NANYANG TECHNOLOGICAL UNIVERSITY
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ECONOMIC ANALYSIS OF MEMBRANE-BASED SEPARATION OF BIOCATALYST: MODE OF OPERATION AND STAGE CONFIGURATION

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SCHOOL OF CHEMICAL AND BIOMEDICAL ENGINEERING

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A thesis submitted to the Nanyang Technological University in partial fulfilment of the requirement for the degree of Master of Engineering

2021

Statement of Originality

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Sridhar Kapavarapu

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Abstract

In the pharmaceutical industry, biocatalysts are mainly utilized for synthesizing Active Pharmaceutical Ingredients (API's) and their intermediates. API purification is one of the vital steps in pharmaceutical downstream processing as the product purity affects the market value of the drug. Membrane separation is a cost-effective and sustainable separation process mainly preferred due to its lower energy consumption. However, there is not any specific analysis that deals with the economics of a membrane separation unit specific to biocatalyst separation in pharmaceutical industry. So, this study presents insights into the economics of an ultrafiltration (UF) unit for various operating modes and stage configurations in biocatalyst separation. It was estimated from the current study that a capital expenditure of $1.35 million and an annual operating expenditure of $85 thousand are required to set up a new UF unit to obtain 640 million litres of permeate annually for input of 100,000 L/hr of feed. The cost components of the UF unit at constant flux mode, constant transmembrane pressure (TMP) mode and four different stage configurations were assessed. The analysis on the mode of operation to obtain the desired recovery of 80% suggests operating the unit at a constant flux mode (capital of $1.35 million and annual operating cost of $85.60 thousand at 55 LMH) rather than constant TMP (capital of $2.34 million and annual operating cost of $124.25 thousand at 0.25 MPa) mode due to higher area requirement and annual membrane replacement costs in the latter case. The analysis of the stage configuration shows the variation of cost expenditures with additional stages to improve recovery and purity. When compared to the single-stage configuration, the costs nearly doubled (capital of $2.82 million and annual operating cost of $145.77 thousand) in the three-stage configuration to operate the unit with the highest purity and recovery. This study can be used to understand the variations in expenditure to choose the right operating values and make decisions during industrial design and planning.

CHAPTER 1. Background and Research Objective

Generally, biocatalysts are used in the pharmaceutical industry as an additive to get pure Active Pharmaceutical Ingredients (APIs). However, removing the biocatalyst is necessary to maintain the purity of APIs post-formation in the downstream processing of drugs. Membrane technology is one of the separation techniques considered advantageous in this regard due to good selectivity, lower footprint, continuous processing, and eliminating the use of additional solvents or immobilizers for the biocatalyst. The bio-catalysis happens upstream and consists of the API-biocatalyst mixture which is separated downstream as pre-concentration, diafiltration, and final concentration. The pre-concentration of this mixture occurs in a UF unit, where the API is removed as permeate and biocatalyst as retentate. The biocatalyst stream is then directed to the diafiltration unit and part of it is recycled back for reuse, and finally, the final permeate and retentate streams are concentrated in a final concentration unit using advanced membrane separation techniques. Figure 1.1 illustrates the membrane separation step through ultrafiltration, where approximately 90% of the biocatalyst has been retained.

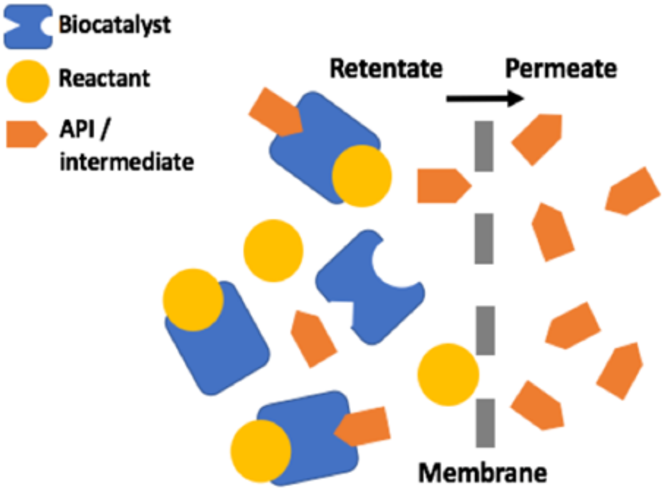


Figure 1.1. Membrane-based purification of Active Pharmaceutical Ingredients (API)

The current objective of the study is to estimate the various cost components in installing an ultrafiltration membrane unit in the pharmaceutical industry. And then to study the variation in trends of the cost components with the membrane parameters for the unit operated at different modes. Further, the variation of the cost components with the stage configuration and pH is discussed. The obtained results can be used while designing and installing an ultrafiltration membrane unit. This study is novel based on how the economics of a UF unit is affected by the change in membrane parameters for two different modes of operation and change in stage configuration specific to a general biocatalyst separation. This study suggests a viable mode of operation and can be used as a basis in future studies to obtain various results for various other biocatalyst separations.

CHAPTER 2. Introduction

2.1 Literature Review

Over the past few years, the use of biocatalysts in the manufacture of active pharmaceutical ingredients (API) has been growing in the pharmaceutical industry. This is because biocatalysts are capable of enabling high specificity of targeted molecules due to their inherent structures. As a result, the synthesis of unconventional intermediates and specific chiral species has grown in API production. So, the use of biocatalysts is expected to grow at a faster pace in the aspect of advances in the stabilization of proteins and the ability of protein generation with novel activities, and many other advantages concerning safer and sustainable chemical synthesis. But, unfortunately, the exploitation of the benefits of biocatalysts remains hindered, mainly because of the challenge in the separation of the biocatalysts that necessitates its use in the immobilized form instead of the free native form that gives superior bioactivity [1]. To this end, membrane-based separation will not only provide for high-precision partition without the need for additional solvents but also allow for the use of the biocatalysts in free solution as part of a continuous process [2].

The pharmaceutical industry plays an essential role in the manufacture of drugs that are critical for human lives. The drugs formulated in the upstream process consist of APIs and biocatalysts separated in the final purification step of the downstream process [3]. APIs are the final drug components that are biologically active and functional [4]. So, the final purity of the product plays a critical role in determining the launch of the product and revenue generation in the market.

The bio-catalysis reaction, which happens upstream, consists of APIs and biocatalysts purified downstream using membrane filtration [3]. The biocatalyst separation in the downstream takes place in three units: (i) pre-concentration, (ii) diafiltration, and (iii) final concentration. The pre-concentration of API and biocatalyst stream occurs in a UF unit, where the biocatalyst is removed as retentate. It is then directed to the diafiltration unit, and further, the final permeate and final retentate streams are concentrated in a final concentration unit using nanofiltration (NF)/reverse osmosis (RO) techniques depending on the required product [5–7].

Biocatalysts are predominantly used in the synthesis of pharmaceutical intermediates [8,9]. For example, Bovine Serum Albumin (BSA) is one of the biocatalysts employed in many organic synthesis reactions [10,11]. The various advantages of using BSA in pharmaceutical drug processing were mentioned by Nora'aini et al. [12]. The purity of the final product is generally considered the highest at the point where the biocatalyst rejection is maximum. Previously many experiments were conducted to study the rejection of BSA (biocatalyst) in the ultrafiltration processes [12–14].

Many industries use many separation technologies such as chromatography, liquid-liquid extraction, membrane filtration, centrifugation, and crystallization to concentrate and purify the pharmaceutical products in the downstream process [15]. In addition, the APIs are usually heat sensitive, and the separation must be carried out at an ambient temperature [16]. Membrane technology is one of the few sustainable ways to separate the biocatalyst from APIs at low temperatures [17]. Membrane technology is preferred over other separation processes mainly due to its cost-effectiveness, lower footprint, flexible design, and better integration with the hybrid processes [18]. The filtration in pharmaceutical industries is carried out using various membrane separation technologies depending on the size range of the constituents in the feed [19]. The different technologies used in the pharmaceutical industries are listed in the literature [20,21]. Due to the recent advancements in membrane filtration applications and the growing demand for purer drugs, the need for membrane technology application in pharmaceutical industries will rise in the future [22]. The biocatalyst BSA retains on the semipermeable membrane, whereas the APIs pass through the membrane due to its smaller size, as shown in Figure 1.1 previously. Membrane filtration could be used as either a pre-treatment or a post-treatment step depending on the feed type and the desired product properties [23].

The membrane unit can be operated in (i) constant flux mode and (ii) constant TMP mode. In the constant flux mode, the flux is maintained constant by rising the TMP [24]. However, the flux tends to drop in a filtration unit due to the fouling. Therefore, the TMP must be increased accordingly to operate the unit at constant flux to avoid the drop. In the constant TMP mode, the unit is operated at a specific TMP within the ultrafiltration range [25]. And specific TMP has an initial flux value that drops and stabilizes over time. The flux declines due to fouling, thereby decreasing the permeation rate at a specified membrane area.

