.5 µm to remove any suspended solids.

Porous polyethersullfone (PES) hollow fibers of $700/1000 \ \mu m$ ID/OD (Membrana, Charlotte, NC) were used for the fabrication of two modules whose geometrical characteristics are shown in Table 5.1. The PES fibers used have a pore size

between 10-100 nm. The shell side was made of FEP tubing. Module fabrication procedures are similar to the ones already described in Chapter 2 for PHFHEs.

Module	N	Active length (cm)	Total length (cm)	D _s (cm)	A _o (cm ²)
PES #1	12	22.6	26.2	0.76	85.0
PES #2	6	20.5	24.6	0.76	38.7

Table 5.1Geometrical Characteristics of Membrane Hollow Fiber Crystallizers Usedfor Porous Hollow Fiber Emulsion Crystallization

5.3.2 Apparatus and Procedure

Figure 5.2a illustrates a schematic of the experimental setup used for porous hollow fiber emulsion crystallization, while in Figure 5.2b a photograph of the apparatus is given. The continuous phase was pumped to the lumen side of the MHFC by means of a peristaltic pump (Cole Parmer, Vernon Hills, IL). Its flow rate was measured with a flow meter (Cole Parmer, Vernon Hills, IL). The shell side was pressurized by means of a nitrogen cylinder. A valve (V2) was used to allow the dispersed phase to flow into the shell side of the MHFC. At the shell side exit a three-way valve (V1, Crum & Company, Mountainside, NJ) was placed to allow for the removal of air bubbles from the shell side during start up. Two pressure gauges (Cole Parmer, Vernon Hills, IL) were used in the tube and shell side inlets to record the pressure head. Pressure in the shell side can be considered constant and equal to the inlet value because the pressure drop is very small.



Figure 5.2 Experimental setup for porous hollow fiber emulsion crystallization (PHFEC): a) Drawing of the apparatus and b) photograph of the apparatus.

The tube side exit pressure was in all cases 1 bar. Once the dispersed phase was introduced to the shell side, its flux was recorded gravimetrically by means of a balance with an accuracy of 0.1 g (Sartorius BL6100, Sartorius, Edgewood, NY).

The way the crystallization runs were performed is described below. Before each run the membrane was presoaked in water for about 30 min. and the dispersed phase tank was pressurized between 20-30 psig. Then the continuous phase was circulated for 5-10 min. and the feed flow rate was measured and recorded. At that point, the balance was set to zero and the dispersed phase was introduced to the shell side by opening valve V2. Simultaneously, valve V1 was also kept open for about 30-60 seconds to allow for the removal of any trapped air bubbles. Next, valve V1 was closed and emulsification commenced. The pressure head at the tube and shell side inlet as well as the weight of the dispersed phase permeating to the tube side were recorded at appropriate time intervals to obtain the transmembrane pressure and the dispersed phase flux respectively. The former is given from Equation (4.1), while the latter is obtained from

$$J_d = \frac{m_d}{\rho_d} \frac{1}{N\pi D_o L} \tag{5.1}$$

Emulsification was carried out until the dispersed phase weight fraction reached values between 0.1 and 0.15. At that point samples of the emulsion were taken and analyzed for droplet size distribution by means of optical microscopy. Details are given in Subsection 5.3.3. A fraction of the emulsion (200-300 g) was placed in a beaker and a known amount (about 4-5 g) of salicylic acid seed crystals were added. The emulsion was then stirred for at least 1 hr by means of a digitally controlled Caframo Compact Digital stirrer (Fisher Scientific, Pittsburgh, PA) operated at 600-800 rpm. Subsequently, the

emulsion was filtered by using hydrophilized PVDF membranes (Pall Corp., NY) with a cutoff size of 0.2 μ m. The crystals obtained on the filters were thoroughly dried and then weighed. Their mass was compared to the initial mass of the seeds as an indicator of whether crystallization of the droplets actually took place or not. In the case no appreciable difference was found, crystal samples were not analyzed for crystal size distribution since the latter would simply represent the size distribution of the seeds as it is influenced by attrition phenomena induced by the stirrer (Mersmann, 2001).

Immediately after each experiment cleaning of the module was performed to avoid swelling of the membrane. Both the tube and the shell side were initially washed with a detergent solution (VersaClean, Fisher Scientific, Pittsburgh, PA). Then deionized water was circulated on both sides of the membrane hollow fiber crystallizer for about 30 min., followed by permeation of deionized water from shell to lumen to remove any emulsion or salicylic acid solution trapped inside the pores. Finally, the MHFC was dried by passing compressed air from both sides and following with dry nitrogen (99.9%, Matheson, Montgomeryville, PA) permeation from shell to lumen for 30-40 min.

5.3.3 Analytical Methods

Droplet size distributions were determined by means of optical microscopy. An optical microscope (Swift Instruments International, M4000-D) equipped with a digital camera and a stage micrometer was used to obtain sample pictures. Droplet sizing was performed with available free imaging software (Image Tool version 3, Univ. of Texas Health Science Center in San Antonio, TX). The software reports a diameter based on area; since the droplets are spherical, a direct conversion of the area distribution to a volume distribution is not only permissible, but also involves minimal error. The combined

spatial resolution of the microscope and the imaging software was estimated to be $0.45 \ \mu m$.

5.4 Results and Discussion

First, some results representative of the membrane emulsification achieved during the PHFEC runs will be presented since the creation of the emulsion is essential for the success of the method. These results are far from optimal because the primary focus was to identify the best operating procedures to obtain crystallization.

Figure 5.3 illustrates the pressure head profiles obtained during run 2. The shell side pressure was constant throughout the experiments. However, the tube side pressure head increased with time accompanied by a corresponding decrease in the transmembrane pressure. Following the arguments already presented in Chapter 4, this pressure head increase can be explained in terms of Hagen-Poiseuille's law and the increase in viscosity introduced by the presence of the droplets containing the salicylic acid solution in 1-octanol. The latter is amplified with time since the concentration of the dispersed phase in the final emulsion increases.

Figure 5.4 shows a plot of the dispersed phase flux with time for the same run. After an initial transitional stage the transmembrane flux is stabilized at a level, which depends on the transmembrane pressure. Figure 5.5 shows the % number differential droplet size distribution for run 2. The continuous phase velocity used was 0.25 m s⁻¹, which is above the approximate limit below which a strong dependence of droplet size on continuous phase velocity exists. It is apparent that a bimodal distribution was obtained.



Figure 5.3 Porous hollow fiber emulsion crystallization (PHFEC) – Run 2, pressure profiles in the membrane hollow fiber crystallizer.



Figure 5.4 Porous hollow fiber emulsion crystallization (PHFEC) – Run 2, dispersed phase flux.



Figure 5.5 Porous hollow fiber emulsion crystallization (PHFEC) – % number differential emulsion droplet size distribution. Run 2, continuous phase velocity of 0.25 m s^{-1} .