The costs of installation and maintenance of various operations generally play a significant role during the planning and designing of the industry from an economic perspective. The downstream processing cost in the pharmaceutical industry is a major portion of 70-80% of the total production costs [26,27]. Estimating the total cost estimate of an operating unit gives a clear picture of the profitability and economic benefits of installing the unit. An estimation of the cost components for an ultrafiltration unit for the treatment of 20 m^3/h of impure water was done by Drouiche et al. [28] previously. It involved a capital expenditure of $210,000, and it was found that the operating cost to maintain the unit was low, which is not expensive to set up a unit in the region where the study was conducted. Recently a study on process up-gradation of a wastewater treatment plant was done by Bai et al. [29]. It was found that the renovation of the plant with a UF membrane technology is feasible, and the investment amounts up to CNY 25.626 million for a production capacity of 1250 m^3/h of wastewater. Other studies dealt with the economics of UF membrane technology, like using a UF membrane unit in series with an RO unit to treat the secondary wastewater effluent, which was found to be promising with a permeate cost of up to two US \$0.15/m^3 [30]. This study provided estimates of various individual and integrated membrane system combinations of varying capacities as a pre-treatment step for NF, and when compared with the previously existing cost estimates, the costs were in agreement for lower capacity units but not for higher capacity units (>10 mgd). It was observed that the assessments involved in the filtration treatment were much beneficial when the permeate flux and recovery were increased within limits [31]. The cost comparisons of various UF and NF configurations with conventional liquid-solid separation techniques were carried out. For facilities with lower capacities (<5 mgd), low-pressure membrane filtration was cost-effective to remove particles from wastewater having utmost moderate turbidity [32].

Conventional distillation is one of the traditional separation techniques used in industries to separate volatile liquid mixtures. A cost comparison of membrane separation and the traditional distillation of binary mixtures was studied by Hinchliffe et al. [33]. It was found that the membrane separation was cost-effective when compared to distillation unless the separation is carried out at a very high temperature, which is when the membranes tend to degrade, accounting for additional replacement costs thermally. So, the temperature must be in the lower range while using the membrane separation technology for better performance at a lower cost, as reported in the articles [34,35]. The review by Homoh et al. [36] mentioned the relative cost comparison of membrane separation with various adsorption and cryogenic processes depending on the type of processing like gas processing, air separation processing, and liquid hydrocarbon processing. It was concluded that the use of membrane filtration technology is cost-effective at lower flow rates. Economic comparison of membrane chromatography, a hybrid of the membrane filtration and chromatography techniques, was conducted and found cost-effective over conventional chromatography [37]. So, the cost of a membrane filtration unit would be lesser than chromatography. Many other economic comparisons of membrane technology with evaporators [38], conventional processes like flocculation, ozonation [39] have shown that membrane technology is beneficial when used as a separation technique.

During the separation of APIs, the downstream of drug processing, purity, and recovery of the final product plays an essential role in the sale of drugs. A higher amount of purer products is beneficial in improving profits and reducing reactant waste [40]. Drug manufacture is divided into many processing steps, and the recovery of each step is generally less than 100%. When these steps are integrated to function together, the recovery of the final product decreases (recovery of the desired product decreases as the drug manufacture progresses). So, theoretically, the recovery of each step must be maximized to get the maximum overall recovery of the product. The purity of the pharmaceutical product is vital during the separation process as it affects the drug quality. A fraction of impurity could alter the drug formulation that can be dangerous and incur economic losses when manufactured in large quantities, especially in pharmaceutical products, as these impure drugs might pose a danger to human lives [41].

2.2 Purpose and Overview

Though there are a significant number of articles about the economic analyses of membrane filtration applications exist, there was not any related to ultrafiltration of a biocatalyst during the current introspection. So, this motivated me to make an attempt to perform the economic analysis of a UF unit for biocatalyst separation in the pharmaceutical industry. The total cost of a membrane system depends on the mode of membrane operation: constant flux or TMP, thereby explicitly on membrane parameters: feed flowrate, flux, transmembrane pressure (TMP), membrane area, recovery, filtration rate. The current analysis consists of the expenditures involved in installing a UF unit, variation of cost components with the mode of operation, and different stage configurations are built to analyze the cost components for a constant feed flow of 100,000 L/hr. This study provides a theoretical approach on the cost dependence on operating parameters, and the obtained trends can be used during the planning stage of installing an ultrafiltration membrane unit. This study is unique in terms of how the economics of a UF unit is affected by the mode of operation and change in stage configuration of general biocatalyst separation in pharmaceutical industry. This study suggests an economically viable operating mode and can be used as a basis of reference in future studies and can obtain various results for the required set of assumptions. The difference in feed properties such as viscosity and concentration and the module type is not considered in this study.

2.3 Workflow

The methodology used in this study is presented in Chapter 3. It consists of the following: the cost structure, ultrafiltration unit, economic evaluation, variation of cost based on different modes of operation, the effect of various stage configurations, and effect of pH on cost components of the UF unit as subsections, respectively.

The results were presented and discussed in Chapter 4, which details the various costs involved in installing a UF unit for biocatalyst separation and the variation in cost components with different operating modes, stage configurations, and pH. Finally, the conclusion is drawn in Chapter 5, while the challenges posed are detailed in Chapter 6.

CHAPTER 3. Methodology

The total cost of an ultrafiltration membrane unit having a specific cost structure is initially predicted. Then, the variation in cost components with the membrane parameters for different modes of operation is studied. Finally, the variation of cost components with membrane stage configuration and pH was discussed. The complete study is divided into the following parts for a detailed explanation.

3.1 Cost Structure

The various costs involved in installing, operating, and maintaining a unit operation vary depending on the type of operation and the components separated. In the present study, the different types of costs involved in estimating the total cost expenditure of a membrane unit are shown in Figure 3.1 [42]. The four main expenditures are capital cost, operating cost, depreciation cost, and cleaning cost.

Capital cost investment consists of major equipment costs, equipment installation costs, transportation and taxes, contractor and construction overheads, contingency costs, and auxiliary facilities costs. More specifically, the major equipment cost spans the purchased cost of the membrane setup (including membrane elements, membrane skid that includes membrane housing, diaphragm, and parts), feed pump, recirculation pump, and feed storage tank. The equipment installation cost consists of the industrial piping and instrumentation required to construct a unit. The transportation and taxes include the costs and additional purchase taxes to ship and carry the equipment to the setup location. The contractor and construction overhead expenses refer to the employee salaries and benefits. The contingency cost is a buffer to allow for unpredictable price fluctuations and variations in design consideration. The auxiliary facilities cost includes the cost of the site and the required utilities and can be excluded if the planned unit operation is added to an existing plant. As for operating cost, this accounts for labor, electricity and energy, and membrane replacement. Both the capital and operating costs contribute the most towards the total cost expenditure, out of which the former has a comparatively higher contribution. The other types of costs involved are depreciation and cleaning costs. The depreciation cost is generally a fraction of the capital cost and includes the decrease in the unit's value with time [43]. The cleaning costs are part of maintenance to prolong the membrane lifespan and maintain the separation performance.

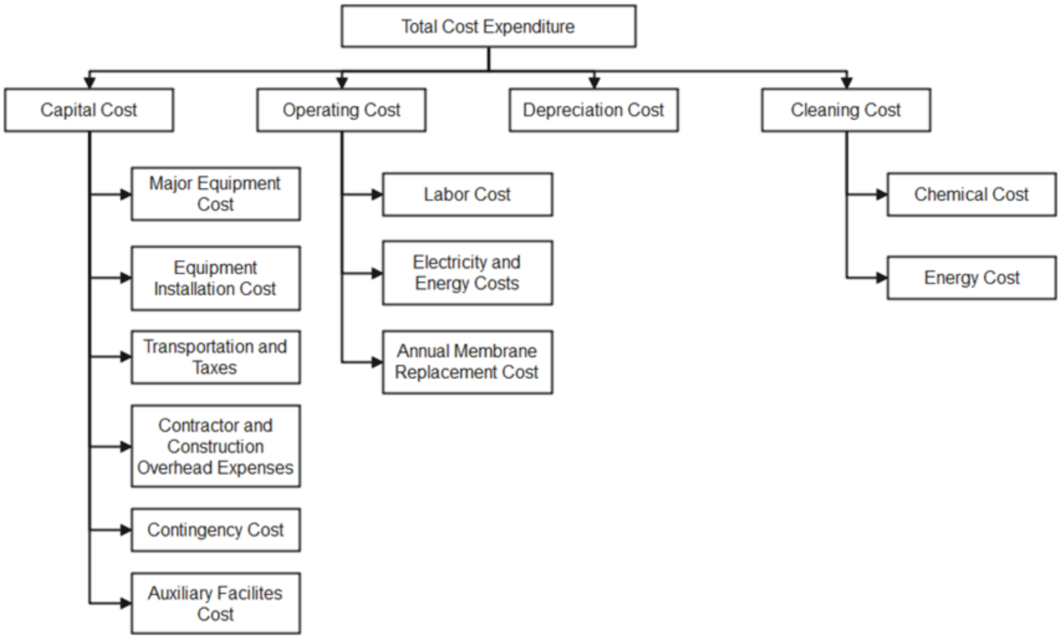


Figure 3.1. Detailed cost breakdown for the installation of a general membrane unit

3.2 Ultrafiltration Unit

Figure 3.2 illustrates the ultrafiltration membrane unit operation considered for evaluating the costs in the present study. The API plus biocatalyst feed is pumped to the pre-concentration UF unit by a centrifugal pump upstream, separating through the membrane module. The number of modules installed depends on the total area of membrane required for attaining the desired separation. The flow rates and absolute pressures are measured using flowmeters and pressure gauges, respectively. After the separation, the retentate (with a higher biocatalyst concentration) is sent to the adjacent diafiltration unit for further processing. At the same time, part of it is recirculated back to the upstream to reuse the biocatalyst [44]. And the permeate has a higher concentration of API which is sent for the final concentration unit.