The same trends were observed for all other runs performed, namely, a bimodal distribution with a peak corresponding to about one fourth of the droplets at a size around 1 μ m and a second peak at larger sizes. This clearly shows that the pores of the membrane are characterized by different emulsification behavior.

The latter can be possibly explained following the arguments of Christov et al. (2002), who showed that two emulsification regimes exist depending on the wetting conditions in the pore mouth. In most of the pores, the continuous phase is completely displaced from the pore; then droplets with diameters larger than four times the pore diameter are obtained and the droplet size distribution is polydisperse. In the rest of the pores, which should represent about one fourth of the total pores, the continuous phase wets the inner wall of the pore near its mouth. In this case a stable droplet size is achieved, which leads to predictable performance and a nearly uniform droplet size distribution is obtained as the peak around 1 µm reveals. This shows that the droplet size distribution can be considerably improved if a different start up protocol is followed, i.e., soaking the membrane with the continuous phase for more time. Another factor that can introduce polydispersity is the swelling of the membrane from 1-octanol.

Table 5.2 summarizes the experimental conditions during the porous hollow fiber emulsion crystallization runs performed. Crystals were present for each run performed, which however were the seeds used. No new crystals were produced as Table 5.2 reveals. The crystal mass before and after stirring the emulsion was negligible in all cases and it also reflects the fact that some of the emulsion adhered on the seeds. Therefore, the technique proved unsuccessful for the production of crystals, despite the fact that emulsions with small droplet sizes were produced. The main reason for this is believed to

Run #	Module	Seed Crystals	Emulsion (g)	Stirring Time	Stirrer RPM	Final Crystal Mass
		(g)		(hr)		(g)
1*	PES #2	1.5	321.4	1	800	0
2	PES #2	4.9	302.2	1	800	5.2
3	PES #2	4.0	290	1	800	4.1
4	PES #3	5.2	252.3	1	600	4.9
5	PES #3	6.4	291.3	8	600	6.5

Table 5.2 Operating Conditions During the Porous Hollow Fiber EmulsionCrystallization Runs

* An undersaturated solution of salicylic acid in 1-octanol was used. Seed crystals were dissolved.

be the layer of adsorbed surfactant between the droplet and the continuous phase. The latter is crucial for the stabilization of the droplet and to obtain a small droplet size. However, it prevents direct contact of the solute with the antisolvent and the creation of supersaturation and consequently crystal formation. Emulsion seeded crystallization has been performed in the absence of surfactant in stirred vessels (Sun, 1978; Reuter, 1998), where mixing was the mechanism leading to emulsion formation. A similar scheme, where no surfactant is used could also be tested with the experimental setup used in this dissertation. In this case though, the solute to be crystallized must have surfactant properties to stabilize the formed droplets without forming any barrier for access to the droplet interior.
5.5 Conclusions

Porous hollow fiber emulsion crystallization encountered difficulties in providing conditions leading to the formation of crystals, despite the fact that emulsion droplets smaller than 50 μ m were produced in all runs performed. The presence of the surfactant in the emulsion, while beneficial to the stability and the size of the produced droplet, prevents the contact between the solute and the antisolvent and consequently supersaturation generation and crystal formation. The addition of seed crystals did not improve the situation. However, future research can possibly exploit membrane emulsification in the crystallization of molecules that possess surfactant properties or in combination with an additional method for supersaturation creation that does not depend on the contact of the solute and the antisolvent.

CHAPTER 6

EPILOGUE

The objective of every research effort is to provide answers to the specific problems it investigates and possibly expand the scientific horizons with new discoveries or possibilities. In this dissertation an attempt to examine crystallization under an environment much different from that available in current industrial practice was made. Three crystallization techniques were examined in the anisotropic flow environment offered by hollow fibers. Two of them proved successful and promising for scale up studies and future commercial application. Moreover, the research spectrum of this dissertation was broadened by testing a new type of heat exchanger based on solid hollow fibers and by investigating the potential use of porous hollow fiber devices as mixing devices.

The small diameter of hollow fibers makes them unique either as heat exchangers or crystallizers. First, the scale of the system is small, on the submillimeter or even the micron level. This offers the ability to produce relatively homogeneous temperature and/or concentration conditions, useful for crystallization or reaction purposes, on a local level without the necessity of energy input other than the one required for flow circulation. The production of homogeneous local conditions is also the objective of mixing. However, in this case one starts from the macroscale and has to provide a considerable amount of energy as well as time to reach the desired homogeneity on a microscale. Second, hollow fiber devices offer extremely large surface area/volume ratios, which make them very efficient transport devices. Membrane devices have been proven superior on a volumetric basis to conventional mass transfer devices numerous times. This dissertation extended this conclusion to heat transfer equipment used for transport of sensible as well as latent heat. Polymeric hollow fiber heat exchangers are inferior only to regenerators and matrix type heat exchangers. Solid hollow fiber crystallizers can transfer 3-60 times more heat per unit time per unit volume compared to cooling equipment used in industrial cooling crystallizers. In addition, they offer 1-2 orders of magnitude more area available for nucleation on a volumetric basis.

The compact and modular design of hollow fiber devices makes them ideal for easy and straightforward scale up. Whether it is cooling or antisolvent crystallization, upon scale up one has to maintain three parameters the same. The first one is the geometrical and flow design of the hollow fiber device. The latter includes the packing fraction, the shell diameter and cross section and the shell-side flow configuration. The second is the velocity inside the hollow fibers. The third is the driving force for heat or mass transfer, which is controlled by adjusting respectively the temperature and the pressure difference across the membrane. All of the above three parameters are easily controlled.

Geometric similarity is a scale up rule also applicable to industrial crystallizers. However, it is complicated by the necessity to use smaller stirrer revolution rates to avoid excessive crystal attrition and energy expenditure. Flow conditions can be also accurately controlled in industrial crystallizers. It is the ability of hollow fiber devices to accurately control and maintain constant the supersaturation generation rate that distinguishes them from industrial crystallizers. Cooling crystallizers suffer from reduced heat transfer performance due to incrustation and the small surface area available. Scale up of antisolvent crystallizers is very sensitive to changes in micromixing and macromixing conditions, which can potentially lead to fluctuations in the crystal size distribution and the product specifications.

The achievements of this dissertation will be briefly summarized in the next few paragraphs. First, polymeric hollow fiber heat exchangers were tested as an alternative to conventional metal and plastic heat transfer equipment for lower temperature and pressure applications. On a volumetric basis, they were proven 3-8 times more efficient than shell-and-tube heat exchangers. Efficiencies as high as 97.5% and up to 3-4 transfer units were obtained in devices less than 30 cm long. The height of a heat transfer unit was 10-20 times lower than metal heat transfer equipment and it can permit the achievement of up to twelve transfer units in the case PHFHEs are designed with the same specifications as commercial membrane contactors. These numbers are currently achieved only in matrix-based heat transfer equipment used in energy generation plants. In addition, the operation of PHFHEs was characterized by considerably lower pressure drops, which translate into a smaller operating cost. Considering that plastic materials are lighter and cheaper than metals, it follows that the fixed and overall cost of PHFHEs per unit energy transferred is projected to be smaller compared to metal heat exchangers.

Solid hollow fiber cooling crystallization was used for crystallization of both aqueous and organic systems. In this aspect, it overcame the limitations imposed to other membrane based crystallization techniques studied earlier. The combination of a solid hollow fiber crystallizer with a mixing device downstream, a completely stirred tank or a static mixer, proved a promising technique for crystal size distribution control. Mean sizes 3-4 times smaller compared to MSMPR crystallizers were obtained for aqueous potassium nitrate crystallization. Moreover, 90% of the crystals formed were smaller than 370 μ m compared to a size of 600 μ m for the MSMPR crystallizer. In addition, 2-3 orders of magnitude higher nucleation rates were observed. Similar results were obtained for a soluble organic system, salicylic acid in ethanol.

The runs with aqueous paracetamol solutions illuminated another operating regime for SHFCs, characterized by high supersaturations and primary nucleation phenomena. It was shown that a SHFC-static mixer assembly can be operated successfully up to 30-40°C below the metastable zone limit. Such a capability is not existent in industrial cooling crystallizers. It also allows the decoupling of nucleation and growth, an opportunity offered currently only by impinging jet mixers for antisolvent crystallization. In addition, it can be potentially used for polymorph control without preferential seeding and for the achievement of very high nucleation rates and hence small crystal sizes. A qualitative comparison with existing literature data showed that the SHFC-static mixer combination confined the CSD to a narrower range. Finally, a linear relationship between the mean crystal size and the cooling medium temperature was observed. The latter is indicative of the CSD control simplicity SHFCs offer.

Porous hollow fiber devices can be used as efficient mixing devices. In experiments during which isopropanol permeated from the shell to the lumen side of the hollow fiber device, its concentration in the final water-isopropanol mixture was as high as 30% by weight. Moreover, it can be further improved by properly rating the hollow fiber device. This gives the unique opportunity to perform reactions on a 1:1 stoichiometric ratio, a task never reported in the membrane literature for liquid-liquid reactions. Porous hollow fiber devices also offer a unique ability for good radial mixing not present in conventional tubular devices. Radial mixing is enhanced by the cross flow of the permeate, which introduces three-dimensional velocity fluctuations characteristic of turbulent flow. For the experimental conditions examined in this dissertation, it was also shown that the time required for complete radial mixing is comparable to the device residence time.

Porous hollow fiber antisolvent crystallization was performed in two ways, by permeating antisolvent from shell to lumen and by permeating the crystallizing solution from lumen to shell. Tested for antisolvent crystallization of L-asparagine monohydrate, the first configuration encountered difficulties. While a CSD confined to sizes below 100 μ m was obtained, it was not possible to achieve prolonged operation of the membrane hollow fiber crystallizer due to pore blockage and/or possible fiber blockage from newly formed crystals.

The second configuration was proved successful despite the fact that the geometrical design of the membrane hollow fiber crystallizers used was not optimal. Mean crystal sizes between 33-40 μ m and 34-86 μ m were obtained respectively for the MHFC-CST in series and the once through operation mode. The CSD was confined below 70 μ m for the former and below 150 μ m for the latter, showing that the combination of a MHFC with a mixing device downstream provides tighter CSD control. These numbers compare favorably to 200 and 300 μ m obtained respectively in batch stirred vessels and MSMPR crystallizers. They are also sufficient for most pharmaceutical crystalline products, for which bioavailability and formulation concerns

dictate the desired CSD. In addition, porous hollow fiber devices achieved 1-5 orders of magnitude higher nucleation rates compared to batch stirred crystallizers. Considerable improvements can be obtained by carefully designing membrane hollow fiber crystallizers.

Porous hollow fiber emulsion crystallization was unsuccessful despite the fact that emulsions with droplet sizes below 50 µm were prepared. The presence of the surfactant between the solution droplet and the antisolvent proved an insurmountable obstacle to crystallization, even when seeding was used. However, exploration of the technique with molecules possessing surfactant properties or in combination with an additional method to induce supersaturation, i.e., cooling, would be of interest.

This dissertation provided an answer to the fundamental question it posed, namely, whether crystallization and crystal size distribution control are possible or not by using hollow fiber devices and a variety of supersaturation generation techniques. In addition, it generated two new areas of research, heat transfer and mixing/reaction in hollow fiber devices, which were explored at different levels. This multitude of research tasks naturally produced more questions than the ones possibly answered by this dissertation. Future research can be focused in several areas.

First, heat transfer studies with cross flow in the shell side of polymeric hollow fiber heat exchangers should be implemented, as well as studies involving condensation or evaporation. Scale up studies must also be performed to prove the long-term operational capabilities of these devices on a commercial scale. Other polymeric materials with better heat transfer and/or mechanical performance characteristics should also be tested, i.e., PEEK, PTFE or fiber reinforced polymeric materials. Scale up studies should also be performed for solid hollow fiber cooling crystallization. Contrary to industrial crystallization experience, it is the author's opinion that the performance of solid hollow fiber crystallizers will be better on a larger scale compared to the results presented in this dissertation. Performance variations in the shell side and cooling non-uniformities in the tube side will be small, while the static mixer can be sized appropriately to deplete all supersaturation created. Future experiments should also examine the possibility of achieving preferential polymorph crystallization without seeding. Also, systems with solubilities in the range between the ones examined here must be studied and the full laminar regime for the tube side should be explored.

Future research for membrane hollow fiber crystallizers should focus on the optimal design of the device and the collection of additional data that could support the encouraging results presented in this dissertation. Implementation of cross flow at the shell side would be particularly useful. Finally, the issue of mixing inside hollow fibers and the possibility of using porous hollow fiber devices for reaction purposes are worth investigating and could possibly provide a different perspective to these processes.

APPENDIX A

SOLUTION OF THE CHARACTERISTIC EQUATION (2.16)

The set of equations and boundary conditions (2.16)-(2.18) was solved by numerical integration of Equation (2.16) with a fourth order Runge-Kutta method. The second order differential equation was converted to a 2x2 system of first order differential equations by making the substitution

$$Z_n = \frac{dY_n}{d\xi} \tag{A.1}$$

Then Equations (2.16)-(2.18) are written respectively as follows:

$$\frac{dZ_n}{d\xi} + \frac{Z_n}{\xi} + \lambda_n^2 \left(1 - \xi^2\right) Y_n = 0 \tag{A.2}$$

$$at \xi = 0 \qquad \qquad \mathbf{Z}_n = 0 \tag{A.3}$$

$$at \xi = 1 \qquad -Z_n = \frac{Nu_w}{2}Y_n \qquad (A.4)$$

Integration of Equations (A.1) and (A.2) starts at $\xi = 0$, something that introduces a singularity in Equation (A.2). The latter was overcome by applying L' Hospital's rule. An estimate of Y_n is required at $\xi = 0$ in order to treat Equation (2.16) as an initial value problem. The initial guess for the eigenfuction at $\xi = 0$ is free (Nunge and Gill, 1966) and a value of 1 was chosen for the calculations.