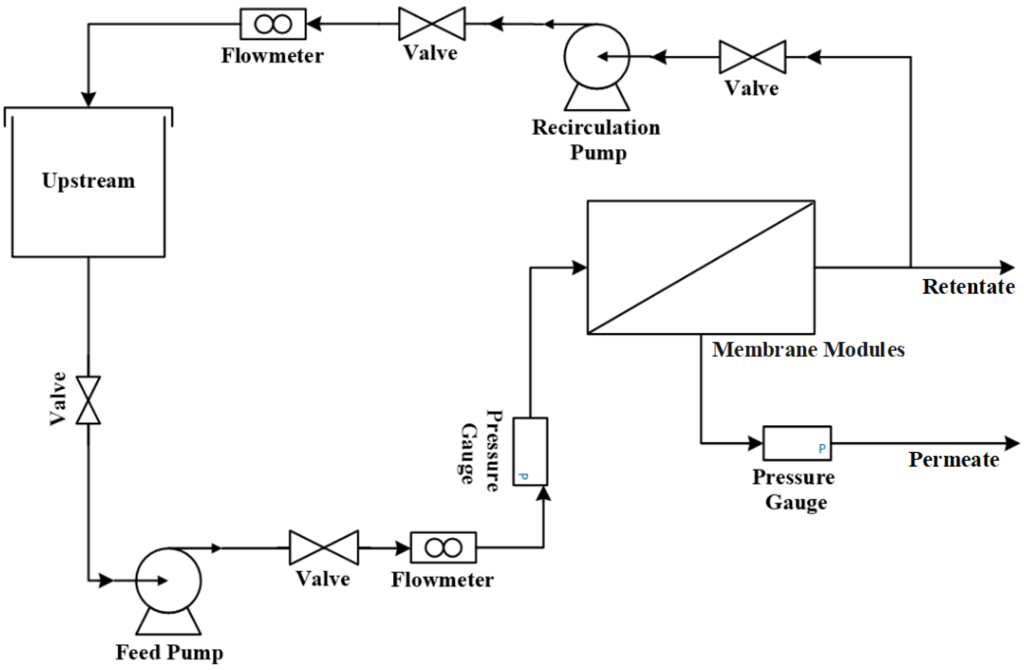


Figure 3.2: Schematic of the ultrafiltration unit with the associated equipment used in the current study

3.3 Economic Evaluation

Total expenditure plays a vital role in the competitive analysis against other technologies and is crucial in the planning stages. The present study evaluates the total annual cost for an ultrafiltration membrane separation while calculating the major cost components. The various types of costs involved, equations used for estimation, and assumptions and comments are clearly shown in Table 3.1. Out of the different capital cost estimation methods, such as the module costing method, CEPCI method, Lang factor method, six-tenths rule [42], the module costing technique was employed to evaluate the total capital expenditure in the current study. The lang-factor technique is avoided over time as the deviation of the estimate from the actual cost is relatively high. This is because it uses a single multiplication factor for the entire unit type, unlike the module costing technique, where multiple factors are used for equipment type [45]. The CEPCI method is used only to estimate individual equipment inflation, and the six-tenths rule is used when the evaluation is done for a similar unit of known capacity. In the module costing method, the purchased costs of the major equipment are multiplied by a bare module factor of the respective equipment to obtain the total bare module cost and hence is considered the best for preliminary cost estimation. It is assumed that the equipment is made of carbon steel and operated at ambient and moderate pressure. Bare module costs of the major equipment are calculated using the cap cost excel program [42]. The costs of the membrane equipment (elements, housing, membrane, diaphragm, and parts) are adjusted from the literature to the present time using the current CEPCI index to consider the inflation. An approximate value of 3.2 is used as the bare module factor for the membrane separators [46]. Technical parameters and costs are used in the study, as shown in Table 3.2, along with the assumptions made.

Table 3.1. Various costs, equations, and assumptions involved in the cost estimation method used in this evaluation

Cost	Equation	Assumptions and Comments	Reference
Total cost of membrane elements ($C_{element}$)	$\boldsymbol{C_{element} = C^{\#}_{one\ element} \times N_{element}}$ $C_{one\ element}$ = Cost of one element $N_{element}$ = Number of elements	The cost of each element varies between \$700 to \$3400. Assumed a spiral wound element.	[47]
Cost of membrane skid (C_{skid})	$\boldsymbol{C_{skid} = C_{one\ housing} \times N_{housing} \times LF}$ $C_{one\ housing}$ = Cost of one housing $N_{housing}$ = Number of housings in skid LF = Labor factor	31 mil thickness feed spacers. 8-inch housing. Range of LF = 5-7. Four elements in each housing.	[47]
Membrane cost ($C_{membrane}$)	$\boldsymbol{C_{membrane} = \frac{C^{\#}_{unit\ area} \times A}{L}}$ $C_{unit\ area}$ = cost of membrane per unit area A = total area of the membrane L = membrane lifetime	The range of L for pharmaceutical application is 0.5 – 1.5 years. Area of the membrane in each element = 37.5 m^2. Cost of membrane in each element = \$1000. Membranes are needed at the start and then replaced when fouling compromises permeation. This is added to both the capital and operating costs.	[47] [28]
Cost of diaphragm and additional parts of housing and skid ($C_{additional}$)		One-time cost of additional parts.	[28]
Purchased equipment cost of membrane setup ($C_{purchased\text{-}membrane}$)	$\boldsymbol{C_{purchase-membrane} = C_{element} + C_{skid} + C^{\#}_{additional}}$	This is the base price paid to the vendor for buying the equipment.	

Bare module cost of membrane setup ($C_{BM\text{-}membrane}$)	$\boldsymbol{C_{BM-membrane} = \left(C_{purchased-membrane} \times BMF_{membrane}\right) + C_{membrane}}$ $BMF_{membrane}$ = bare module factor of the membrane	$C_{membrane}$ is added here as a one-time capital cost because the membrane is installed initially even before the unit is operated. $BMF_{membrane}$ = 3.2 (assumed)	[42] [46]
Purchased equipment cost of feed pump ($C_{purchased\text{-}feed\ pump}$)		Centrifugal pump made of carbon steel (assume no spare). Feed side pressure = 4 bar. Discharge pressure = (Feed side pressure – TMP) = 1.8 bar. Shaft power = 4.6 kW. Calculated using cap cost excel program.	[30]
Bare-module cost of feed pump ($C_{BM\text{-}feed\ pump}$)		Calculated using cap cost excel program.	[28]
Purchased equipment cost of recirculation pump ($C_{purchased\text{-}recirculation\ pump}$)		Centrifugal pump made of carbon steel without any spares. Feed side pressure = 4 bar. Discharge pressure = (Feed side pressure – Pressure drop across module) = 1 bar. Shaft power = 8.33 kW. Calculated using cap cost excel program	[47] [28]
Bare-module cost of recirculation pump ($C_{BM\text{-}recirculation\ pump}$)		Calculated using cap cost excel program.	[28]

Total bare-module cost of the unit ($C_{BM\text{-}total}$)	$\boldsymbol{C_{BM-total} = C_{BM-membrane} + C^{\#}_{BM-feed\,pump} + C^{\#}_{BM-recirculation\,pump} + C_{membrane}}$	The membrane cost is added to the bare module cost because the membrane is installed before the unit is operated. The direct and indirect costs are included here.	
Total module cost of the unit (C_{total})	$\boldsymbol{C_{total} = 1.18 \times C_{BM-total}}$	18% of the total bare module costs are considered contingency (to account for unforeseen circumstances and additional contractor fees). This is the FCI to add the unit to an existing plant.	[46]
Total grassroots cost (or) Fixed capital investment (C_{FCI})	$\boldsymbol{C_{FCI} = 1.5 \times C_{total}}$	50% of the total module cost is for auxiliary facilities cost. This is the FCI required to install a new unit.	[42] [46]
Total working capital investment (C_{WCI})	$\boldsymbol{C_{WCI} = 0.176 \times C_{FCI}}$	WCI is generally 17.6% of the FCI.	[46]
Total capital investment ($C_{capital}$)	$\boldsymbol{C_{capital} = C_{FCI} + C_{WCI}}$	Capital cost is the sum of FCI and WCI.	
Cost of labor per hour ($C_{labor\text{-}per\text{-}hour}$)	$\boldsymbol{C_{labor-per-hour} = \frac{N \times C}{24}}$ N = number of man-hours per day C = cost of labor per man hour	Man-hour is the number of persons working for a specified time in a day. Assuming three persons working for 1.5 hours a day, which means 4.5-man-hours per day.	[48]
Labor Cost (C_{labor})	$\boldsymbol{C_{labor} = C_{labor-per-hour} \times t_{O\&C}}$ $t_{O\&C}$ = operating and cleaning time in hours	$\boldsymbol{C_{labor-per-hour}}$ is assumed to be 18 \$/man-hour. Assumed time distribution: Operating time = 8000 hr/year	

		Cleaning time = 547.5 hr/year Shutdown time = 172.5 hr/year.	
Energy & Electricity costs ($C_{E\&E}$)	$C_{E\&E} = \frac{PE + RE}{3600 \times 1000} \times C_{electricity} \times t_O$ PE = pressure energy RE = recirculation energy $C_{electricity}$ = cost of electricity in \$/kWh t_O = operating time in hours	Cost of electricity is 0.16 \$/kWh. Operating time is 8000 hr/year. The calculation of *PE* and *RE* is discussed in table 3.2.	[49]
Operating Expenditure ($C_{operating}$)	$C_{operating} = C_{labor} + C_{E\&E} + C_{replacement}$	This includes the membrane replacement cost and is calculated on an annual basis.	[47]
Cleaning cost ($C_{cleaning}$)	$C_{cleaning} = C_{energy} + C_{chemical}$	Cleaning frequency is assumed to be once per day.	
Depreciation cost ($C_{depreciation}$)	$C_{depreciation} = 0.1 \times C_{capital}$	This is 10% of the total capital investment.	[47]
Total cost expenditure per year ($C_{expenditure\text{-}annual}$)	$C_{expenditure-annual} = C_{operating} + C_{depreciation}$		
Total cost expenditure ($C_{total\text{-}expenditure}$)	$C_{total-expenditure} = C_{expenditure-annual} \times t$ t = number of years of operation of the unit		

Note: The costs marked with # as superscript are adjusted using the CEPCI index value 607.5 [50]

Table 3.2. Various parameters and assumptions involved in the current cost evaluation

Variable	Equation	Assumptions and Comments	Reference
Crossflow (or) feed-flow rate (Q_{feed})		This is the desired volume of feed that is treated.	