The eigenvalues were sought by a secant method (Rice and Do, 1995), which requires two initial guesses for each eigenvalue and utilizes boundary condition (A.4). The latter is written as follows:

$$f(\lambda_n) = Z_n + \frac{Nu_w}{2}Y_n = 0$$
(A.5)

The iterative formula used for the eigenvalue calculation is

$$\lambda_{n,j} = \lambda_{n,j-1} - \frac{f(\lambda_{n,j-1}) \cdot \left(\lambda_{n,j-1} - \lambda_{n,j-2}\right)}{f(\lambda_{n,j-1}) - f(\lambda_{n,j-2})}$$
(A.6)

where the subscript j refers to the jth iteration.

The calculations then proceed as follows:

- Integrate Equations (A.1) and (A.2) subject to boundary conditions (A.3) and (A.4) for the initial eigenvalue guesses.
- 2. Obtain Y_n and Z_n at $\xi = 1$.
- 3. Calculate $f(\lambda_n)$ based on (A.5).
- 4. Substitute in (A.6) to obtain a next estimate of λ_n .
- 5. Repeat the above procedure until

$$\left|\lambda_{n,j} - \lambda_{n,j-1}\right| < \varepsilon \tag{A.7}$$

where ε was chosen equal to 10^{-8} .

Since successive eigenvalues differ by about 4 (Hsu, 1971), once the first eigenvalue is calculated, the initial guesses for the next eigenvalue are obtained by adding 3.8 and 3.9 to the former. Therefore, the whole procedure can be initiated by giving two initial guesses for the first eigenvalue. Any guess in the interval between 1 and 2 is sufficient.

APPENDIX B

SOURCE CODE FOR THE SOLUTION OF THE ENERGY EQUATION (2.7) WITH THE T3 BOUNDARY CONDITION

The code was written in Visual Basic for Applications and implemented in Microsoft Excel 2000 in the form of an AddInn that contains spreadsheet functions. Each function can be used independently for a separate part of the problem, i.e., eigenvalue, temperature, inside Nusselt number calculations etc. and utilizes subutilities in the form of private or public functions. The code will run properly if copied exactly as written, saved as an AddInn file and loaded every time Excel opens. The main part of the code used for the calculation of temperature, heat flux and inside Nusselt number is given first; it is followed by the subroutines necessary for implementation of the solution.

'// Extended Graetz Problem in circular tubes '// Copyright (C) 2004 Dimitrios M. Zarkadas '//e-mail: dmz1916@njit.edu

'// Finds the temperature of a fluid cooled under laminar flow conditions and by a '//medium of constant temperature as a function of radial and axial displacement.
'// Nomenclature is as follows

- *'// n number of eigenvalues used in the calculations*
- *'// x radial displacement*
- *'// y eigenfuction*

- *'// z derivative of the eigenfunction*
- '// zdisp axial displacement
- *'// Bi Biot number*
- *'// h* step size used in the Runge Kutta procedure used to find the eigenfunctions
- *'// lamda1,2 eigenvalues used to initiate the secant procedure used to calculate the eigenvalues*
- *'// S heat source term*
- *'// Re Reynolds number*
- *'// Pr Prandtl number*
- *'// k fluid thermal conductivity*
- *'// Ta cooling medium temperature*
- *'// T0 inlet fluid temperature*
- *'// r0 tube radius*
- *'// L tube length*
- 1// 20 and 50 grid points are used in the radial and axial direction respectively

Option Base 1 // All arrays are numbered from 1

Public Function ExtendedGraetzProblemT(n, x, y, z, Bi, h, lamda1, lamda2, S, Re, Pr, k,

Ta, T0, r0, L)

Dim YnArray As Variant

// This is the array where the eigenfunction values are stored. The first index refers

'// to the eigenvalues counter while the second to radial displacement

Dim EigenfunctionArray As Variant

'// This is the array used to store the calculated temperature values

Dim TArray(51, 21)

m = 1 / h /// Runge-Kutta loop number of steps

ReDim YnArray(m) /// Runge-Kutta eigenfunction array (internal array)

ReDim EigenfunctionArray(n, 21)

'// Obtain eigenvalues and Cn coefficients

Dim EigenArray2 As Variant

EigenArray2 = GetEigenvaluesandCoefficients(n, x, y, z, Bi, h, lamda1, lamda2, S, Ta,

T0)

'// Calculate eigenfunctions as a function of eigenvalues and radial displacement
'// i is the eigenvalue counter, r the radial displacement counter

For i = 1 To n

EigenfunctionArray(i, 1) = 1

lamda = EigenArray2(i, 1)

'// Runge Kutta loop

For RK = 1 To m

k1 = h * z

11 = h * GRungekutta(x, y, z, lamda)

```
k2 = h * (z + 0.5 * 11)
```

12 = h * GRungekutta(x + 0.5 * h, y + 0.5 * k1, z + 0.5 * l1, lamda)

k3 = h * (z + 0.5 * 12)

13 = h * GRungekutta(x + 0.5 * h, y + 0.5 * k2, z + 0.5 * l2, lamda)

k4 = h * (z + 13) l4 = h * GRungekutta(x + h, y + k3, z + 13, lamda) x = x + h y = y + (1 / 6) * (k1 + 2 * k2 + 2 * k3 + k4) z = z + (1 / 6) * (l1 + 2 * l2 + 2 * l3 + l4) YnArray(RK) = y

Next RK

'// Loop to fill the eigenfunctions array. 11 is used to subdivide the 0,r0 domain to 20 grid points

For r = 1 To 20

11 = r * m / 20

EigenfunctionArray(i, r + 1) = YnArray(11)

Next r

x = 0 /// reset x, y, z for next eigenvalue

y = 1

z = 0

'// Final loop starts. J counter is for axial displacement, i for eigenvalues and

'// eigenfunctions and r for the radial direction

interval = L / 50

zdisp = 0

For j = 1 To 51

zstar = zdisp / (r0 * Re * Pr)

For r = 0 To 20

```
Sum = 0

Sourceterm = -(S / 4) * ((0.05 * r * r0)^2) + (S / 2) * ((1 / Bi) + 0.5)

For i = 1 To n

Expoterm = Exp(-((EigenArray2(i, 1))^2) * zstar)

Sum = Sum + EigenArray2(i, 5) * EigenfunctionArray(i, r + 1) * Expoterm

Next i

TArray(j, r + 1) = Ta + (Sourceterm + Sum) * T0

Next r

zdisp = zdisp + interval

Next j

ExtendedGraetzProblemT = TArray

End Function
```