Recovery (*R*)		An assumed value of 80% is fixed for the current UF unit.	
Filtration rate ($Q_{permeate}$)	$\boldsymbol{Q_{permeate} = Q_{feed} \times Rec}$	The volume of permeate produced.	
Retentate Flowrate ($Q_{retentate}$)	$\boldsymbol{Q_{retentate} = Q_{feed} - Q_{permeate}}$		
Transmembrane Pressure (TMP)		The range of TMP for UF is 0-0.35 MPa.	[51]
Flux (*J*)		In most cases, the practical maximum is around 70 LMH. However, it cannot exceed 100 LMH.	[52]
Membrane Area (*A*)	$\boldsymbol{A = \frac{Q_{permeate}}{Flux}}$	Calculated from targeted flux and permeate flow rate.	
Pump Efficiency		A general range is 75-93%. Assumed conservatively here as 75%.	[53]
Pressure Energy (*PE*)	$\boldsymbol{PE = Q_{permeate} \times TMP}$		
Pressure-drop across modules (*ΔP*)	$\boldsymbol{\Delta P = \Delta P_{modules} + \Delta P_{piping}}$	Pressure-drop across the modules ($\Delta P_{modules}$) is assumed as 3 bar. Pressure drop across the piping (ΔP_{piping}) is calculated from average flow across the module. Assumed DN125 (around 4.8 inches) pipe diameter and 30.48 m of a total piping length, as the pressure head, should not exceed 3 ft for 100 ft length of pipe.	[54] [47] [55]
Recirculation Rate ($Q_{recycle}$)	$\boldsymbol{Q_{recycle} = R \times Q_{retentate}}$	*R* is the recycle ratio.	[56] [57] [58]
Recirculation Energy (*RE*)	$\boldsymbol{RE = Q_{recycle} \times \Delta P}$	Assumed that both the permeate and retentate are recirculated back to the feed tank.	

Annual Production (V)	$V = \frac{Q_{permeate} \times t_O}{1000}$ t_O = operating time	Depends on the amount of permeate produced.	

3.4 Variation of Cost Components Based on the Mode of Operation

The filtration process depends on six filtration parameters: flux, TMP, feed flowrate, filtration rate, membrane area, and recovery. But these parameters depend on one another. The feed flow rate and filtration rate are related to each other based on the desired recovery, as shown in equation (2). The pressure drop across the module depends on the feed flow rate. The filtration rate depends on the membrane area and flux shown by equation (3), depending on TMP through Darcy's law [59,60]. The degrees of freedom are calculated to account for the interdependency of these membrane parameters:

$$DOF = N_v - N_e \qquad (1)$$

Where N_v is the number of variables and N_e is the number of independent equations. The flux, which depends on the threshold flux characteristic of the particular membrane is used [61]. A TMP within the UF range of 0 - 0.35 MPa was evaluated in this study; the flux depends on TMP and stabilizes at higher TMP [62]. The variables are filtration rate, feed flow rate, recovery, flux, TMP, and membrane area, so N_v = 6. The two independent equations (2) and (3), along with Darcy's law [63] (i.e., $N_e = 3$), indicate recovery as the ratio of filtration rate to feed flowrate and membrane area as the ratio of filtration rate to flux:

$$\boldsymbol{Q_{filtration} = Q_{feed} \times Rec} \tag{2}$$

$$\boldsymbol{A = \frac{Q_{filtration}}{Flux}} \tag{3}$$

Therefore, calculating from equation (1), we get DOF = 3, which is the number of variables needed to define the operation of a membrane unit.

A constant feed flowrate is taken as the basis in the current section for evaluation as the membrane unit is installed downstream, the feed entering (depends on the upstream) doesn't alter amidst the operation. The amount of filtrate varies depending on the variation in the membrane parameters, as discussed below.

In industrial applications, the membrane area is generally fixed once the unit starts operating because it is tedious and expensive to replace or add more membrane area. So, there is a requirement to know how the cost components vary with respect to the membrane parameters (membrane area in specific as it highly affects the initial capital investment) during the design stage of a membrane unit.

In an ultrafiltration protein separation process, as the TMP rises, the flux will increase and become constant at a certain TMP called the limiting flux [64]. At low TMP's the flux depends on TMP in the pressure-dependent regime. And the limiting flux is reached at a higher TMP in the pressure-independent regime [65]. There is a transition point between these regimes where the flux starts to stabilize, called critical flux, where the irreversible fouling starts to happen, above which limiting flux is attained [65,66]. The essential onset of critical flux marks the transition from concentration polarization to extensive fouling [67,68]. The variation of flux with TMP of protein UF separation was investigated in the literature [69–71].

The approach in which both flux and TMP are varying is generally not preferred in the filtration operation as it makes it difficult to control both the system parameters from a process control point of view. So, typically, either the constant flux mode or the constant TMP mode is used for membrane filtration [72]. Due to the uniform deposition of foulants in case of a constant flux operation compared to the constant TMP mode, it is used in industries widely [73].

3.4.1 Constant Flux Mode

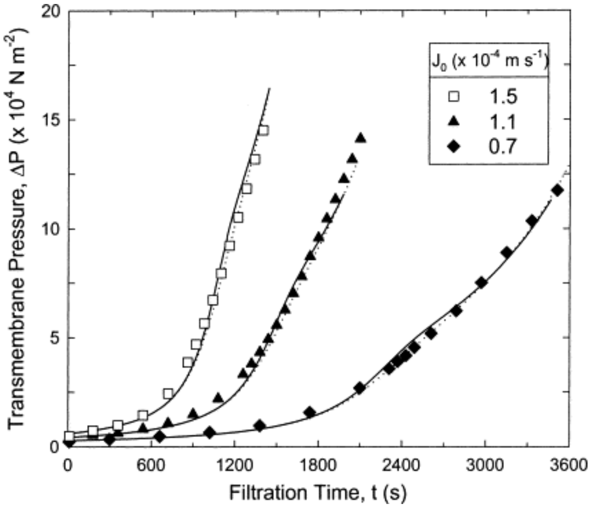
The flux of a filtration unit always drops due to the fouling phenomena. Therefore, to maintain the flux at a constant value, the TMP must be increased accordingly to operate the unit at a constant flux mode. In detail, fouling happens cumulatively over time, and there is a strong tendency for the permeate rate to decrease due to particle buildup. Therefore, the feed increases pressure to make way through the fouling layer and maintain constant flux [24].

Initially, the unit is operated at a specific desired flux at the corresponding TMP. But to avoid the drop in flux, the TMP is increased from its corresponding value to a maximum permissible value to maintain the flux. So, the current section deals with the variation of cost components in the constant flux mode. As shown in the Figure 3.3 (b), the unit can, in general, be operated in three different flux ranges: (i) high, which is around 85 LMH, where the membrane gets fouled quickly within a short period and the TMP should be increased abruptly to maintain the constant flux, (ii) low which is below 25 LMH, where the amount of permeate produced would be generally low and is not desirable. So, a constant flux within the intermediate range 85-25 (better avoiding the extremes) can be employed for obtaining better permeate at lower fouling for a better membrane life.

Now when the unit is operated in a constant flux mode, two cases arise: (i) when the membrane area is constant and (ii) the membrane area varies.

3.4.1.1 Case – 1: Constant Flux Mode and Constant Membrane Area

The current scenario is when the unit is operated at a constant flux and a fixed membrane area. At these conditions, a constant permeate will be recovered from the unit as the amount of permeate is the product of flux and membrane area used. In this case, the operating cost component increases due to an increase in the TMP. The fouling rate increases with an increase in the TMP, thereby reducing the membrane lifetime and might increase the frequency of cleaning and membrane replacement, which causes additional expenditure [74]. The present case's cost variation is calculated at a reasonable constant flux value within the range of 25-85 LMH and a varying TMP within the typical UF TMP range of 0 to 3.5 bar. It can be observed that the flux variation behavior will be almost similar at the different flux values as seen in Figure 3.3 but the initial and ending values vary as higher TMP has to be maintained for a higher initial flux.