'// Returns the exit temperature and the overall Nusselt number. The procedure first
'// calculates the eigenvalues, then all necessary intermediate values (bulk and wall T,
'// heat flux and local Nusselt number) and finally the overall Nusselt number by a
'// dimensionless heat flux expression proposed by Hickman, 1974

Public Function GetExitTandOverallNusselt(n, x, y, z, Bi, h, lamda1, lamda2, S, Re, Pr, k, Ta, T0, r0, L) Dim EigenArray1 As Variant

EigenArray1 = GetEigenvaluesandCoefficients(n, x, y, z, Bi, h, lamda1, lamda2, S, Ta, T0)

interval = L / 5000

z = 0 *''/ zstar is the x* found in the literature or the inverse of the Graetz*

number

For j = 1 To 5001 /// Outer loop for axial displacement

Sum = 0 /// Summation for series expansion

Sum1 = 0 /// Summation for bulk temperature

For i = 1 To n

zstar = z / (r0 * Re * Pr)

Expoterm = $Exp(-((EigenArray1(i, 1))^2) * zstar)$

SummationTerm = EigenArray1(i, 5) * EigenArray1(i, 2) * Expoterm

SummationTerm1 = EigenArray1(i, 5) * EigenArray1(i, 2) * Expoterm /

 $((EigenArray1(i, 1))^2)$

Sum = Sum + SummationTerm

Sum1 = Sum1 + SummationTerm1

Next i

Twall = (-(S / 4) + (S / 2) * ((1 / Bi) + 0.5) + Sum) * T0 + Ta ''/ Fill out array, Wall T

qwall = (Bi * k / r0) * T0 * ((S / (2 * Bi)) + Sum) /// Wall heat flux

Tbulk = Ta + 4 * T0 * ((S / 24) + (S / (8 * Bi)) + Bi * Sum1) '// Bulk T

z = z + interval

Next j

thetam = (Ta - Tbulk) / (Ta - T0)

Texit = Tbulk

xstar = L / (2 * r0 * Re * Pr)

Nuoverallm = -Log(thetam) / (4 * xstar)

NumT3 = 1 / ((1 / Nuoverallm) - (1 / (2 * Bi))) GetExitTandOverallNusselt = Array(Texit, NumT3)

End Function

'// This procedure returns an array containing the wall temperature, the wall heat flux,
'// the bulk temperature and the local Nusselt number. Up to the first 150 eigenvalues,
'// eigenfunctions and the coefficients are used for the calculations. The length of the
'// module is subdivided in 100 intervals (j summation). n gives the number of
'// eigenvalues, eigenfunctions and coefficients used in the calculations (i summation)

Public Function GetHeatFluxWallandBulkTandNusseltlocal(n, x, y, z, Bi, h, lamda1, lamda2, S, Re, Pr, k, Ta, T0, r0, L)

Dim EigenArray As Variant

EigenArray = GetEigenvaluesandCoefficients(n, x, y, z, Bi, h, lamda1, lamda2, S, Ta,

T0)

Dim GlobalArray(101, 6) As Double

interval = L / 100

z = 0

SumNu = 0 /// Integration for overall Nusselt number

For j = 1 To 101 // Outer loop for axial displacement

Sum = 0 /// Summation for series expansion

Sum1 = 0 /// Summation for bulk temperature

For i = 1 To n

zstar = z / (r0 * Re * Pr)

Expoterm = $Exp(-((EigenArray(i, 1))^2) * zstar)$

SummationTerm = EigenArray(i, 5) * EigenArray(i, 2) * Expoterm

SummationTerm1 = EigenArray(i, 5) * EigenArray(i, 2) * Expoterm / ((EigenArray(i,

1))^2)

```
Sum = Sum + SummationTerm
```

Sum1 = Sum1 + SummationTerm1

Next i

GlobalArray(j, 1) = z /// fill out the z-coordinate

GlobalArray(j, 2) = zstar / 2 ''/ divide by 2 because x* in the literature is based on

'// diameter and not radius. This is only to obtain the correct value of x^* and it does not

'// affect the rest of the solution

GlobalArray(j, 3) = (-(S / 4) + (S / 2) * ((1 / Bi) + 0.5) + Sum) * T0 + Ta''/ Fill out

array, Wall T

 $\begin{aligned} & \text{GlobalArray}(j, 4) = (\text{Bi} * \text{k} / \text{r0}) * \text{T0} * ((\text{S} / (2 * \text{Bi})) + \text{Sum}) & /// Wall \ heat \ flux \\ & \text{GlobalArray}(j, 5) = \text{Ta} + 4 * \text{T0} * ((\text{S} / 24) + (\text{S} / (8 * \text{Bi})) + \text{Bi} * \text{Sum1}) & /// Bulk \ T \\ & \text{GlobalArray}(j, 6) = (2 * \text{r0} / \text{k}) * \text{GlobalArray}(j, 4) / (\text{GlobalArray}(j, 5) - \text{GlobalArray}(j, 3)) \end{aligned}$

z = z + interval

Next j

GetHeatFluxWallandBulkTandNusseltlocal = GlobalArray

End Function

'// Finds the eigenvalues and the series expansion coefficients for the temperature
'// function. All code is based on the functions written in the previous module. Depending
'// on the number of terms desirable in the series expansion one has to change the upper
'// limit for the j summation (20 to 50 terms should suffice for most cases)

Public Function GetEigenvaluesandCoefficients(n, x, y, z, Bi, h, lamda1, lamda2, S, Ta, T0)

Dim EigenvaluesandCoefficientsArray(201, 5) As Double

m = 1 / h

'// calculation of first eigenvalue

lamda = EigenvalueCalculation(x, y, z, h, Bi, lamda1, lamda2)

'// Runge Kutta loop starts

¹// Simultaneous calculation of In, Gn, Cn coefficients

For j = 1 To n

lamda = EigenvalueCalculation(x, y, z, h, Bi, lamda1, lamda2)

$\mathbf{x} = 0$	'// must reset in every j step in order to start	
y = 1	'// the integration at the center of the tube	
z = 0		
InSum1 = 0	<pre>'// In coefficient summation</pre>	
GnSum1 = 0	'// Gn coefficient summation	
Sum2 = 0	<pre>'// denominator summation</pre>	

For k = 1 To m

k1 = h * z11 = h * GRungekutta(x, y, z, lamda)k2 = h * (z + 0.5 * 11)12 = h * GRungekutta(x + 0.5 * h, y + 0.5 * k1, z + 0.5 * l1, lamda)k3 = h * (z + 0.5 * 12)13 = h * GRungekutta(x + 0.5 * h, y + 0.5 * k2, z + 0.5 * l2, lamda)k4 = h * (z + 13)14 = h * GRungekutta(x + h, y + k3, z + 13, lamda) $\mathbf{x} = \mathbf{x} + \mathbf{h}$ y = y + (1 / 6) * (k1 + 2 * k2 + 2 * k3 + k4)z = z + (1 / 6) * (11 + 2 * 12 + 2 * 13 + 14) $Infx1 = x * (1 - x^{2}) * y$ /// numerator functional, In coefficient '// numerator functional, Gn coefficient Gnfx1 = x * y $fx^2 = x * (1 - x^2) * y^2$ '// denominator functional, same for In or Gn '// used for the summation at the end point If k = m Then InSum1 = InSum1 + Infx1GnSum1 = GnSum1 + Gnfx1Sum2 = Sum2 + fx2Else InSum1 = InSum1 + 2 * Infx1GnSum1 = GnSum1 + 2 * Gnfx1Sum2 = Sum2 + 2 * fx2End If

Next k

EigenvaluesandCoefficientsArray(j, 1) = lamda

EigenvaluesandCoefficientsArray(j, 2) = y

EigenvaluesandCoefficientsArray(j, 3) = InSum1 / Sum2

EigenvaluesandCoefficientsArray(j, 4) = -GnSum1 / ((lamda 2) * Sum2)

EigenvaluesandCoefficientsArray(j, 5) = (1 - (Ta / T0)) * (InSum1 / Sum2) + S * (-

```
GnSum1 / ((lamda ^ 2) * Sum2))
```

$\mathbf{x} = 0$	'// must reset to initiate the next eigenvalue	
y = 1	'// calculation in the next j step	
z = 0		
lamda1 = lamda + 3.7	<pre>'// new initial eigenvalue guesses</pre>	
lamda2 = lamda + 3.8	'// eigenvalues differ by about 4	
Next j		
GetEigenvaluesandCoeffi	cients = EigenvaluesandCoefficientsArray	

End Function

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'// Finds nth eigenvalue for the extended Graetz problem according to Hsu's procedure
'// Needs two initial guesses for the eigenvalue to initiate a secant (essentially Newton
'// Raphson procedure, see problem 7.12 in Rice & Do, 1995) procedure. This procedure
'// calculates only one eigenvalue!! 15 iterations are more than enough

Public Function EigenvalueCalculation(x, y, z, h, Bi, lamda1, lamda2) Dim MyArray(50) As Double Dim BCinnerwallarray(50) As Double

MyArray(1) = lamda1

MyArray(2) = lamda2

lamda = MyArray(1)

yarray1 = RungeKuttaEigenvalues(x, y, z, lamda, h)

```
y1 = yarray1(1)
```

```
z1 = yarray1(2)
```

BCinnerwallarray(1) = BCinnerwall(y1, z1, Bi)

$\mathbf{x} = 0$	'// Reset to perform	the Runge Kutta procedure

y = 1 /// otherwise, x, y and z are the values from the last

$$z = 0$$
 /// time the procedure was performed

lamda = MyArray(2)

yarray1 = RungeKuttaEigenvalues(x, y, z, lamda, h)

 $y_1 = yarray_1(1)$

z1 = yarray1(2)

BCinnerwallarray(2) = BCinnerwall(y1, z1, Bi)

For i = 3 To 15

```
MyArray(i) = MyArray(i - 1) - BCinnerwallarray(i - 1) / ((BCinnerwallarray(i - 1) -
```

```
BCinnerwallarray(i - 2)) / (MyArray(i - 1) - MyArray(i - 2)))
```

If Abs(MyArray(i) - MyArray(i - 1)) < 0.00000001 Then GoTo 10

lamda = MyArray(i)

 $\mathbf{x} = \mathbf{0}$

y = 1

z = 0

```
yarray1 = RungeKuttaEigenvalues(x, y, z, lamda, h)
```

y1 = yarray1(1)

z1 = yarray1(2)

BCinnerwallarray(i) = BCinnerwall(y1, z1, Bi)