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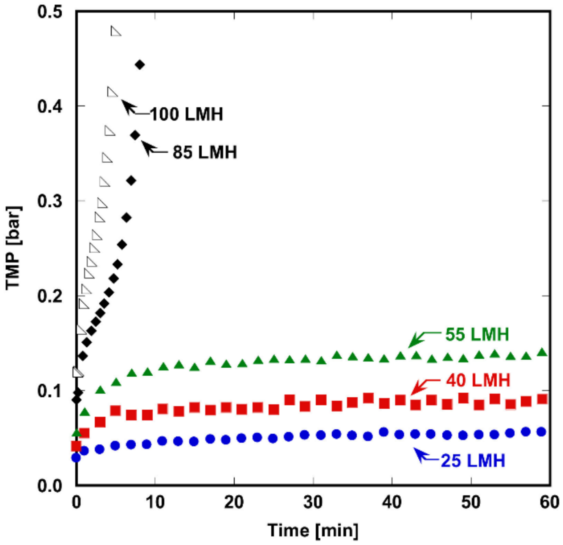


(b)

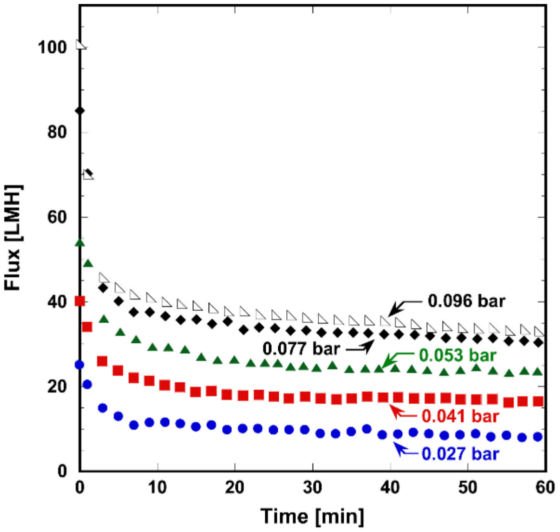
Figure 3.3: (a) Variation of TMP in a constant flux operation. Reprinted with permission from " Transmembrane pressure profiles during constant flux microfiltration of bovine serum albumin" by Chia-Chi Ho, Andrew L. Zydney, Journal of Membrane Science, Volume 209, Issue 2, 15 November 2002, Pages 363-377. Copyright (20002) Elsevier B.V [75], (b) Variation of TMP with time at various constant fluxes. Reprinted with permission from " Comparison of membrane fouling at constant flux and constant transmembrane pressure conditions " by Daniel J. Miller, Sirirat Kasemset, Donald R. Paul, Benny D. Freeman, Journal of Membrane Science, Volume 454, 15 March 2014, Pages 505-515. Copyright (2014) Elsevier B.V [76]

3.4.1.2 Case – 2: Constant Flux Mode and Varying Membrane Area

This scenario is where the recovery obtained at a particular flux is increased by adding additional area. In the current situation, when the permeate produced in Case 1 is less than the desired permeate flow, an additional area is added to increase permeate recovery. The capital increases due to an increase in membrane area, and the operating cost component increases due to the rise in TMP and the permeate rate. In a constant flux mode, since the operating flux is lower than the critical flux, fouling is comparatively low than the constant TMP mode [77].

3.4.2 Constant TMP Mode

In this mode of operation, the unit is operated at a specific TMP within the ultrafiltration range [25]. Each specific TMP has an initial flux value that drops and stabilizes over time. The flux declines due to fouling, and due to this decline; the permeation rate reduces at a specified membrane area. An additional area of a membrane can be added like in the constant flux mode to recover more permeate. Depending on the initial operating TMP, the initial flux can be adjusted at a higher or a lower value. But the flux drop behavior is similar within the TMP range, as shown in Figure 3.4. When the flux drops to a meager value due to the reversible fouling, cleaning must be done to improve the flux recovery. So, the unit is operated at the stabilized flux rather than the initial flux.



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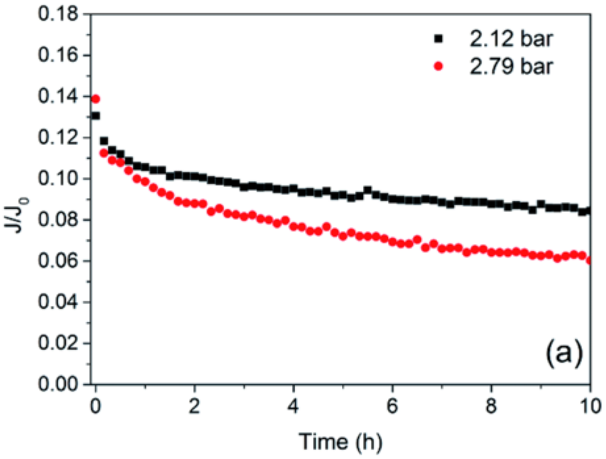


(b)

Figure 3.4: (a) Drop-in flux with time at a constant TMP mode. Reprinted with permission from " Comparison of membrane fouling at constant flux and constant transmembrane pressure conditions " by Daniel J. Miller, Sirirat Kasemset, Donald R. Paul, Benny D. Freeman, Journal of Membrane Science, Volume 454, 15 March 2014, Pages 505-515. Copyright (2014) Elsevier B.V [76], (b) Drop-in flux with time at a constant TMP mode. Reprinted from the open-access article " Pilot study on the effects of operating parameters on membrane fouling during ultrafiltration of alkali/surfactant/polymer flooding wastewater: optimization and modeling " by Liumo Ren, Shuili Yu, Jianfeng Li and Lei Li, RSC Advances, 9 April 2019, 9, 11111-11122. Copyright (2019) Royal Society of Chemistry with a license [78].

When the unit is operated at a constant TMP mode, there are two possible cases: (i) when the membrane area is constant and (ii) when the membrane area varies.

3.4.2.1 Case – 3: Constant TMP Mode and Constant Membrane Area

In this case, the membrane area is assumed to be constant for the filtration unit in operation. During operation, the amount of permeate falls with the drop in flux due to reversible and irreversible fouling [79]. Therefore, the current estimation can be used for studying the effect of operating the unit at different TMP's on the variation in cost components. As the flux drops, the decrease in permeate rate reduces the operating cost. But, the final amount of permeate reduces, thereby lowering the recovery. As the recovery of permeate is critical, the cost reduction could be very beneficial.

If the operating TMP is low (initial flux will be lower), then the fouling will be slow, and the rate at which flux drops will be slow. And at a higher TMP (initial flux will be high), the membrane fouling accelerates, and over the long run, the permeate drops faster. So, it is generally operated at lower pressure for longer membrane life [78]. The behavior of cost variation will be similar at all TMPs, but the values of the stabilized fluxes are different and vary with the specified TMP, which changes the costs.

3.4.2.2 Case – 4: Constant TMP Mode and Varying Membrane Area

As the recovery of permeate reduces in the Case 3 with a drop in flux, adding additional membrane area needs to improve the amount of permeate recovered at a constant TMP. So, the capital cost increases due to the addition of more areas. And the operating component increases due to an increase in the permeate recovered. Therefore, the area is increased from a design point of view to recover more permeate from benefiting from more product.

3.5 Effect of Stage Configuration on the Variation in Cost Components

In a general membrane process, under-design could reduce the yield due to partial separation, whereas over-design leads to excess capacity affecting the final volume produced. So, multiple stages are needed to overcome this inflexibility. Therefore, when multiple membrane stages are required [47], judicious staging of different configurations for membrane-based processes, like gas separation [80], membrane distillation [81,82], membrane chromatography [83], ultrafiltration [84], are carried out to improve the separation. In addition, the functionality of employing various stage configurations increases the recovery and purity of the product [85].

In the UF process, the flux reduces during operation due to fouling at a constant TMP. So, there will be a drop in the amount of permeate recovered. However, the membrane area which is utilized during the operation remains stable for the respective stage post-design. Therefore, there is a need to stabilize the recovery of the product by increasing the TMP to maintain constant flux or increase the recovery by adding a stage. The variation in cost by increasing TMP to maintain constant flux is evaluated in the previous section. And by increasing the TMP, the change in purity was not significant enough (mentioned in the literature discussed in section 3.4.2.1). So, the cost varies with the addition of extra stages is discussed in the current section. This is done by filtering the concentrate further using the additional stage to obtain more product, thereby increasing the recovery. Also, the permeate stream from the first stage might have impurities present in it. Therefore, the purity of the filtration step has to be improved to increase the overall purity of the product. This is done by directing the permeate of the current stage to the subsequent stage for further filtration.