Next i

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```
10 EigenvalueCalculation = MyArray(i)
```

End Function

'// This is the Newton-Raphson function used in the secant method for the boundary '// condition at the inner wall (r=ri)'

Private Function BCinnerwall(y1, z1, Bi)

BCinnerwall = Bi * y1 + z1

End Function

'// Used by EigenvalueCalculation

Private Function RungeKuttaEigenvalues(x, y, z, lamda, h)

m = 1 / h

For i = 1 To m

k1 = h * z

11 = h * GRungekutta(x, y, z, lamda)

k2 = h * (z + 0.5 * 11) l2 = h * GRungekutta(x + 0.5 * h, y + 0.5 * k1, z + 0.5 * 11, lamda) k3 = h * (z + 0.5 * 12) l3 = h * GRungekutta(x + 0.5 * h, y + 0.5 * k2, z + 0.5 * 12, lamda) k4 = h * (z + 13) l4 = h * GRungekutta(x + h, y + k3, z + 13, lamda) x = x + h y = y + (1 / 6) * (k1 + 2 * k2 + 2 * k3 + k4) z = z + (1 / 6) * (l1 + 2 * l2 + 2 * l3 + l4)Next i RungeKuttaEigenvalues = Array(y, z)

End Function

'// Used by RungeKuttaEigenvalues

Private Function GRungekutta(x, y, z, lamda) If x = 0 Then GRungekutta = -(lamda 2) * (1 - (x 2)) * y /// For r = 0 Else GRungekutta = -(z / x) - (lamda 2) * (1 - (x 2)) * y /// For r > 0 End If End Function

APPENDIX C

CALCULATION OF HEAT TRANSFER PARAMETERS AND FRICTION FACTORS IN PHFHEs FROM EXPERIMENTAL DATA

C.1 Calculation of Overall Heat Transfer Coefficient, Exchanger Effectiveness,

NTU and HTU

The total rate of heat transfer for each stream was calculated from the following relationship:

$$Q_j = m_j C_{pj} \Delta T_j \tag{C.1}$$

where j = t for tube side and j = s for shell side. The logarithmic mean temperature difference and the overall heat transfer coefficient based on the inside area were estimated from the following relationships:

$$\Delta T_{lm} = \frac{(T_{t,in} - T_{s,out}) - (T_{t,out} - T_{s,in})}{\ln \frac{T_{t,in} - T_{s,out}}{T_{t,out} - T_{s,in}}}$$
(C.2)

$$U_i = \frac{Q}{A_i \cdot \Delta T_{lm}} \tag{C.3}$$

where Q is an average value of both streams. For all runs the difference in the Q values calculated from Equation (C.1) for each stream was less than 7%, the discrepancy being amplified by the fact that small temperature differences were recorded for the shell side. The heat exchanger effectiveness, number of transfer units and height of a transfer unit were calculated from the following equations (Shah, 1983b):

$$\varepsilon = \frac{U_i A_i}{C_{\min}^{\bullet}} \frac{\Delta T_{mean}}{T_{t,in} - T_{s,in}} = \frac{U_o A_o}{C_{\min}^{\bullet}} \frac{\Delta T_{mean}}{T_{t,in} - T_{s,in}}$$
(C.4)

$$NTU = \frac{U_i A_i}{C_{\min}} = \frac{U_o A_o}{C_{\min}}$$
(C.5)

$$HTU = \frac{L}{NTU} \tag{C.6}$$

where ΔT_{mean} is the true mean temperature difference used to calculate the rate of heat transfer, equal to ΔT_{lm} given by Equation (C.2) in the case of a true counterflow heat exchanger and \dot{C}_{min} is given by:

$$C_{\min}^{\bullet} = \left\{ \overset{\bullet}{m_t} C_{p,t}, \overset{\bullet}{m_s} C_{p,s} \right\}_{\min}$$
(C.7)

C.2 Calculation of Tube Side Friction Factors

The Fanning friction factor can be calculated based on experimental measurements according to the following relationship (Mala and Li, 1999)

$$f = \frac{\Delta P}{L} \frac{D_i}{2\rho u^2} \tag{C.8}$$

Note that in Equation (C.8), ΔP is the pressure drop corresponding to the flow of the fluid through the tube. Therefore, the experimentally obtained pressure drop should be corrected for entrance and exit effects, as well as for the hydrodynamic entrance effect if the tubes are not sufficiently long. The entrance and exit losses were obtained based on literature graphs and the following relationships (Kays and London, 1984)

$$\Delta P_{en} = \rho \left[\frac{u^2}{2} \left(1 - A_{frontal} \right) + K_{en} \frac{u^2}{2} \right]$$
(C.9)

$$\Delta P_{ex} = \rho \left[\frac{u^2}{2} \left(1 - A_{frontal} \right) - K_{ex} \frac{u^2}{2} \right]$$
(C.10)

where u is the velocity inside the tubes. Then, the true pressure drop inside the tubes can be found by

$$\Delta P_{true} = \Delta P_{exp} - \Delta P_{en} - \Delta P_{ex} \tag{C.11}$$

and if substituted in Equation (C.8) the apparent friction factor f_{app} can be calculated. The latter is higher than the friction factor obtained in fully developed flow, which is the desired result from a design point of view. The friction factor for fully developed flow was calculated according to Shah and London (1978) by

$$f = \frac{f_{app} \operatorname{Re}(4x^{+}) - 1.25}{\operatorname{Re}(4x^{+})}$$
(C.12)

Finally, it should be noticed that the ratio f/f_{app} or the equivalent pressure drop ratio should never exceed the ratio of the hydrodynamic entrance length to the actual length of the device (Bird et al., 1960). The hydrodynamic entrance length can be found by (Perry and Green, 1999)

$$\frac{L_e}{D} = 0.370 \exp(-0.148 \operatorname{Re}) + 0.055 \operatorname{Re} + 0.260 \cong 0.055 \operatorname{Re} \text{ for } \operatorname{Re} > 40 - 50$$
(C.13)

The calculations performed, showed that the above constraint was never exceeded. Therefore, the friction factors reported correspond to fully developed flow.

APPENDIX D

ANALYTICAL METHODS

D.1 UV-Vis Measurements

All measurements were performed with a Hitachi U-2000 spectrophotometer. All calibration curves are on a mass basis. The standards for the calibration curve were prepared gravimetrically by dissolving a known amount of solute to a certain mass of solvent. The solvent used for both potassium nitrate and paracetamol was deionized water. Measurements were performed at 300.6 nm and 290 nm for KNO₃ and paracetamol respectively. The respective calibration curves are given in Figures D.1 and D.2.

D.2 Density Measurements

Density measurements were performed for aqueous KNO₃ and ethanolic salicylic acid solutions. All measurements were obtained with an Anton-Paar DMA-46 density meter at 25°C with an accuracy of ±0.0001 g cm⁻³. Calibration of the instrument was performed with deionized water of a resistivity larger than 10 megohm cm and air. The calibration was checked by measuring the densities of ethanol (99.9%, Sigma Aldrich, St Louis, MO), methanol (99%>, HPLC grade, Fisher Scientific, Pittsburgh, PA) and ethyl acetate (99.9% Assay, Fisher Scientific) and comparing the results with literature values (Perry and Green, 1999). The agreement was better than 0.0006 g cm⁻³.



Figure D.1 UV calibration curve for aqueous KNO₃ solutions.



Figure D.2 UV calibration curve for paracetamol.

Calibration standards were prepared gravimetrically by dissolving a known mass of solute in a predetermined mass of solvent. The whole concentration range, from almost zero to concentrations close to the saturation point, was explored. Each value presented is the average of at least two measurements, with the reproducibility between measurements being better than ± 0.0004 g cm⁻³ for all data points. The data obtained for KNO₃ and salicylic acid are shown in Figures D.3 and D.4 respectively. Figure D.3 also contains data obtained from the literature (Daniel and Albright, 1991; Isono, 1984), which show very good agreement with the present measurements.

D.3 Determination of the Refractive Index of a Solid with the Method of Oblique Illumination

The method of oblique illumination utilizes a microscope and a series of liquids with known refractive index. It is an immersion technique, namely, the solid is immersed into a liquid of known refractive index and the goal is to match the refractive index of the liquid and the solid. It also consists of a trial and error procedure, which will usually give a precision in the determination of the solid's refractive index within 0.005 units. The latter is reasonably good for use in optical models when performing laser diffraction measurements. The method of oblique illumination consists of the following steps.

- 1. The solid is spread on a glass piece and a few drops of a liquid of known refractive index are applied.
- 2. The decentering iris diaphragm of the microscope is positioned in such a way that approximately half the field of view is dark (which side is dark does not matter).



Figure D.3 Density calibration curve at 25°C for aqueous KNO₃ solutions.



Figure D.4 Density calibration curve at 25°C for ethanolic salicylic acid solutions.

- 3 If the solids have a higher refractive index than the liquid then they will be brighter towards the dark half of the field view, see Figure D.5a.
- 4. If the solids have a lower refractive index than the liquid then they will be darker towards the dark half and brighter towards the bright half, see Figure D.5b.
- 5. The last two liquids used should also be measured for refractive index. In these experiments the measurements were performed with an Abbe–3L refractometer.



Figure D.5 Determination of the refractive index of L-asparagine monohydrate: a) The refractive index of the solid is higher; b) the refractive index of the solid is lower.

D. 4 GC Analysis of Isopropanol

Analysis of isopropanol was performed in a HP 6890 series gas chromatography system interfaced with a HP 7694 automated headspace sampler. An Innowax column (19092N-123, 30 m x 0.0530 mm x 1.0 μ m film thickness) suitable for polar compounds was used for the analysis. The operating conditions for the analysis are listed below.

GC Parameters		
Sample size (µl)	5	
Column Flow (cm ³ /min)	7.7	
Column P (psig)	7	
Detector T (°C)	260	
Oven T (°C)	110	
Inlet T (°C)	120	
H_2 flow (cm ³ /min)	40	
Air Flow (cm ³ /min)	450	
Make up He (cm ³ /min)	30	
Run Time (min)	10	
Inlet flow (cm ³ /min)	8	

Autosampler Parameters		
Oven T (C)	85	
Loop T (C)	90	
Transfer line T (C)	100	
Vial P (psig)	25.1	
Carrier P (psig)	5.6	
GC Cycle time (min)	12	
Vial Equil time (min)	15	
Pressure equil time (min)	0.5	
Loop fill time (min)	0.3	
Loop equilibration time (min)	0.2	
Injection time (min)	0.1	

A calibration curve covering % weight concentrations between 0 and 1.3 % was constructed; it is shown in Figure D.6. Therefore, the samples obtained from the MHFC were diluted before analysis.



Figure D.6 GC calibration curve for isopropanol.

APPENDIX E

CALCULATION OF PRIMARY NUCLEATION RATES

E.1 Theory

The relationships presented below are all extensions or refinements of the classical nucleation theory. As such, they are appropriate only for order of magnitude calculations of primary nucleation rates. However, they can indicate the dominant nucleation mechanism (Mersmann, 1996) or serve as means to provide general relationships for the prediction of the metastable zone width (Mersmann and Bartosch, 1998; Kim and Mersmann, 2001).

Primary nucleation rates can be obtained from the following equation

$$B_{primary} = 0.965\phi_{het} \frac{D_{AB}}{d_m^5} \left(\frac{\Delta C}{C_c}\right)^{7/3} \sqrt{f_{het} \ln \frac{C_c}{C^*}} \exp\left(-1.19f_{het} \frac{\left[\ln \frac{C_c}{C^*}\right]^3}{\left(\nu \ln S\right)^2}\right)$$
(E.1)

where in the absence of data the diffusion coefficient can be obtained from the Stokes-Einstein equation

$$D_{AB} = \frac{k_B T}{3\pi\mu d_m} \tag{E.2}$$

and the molecular diameter is approximated by (Mersmann, 2001)

$$d_m = \sqrt[3]{\frac{1}{C_c N_A}} \tag{E.3}$$

The heterogeneity factor φ_{het} was found to be approximately equal to 10^{-11} , while the heterogeneity nucleation factor f_{het} is close to 0.1 for most inorganic systems (Mersmann, 2001). These two quantities are unity in the case of homogeneous nucleation. In the latter case the following relationship is also used (Mersmann, 2001)

$$B_{hom} = 1.5 \frac{D_{AB}}{d_m^5} \left(\frac{C}{C_c}\right)^{7/3} \sqrt{K \ln \frac{C_c}{C^*}} \exp\left(-\frac{16\pi}{3} \left[K \ln \frac{C_c}{C^*}\right]^3 \frac{1}{\left(v \ln S\right)^2}\right)$$
(E.4)

where the constant K is usually assumed to be equal to 0.414.

E. 2 KNO₃ Calculations

Sample calculations for Run 10 of the SHFC-CST in series and Run 8 of the once through operation mode presented in Figures 3.7 and 3.9 respectively are given here. The following parameters were used in the calculations:

C _c (Mersmann, 2001)	2110
d_m (m), as found from Equation (E.4)	9.23 x 10 ⁻¹⁰
φ _{het}	10-11
fhet	0.1
D _{AB} (Daniel and Albright, 1991)	10 ⁻⁹
Ν	2

Based on the temperatures and concentrations quoted in Figures 3.7 and 3.9, Equation (E.4) yields:

	Run 10, SHFC-CST in series	Run 8, Once through
С	3.412	3.317
C*	3.135	2.976
B _{het}	$1.46 \ge 10^8$	3.36×10^{12}
E. 3 Paracetamol Calculations

The following parameters were used for the calculations (Worlitschek and Mazzotti, 2004)

C _c	8.573
d _m	7.18 x 10 ⁻¹⁰
Phet	10 ⁻¹¹
fhet	0.1
D_{AB} (found from Equation (E.2))	7.70 x 10 ⁻¹⁰
ν	1

Heterogeneous and homogeneous nucleation rates were obtained by Equation (E.4). In the later case both the heterogeneity factor and the heterogeneous nucleation factor were set equal to unity. Results are as follows:

	B_{hom} (no m ⁻³ s ⁻¹)	B_{het} (no m ⁻³ s ⁻¹)
Run 1	2.04×10^8	2.65×10^{19}
Run 2	4.05 x 10 ⁻¹⁷	$4.09 \ge 10^{16}$
Run 3	$1.36 \ge 10^{-40}$	$1.22 \ge 10^{14}$
Run 4	1.75 x 10 ⁻⁶²	$6.09 \ge 10^{11}$

APPENDIX F

DERIVATION OF EQUATION (4.4)

The cross flow velocity of an antisolvent exiting the pores of a membrane can be simply calculated by

$$u_{AS,cr} = \frac{V_{AS}}{A_{p,tot}} = \frac{J_{As}A_m}{N_p \pi \frac{d_p^2}{4}} = \frac{J_{As}N\pi D_o L}{N_p \pi \frac{d_p^2}{4}} \Longrightarrow u_{AS,cr} = \frac{4J_{As}ND_o L}{N_p d_p^2}$$
(F.1)

One then has to calculate the number of pores of the membrane to obtain a measure of the cross flow velocity. This task is performed here by assuming pores of circular cross section with no constrictions or enlargements, which can be tortuous. This model becomes equivalent to the straight cylindrical pore model if $\tau_m = 1$; it presents the advantage that it can account for the additional pore volume induced by the tortuous nature of the pores.

The total volume of the pores can be found based on the membrane porosity and its total volume:

$$V_{p,tot} = N_p V_p = \varepsilon_m V_m = \varepsilon_m N \pi \frac{D_o^2 - D_i^2}{4} L$$
 (F.2)

The volume of an individual pore is given by

.

$$V_{p} = \pi d_{p}^{2} \frac{D_{o} - D_{i}}{4} \tau_{m}$$
(F.3)

The number of pores is then found by combining Equations (F.2) and (F.3)

$$N_{p} = \frac{V_{p,tot}}{V_{p}} = \frac{\varepsilon_{m} N \pi \frac{D_{o}^{2} - D_{i}^{2}}{4}L}{\pi d_{p}^{2} \frac{D_{o} - D_{i}}{4}\tau_{m}} \Longrightarrow N_{p} = \frac{\varepsilon_{m} N (D_{o} + D_{i})L}{d_{p}^{2} \tau_{m}}$$
(F.4)

Substituting Equation (F.4) in Equation (F.1) the final form of the sought relationship is obtained:

$$u_{AS,cr} = \frac{4J_{As}ND_oL}{\frac{\varepsilon_m N(D_o + D_i)L}{d_p^2 \tau_m} d_p^2} \Rightarrow u_{AS,cr} = 4J_{As} \frac{D_o}{(D_o + D_i)} \frac{\tau_m}{\varepsilon_m}$$
(F.5)

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