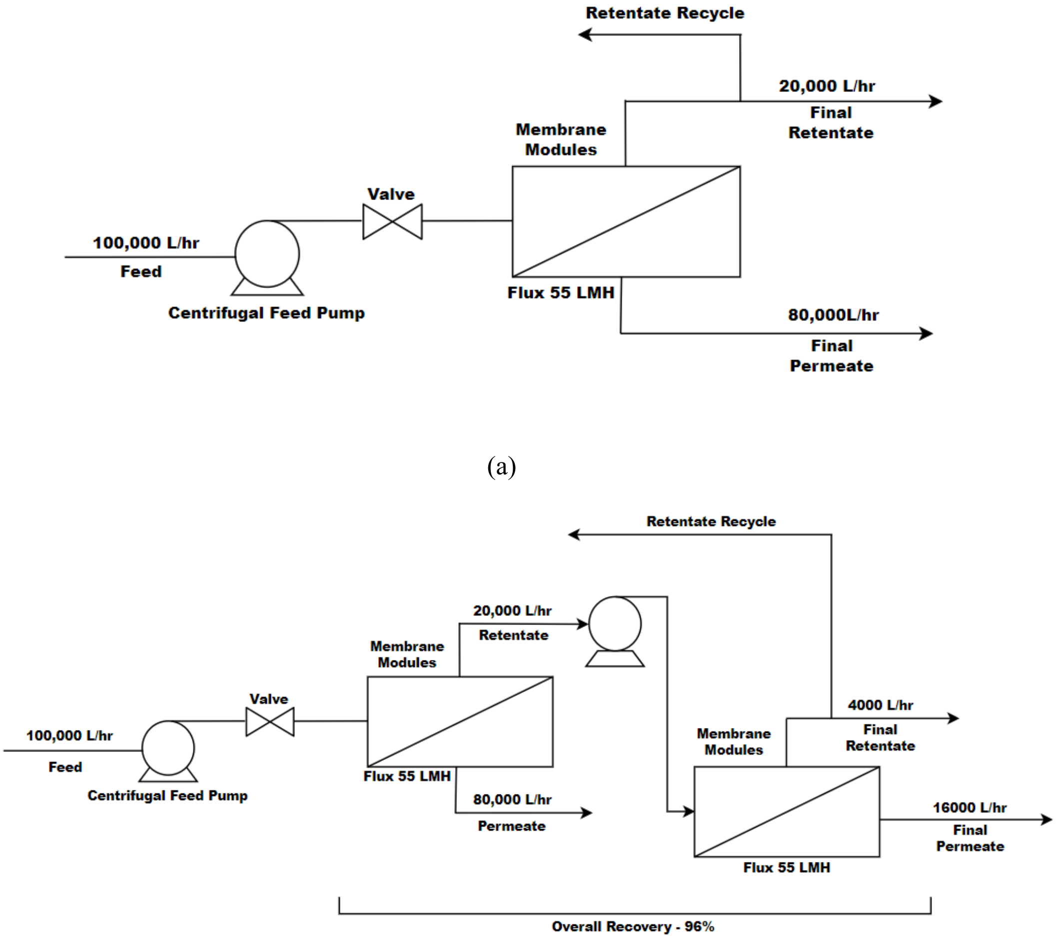
In the current section, the four different stage configurations are depicted in Figure 3.5. First, the setup in Figure 3.5 (a) with one stage is used throughout the study, where the filtered feed is separated in the form of permeate, and the retentate is then recycled back to the upstream as done previously in Figure 3.2. The recovery of this stage is 80% and has a certain purity.

The setup is shown in Figure 3.5 (b), where an additional stage is used to improve the product recovery by directing the retentate from the first stage to the second stage. The recovery of the first stage is at 80%. Then, the retentate of 20,000 L/hr is pumped into the second stage for improving the overall product recovery to 96%. The purity of the filtrates from both stages will be approximately identical as they undergo separation from a single stage because the properties of feed and retentate of the first stage are nearly similar.

In the configuration shown in Figure 3.5 (c), the permeate from the first stage is filtered using an additional stage to improve the purity of the product. By doing so, the recovery of the configuration dropped to 64% from 80%. In addition, the impurities present in the permeate of the first stage are removed in stage 2, improving the purity of the product.

The configuration is shown in Figure 3.5 (d) is the combination of the previous two designs, in which both the purity and recovery are increased by adding two additional stages, one to increase the purity from permeate of the first stage and the other to increase product recovery from retentate of the first stage. As a result, the product recovery increased to 93% by improving the purity as well.

Adding stages increases the required membrane area and pumps, thereby increasing the capital cost of the unit. But the purity and yield are more critical to make a trade-off with the additional cost expenditure. The base conditions and the assumptions mentioned in Tables 3.1 and 3.2 are used in this section for evaluation. The input feed flow rate is taken as the basis in the current evaluation. Additionally, it is assumed that: (i) the individual recovery of a stage is 80%, (ii) the unit is operated at a constant flux mode of 55 LMH, (iii) operating TMP at this constant flux mode is optimum at 0.22 MPa and doesn’t vary, (iv) neglected the slight variation in the cost of the pumps used to pump varying flowrates through the membrane, (v) additional parts and diaphragm required for both stages separately. This evaluation can be used to theoretically assess the economic inclusion of an additional stage either to improve recovery, purity, or both for the separation of small molecule API in the pharmaceutical industry.



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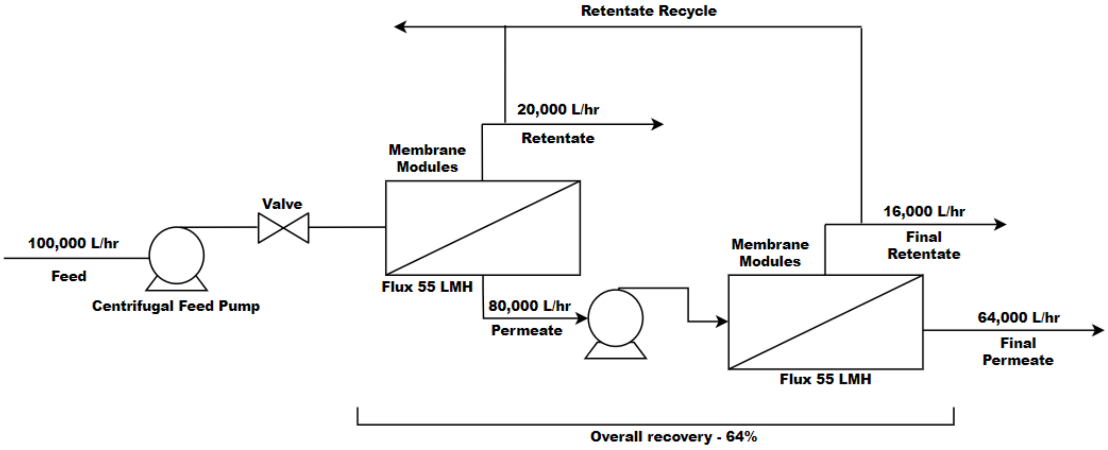

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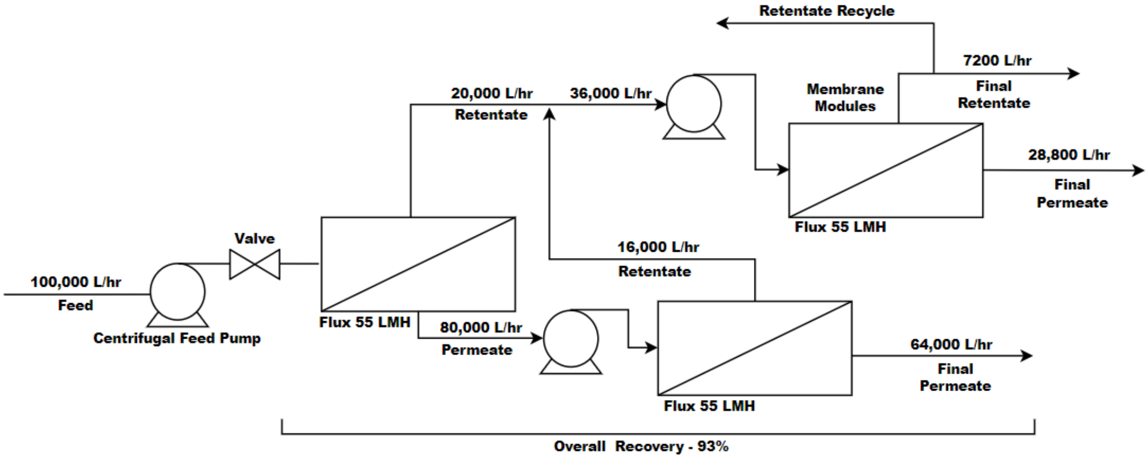


(d)

Figure 3.5: Various membrane stage configurations (a) single-stage, (b) two-stage to improve recovery, (c) two-stage to improve the purity (d) three-stage to improve both recovery and purity

3.6 Effect of pH on the Variation in Cost Components

The cost evaluation method used in this study was extended to understand the variation of the cost components as pH changes. As the pH changes, the rejection and flux of BSA (model biocatalyst) can be seen in the article [86]. Szaniawska et al. used a single module and a membrane skid in their pilot installation; accordingly, the pumps in the current evaluation were sized by the minimum power requirement of 1 kW (using cap cost excel program) [42]. The flux in the pilot study varied with TMP at a BSA rejection of 98.2% - 99.8%, as reported by Szaniawska et al. [86]. Currently, a recovery of 80% was assumed, and the membrane area was taken to be constant at 1500 m^2 based on the current study. An approximate variation in the cost components with TMP at three different pH values was evaluated.

CHAPTER 4. Results and Discussion

4.1 Cost Estimation of an Ultrafiltration Unit

The flux varies with TMP for a biocatalyst separation, as shown in Table 4.1 [65,87,88]. Figure 4.1 depicts the recovery increase with the corresponding rise in flux for different membrane areas. To obtain the desired recovery of 80%, the unit can be operated using either 1250 m^2 or 1500 m^2 (Note that other membrane areas could be used as well, say 1300 m^2 to reach 80% recovery at a flux of around 61 TMP 0.28 Mpa). However, while using 1250 m^2, the unit is operated at a TMP of 0.3 Mpa, which is relatively high, and that in turn intensifies the fouling, which is practically not desirable as it incurs more replacement and maintenance. But by using a membrane area of 1500 m^2, a moderate TMP of 0.22 Mpa (considered optimum, which is not too high for fouling and too low for lower flux [89]) recovers 80% of the permeate for 100,000 L/hr of feed. Hence, these parameters are considered as the base parameters for estimation, as shown in Table 4.2. Also, the membrane area has a vast influence on capital expenditure as it directly increases the cost associated with modules and skids. So, the membrane area must be chosen to be low for the separation needed to minimize the capital cost.

Table 4.1. Flux variation with TMP for biocatalyst separation. The corresponding values from the TMP vs flux plot of biocatalyst separation were approximately taken from the literature[65,87,88]

TMP (Mpa)	Flux (LMH)
0.07	19
0.14	38

0.21	52
0.28	63
0.35	70

Table 4.2. Base membrane parameters used and comments made in the current evaluation [47],[89]

Parameter	Notation	Value	Comments
Feed Flowrate (L/h)	Q_{feed}	100,000	Constant Input
Recovery (%)	*Rec*	80	Desired Output
Filtration Rate (L/h)	$Q_{filtration}$	80,000	Calculated from equation 2
TMP (MPa)	*TMP*	0.22±0.01	Obtained from Figure 4.1
Flux (LMH)	*J*	55±1	Obtained from Table 3.2
Membrane Area (m^2)	*A*	1500±25	Calculated from equation 3

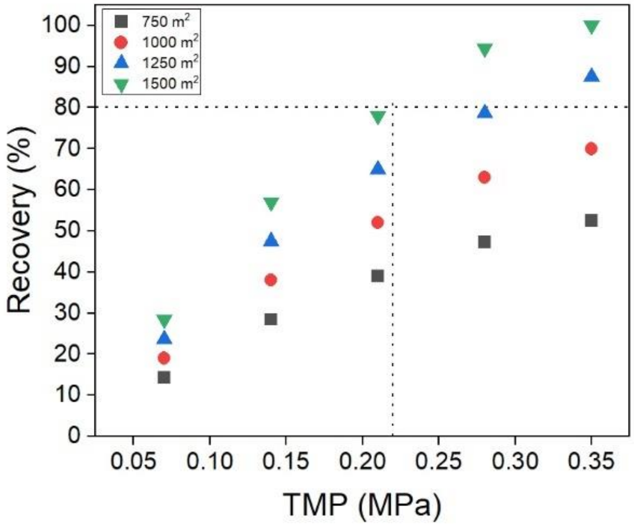
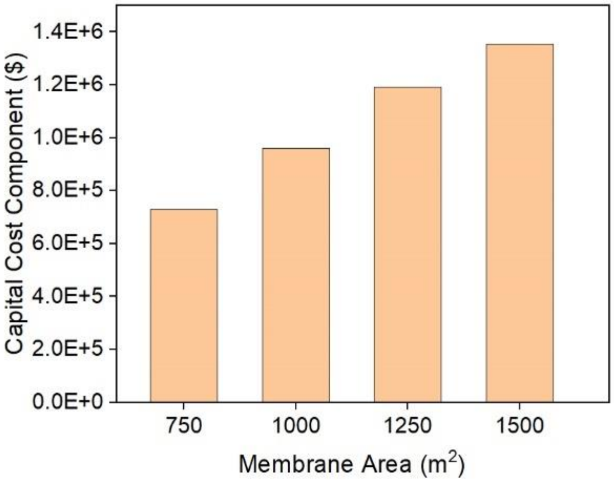


Figure 4.1. Variation in recovery with TMP as shown in Table 4.1 for membrane areas in increments of 250 m^2 in this study

From the plot, for a lower membrane area of 750 m^2, the max recovery after the flux stabilizes (assuming the actual flux stabilizes over the UF upper-pressure limit of

0.35 MPa) is around 50% which is generally considered very low in practical application. Then increasing the area by 250 m^2 improved the maximum recovery to 70%. And for a higher overall membrane area of 1500 m^2, the full recovery reaches 100% at an upper limit of 0.35 Mpa. The recovery of 100% product is practically not possible. So, the desired recovery of 80% (considerate) could be attainable by a unit of area around 1500 m^2 approximately at an intermediate TMP of 0.22 Mpa that can be deduced from Figure 4.1. And the TMP can be increased slightly from the intermediate value to improve the recovery during short-term operations. But in the case of a more extended function, the TMP cannot be kept too high, making the membranes foul rapidly and incur extra replacement costs due to frequent replacement and maintenance.



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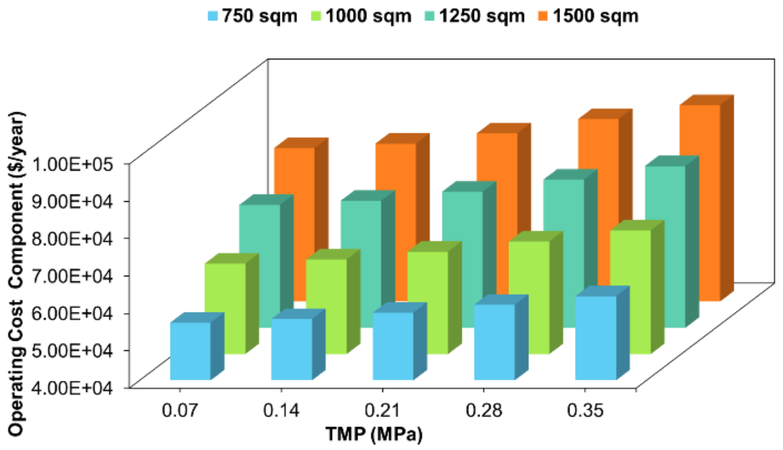


(b)

Figure 4.2. Variation in (a) capital cost component, (b) operating cost component with TMP for different membrane areas.

The capital expenditures for different membrane areas can be seen in Figure 4.2 (a). The capital cost remained constant as no additional modules or parts were added to the unit for a specific membrane area. However, the operating expenses increased with a rise in TMP due to (i) TMP and (ii) fluid flow across unit (as flux increases with TMP, the filtration rate increases, thereby increasing the crossflow volume) at a fixed membrane area. At a fixed TMP, the operating cost component increased with the area as the fluid flow increased due to more fluid flow attributed to the additional area at constant flux. This substantial increase in the TMP and fluid flow across the unit increases the pressure energy required by the feed pump to pressurize feed through the membrane. It can be seen that the operating cost is highest for a unit with a higher membrane area at a higher TMP in Figure 4.2 (b). This is because the permeation rate is higher for a unit operating with a higher area when compared to the one of a lower area at corresponding TMP.

The final quantities obtained for installing a new UF unit to obtain 80% recovery for a given feed input of 100,000 L/hr are shown in Table 4.3, calculated following the equations detailed in Table 3.1. The values of the base membrane parameters used in the current estimation are listed in Table 4.2, and the remaining values are used accordingly from Tables 3.1 and 3.2.

Table 4.3. Calculated quantities of the current UF unit for installation in the pharmaceutical industry

Quantity	Value
Capital Expenditure	\$1,354,551
Annual Operating Expenditure	\$85,600
Annual Production Volume	640,200 m^3
Pressure Energy	23,474 kJ/h
Recirculation energy	3230 kJ/h
Cleaning Cost	\$40,100
Depreciation Cost	\$133,626
Total Expenditure	\$217,696

Compared to a 1998 study, the total cost of a UF process with a capacity of 6,916,000 m^3 per year was estimated around \$622,440 [31], with the higher cost tied to (i) nearly ten times higher capacity than that considered here; (ii) a recovery of 95% and a flux of 85 LMH, compared to a recovery of 75% and flux of 50 LMH used in the present study; and (iii) larger membrane area of 9200 m^2 compared to 1500 m^2 in the current study. Another study estimated the capital cost of an annual production capacity of 160,000 m^3 is $210,000, while the operating expenditure per annum is $41,059 [28]. The lower price is reasonable, because of (i) lower filtration rate of 20,000 L/h, compared to that of 75,000 L/h in the current study; (ii) lower capacity of 3.75 times less; and (iii) inflation. More is considered in this study, and considering inflation, owing to both factors, the rise in the cost seems reasonable. The comparisons provide validation of the cost estimates here.

4.2 Variation of the Cost Components with the Mode of Operation

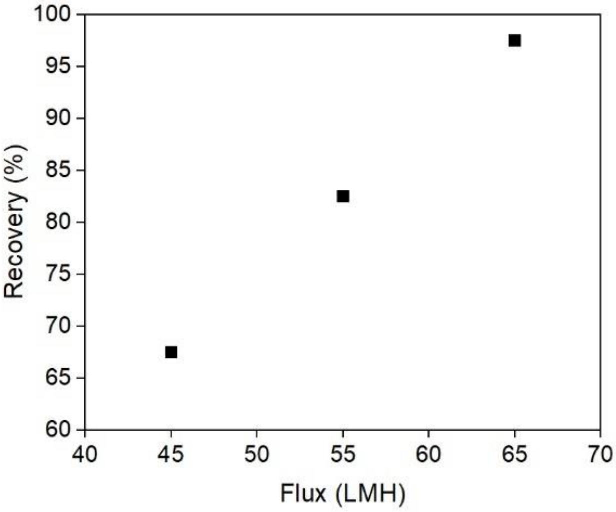
According to previous sections, when the flux rises with an increase in TMP according to Table 4.1, it keeps increasing and attains a limiting value of around 70 LMH due to fouling on the membrane surface. Because of the scaling of foulants on the membrane surface and internal pore blockage, the flux doesn't increase with a further increase in TMP. Also, lower flux is undesirable as the flux is low, tied with the amount of permeate. For the operation to run smoothly for a more extended period, it has to be operated at an optimum TMP that is not too high nor too low. Process control in industries is challenging, especially when controlling two parameters at the same time. So, controlling one of the parameters, either flux or TMP, at the one time is mainly employed in industries. The current section presents the analysis of constant flux mode followed by constant TMP mode at constant and varying areas to obtain the desired recovery.

4.2.1 Case – 1: Operated at Constant Flux Mode and Constant Membrane Area

From the previous section, a unit with a membrane area of 1500 m^2 is used for analysis in the current section. Figure 4.3 (a) depicts the various recoveries of the permeate when operated at corresponding fluxes. For example, to operate at a flux of 65 LMH, the unit should be operated at an initial TMP of 0.29 Mpa. And for the operation of the unit at a lower flux of 45 LMH, the TMP must be initially operated at 0.18 Mpa and then increased to a maximum TMP to maintain the flux constant. As the unit is operated at a lower flux, the initial operating value of TMP is lower.

Similarly, for a flux of 55 LMH, the TMP is increased from an initial value of 0.22 MPa to the upper limit TMP of 0.35 MPa. But as the operating flux is lowered more, the recovery of the permeate reduces. Currently, at a constant flux of 65 LMH, the recovery is 97% which reduces to 67% if the unit is operated at a constant flux of 45 LMH, lower than the desired recovery.

Figure 4.3 (b) shows the variation in operating cost component with the TMP at a constant membrane area when the unit is operated at constant and distinct fluxes. The capital cost is constant at $1,354,551 as there is no change in membrane area at all the three different fluxes, 65 LMH, 55 LMH, and 45 LMH. But it is fair to comment that at higher operating fluxes (operated at higher TMP to get higher flux), the replacement cost of membrane might increase as the membrane has to be replaced or cleaned frequently due to higher and faster fouling. As the TMP increases, there is almost a linear increase in operating cost due to the rise in pressure energy at a constant flux (constant permeate). But when the unit is operated at a lower flux, the amount of permeate reduces, so the pressure energy associated with it reduces, and the operating cost drops. Depending on the desired recovery, the unit can be operated at the required flux. And the TMP can be adjusted to maintain that flux. Currently, it is suggested to operate at a considerate recovery of 80%, a flux of 55 LMH for a 100,000 L/hr feed inlet and 1500 m^2 area.



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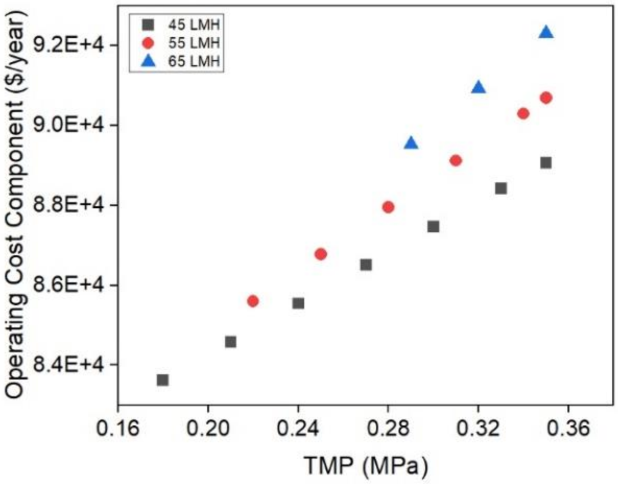


(b)

Figure 4.3. Change in (a) the recoveries at different operating fluxes for a unit with an area of 1500 m^2, (b) the operating cost component with TMP at different operating fluxes.

The sensitivities of cost changes with TMP for 45 LMH, 55 LMH, 65 LMH are 32,000 $/MPa, 39,000 $/MPa, 46,000 $/MPa respectively. The increase in sensitivity is due to increased flux, which improves the filtration rate and cost sensitivity. Depending on the desired recovery, the unit can be operated at the required flux. But it can be observed that if the unit has to be operated at a lower flux of 45 LMH, the unit's recovery is below the desired recovery. So, there is a scope for improving the recovery here by adding additional areas, which is discussed in the next section.

4.2.2 Case – 2: Operated at Constant Flux Mode and Varying Membrane Area

When the unit is maintained at a constant flux of 45 LMH and an area of 1500 m^2, the recovery is around 67%, discussed in Case 1. Membrane areas in increments of

250 m^2 are added, and the change in recoveries is shown in Figure 4.4. To improve the recovery at a flux of 45 LMH to the desired value of 80%, it can be seen from Figure 4.4 that an additional area of 250 m^2 is needed. The variation of capital cost component for increasing membrane areas (to recover more permeate) can be seen in Figure 4.5 (a). The sensitivity of capital cost with regard to an increasing area at 45 LMH is 906.14 \$/m^2 compared to a sensitivity of 903.03 \$/m^2 at 55 LMH. So, additional capital of \$231,195 (nearly \$0.23 million) is needed to achieve the desired recovery at 45 LMH compared to the cost at 55 LMH in Case 1. The capital cost component increased by 17.1% by adding a 250 m^2 area of the membrane at the same flux because additional modules are added to the unit.

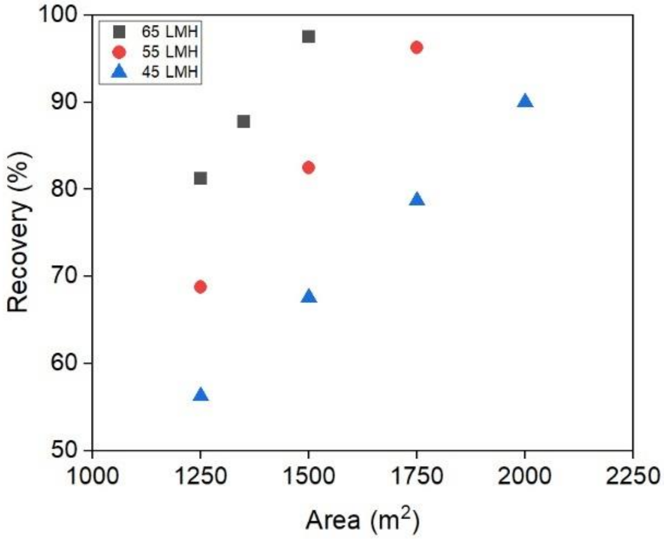
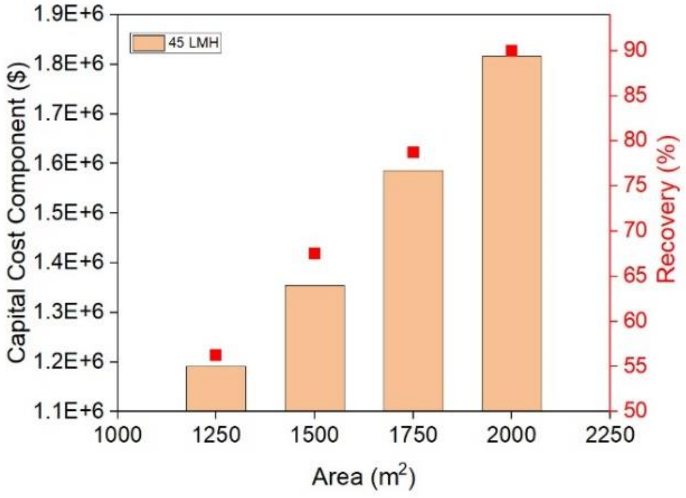


Figure 4.4. Variation of recoveries with membrane area at respective constant fluxes



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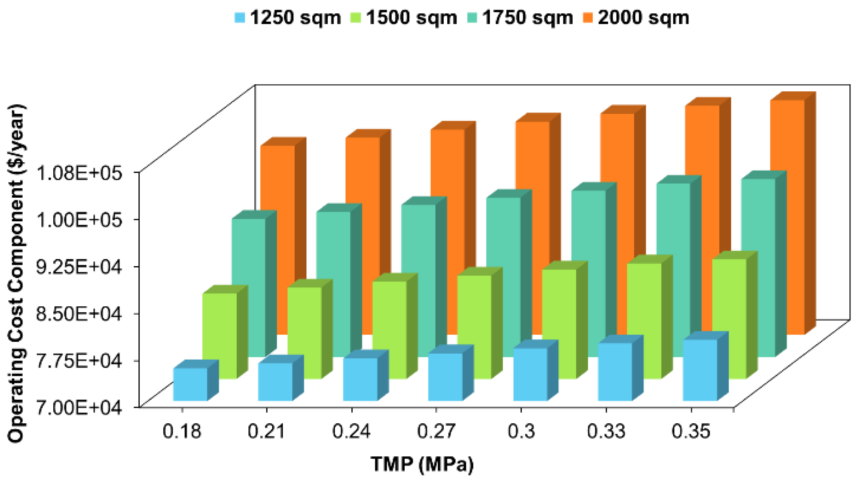


(b)

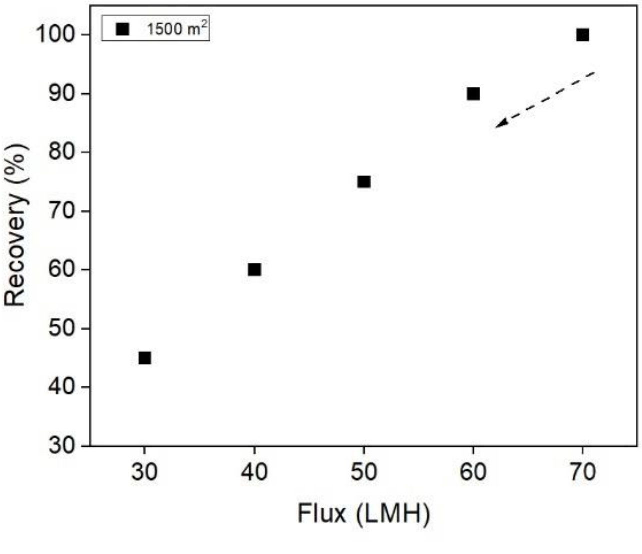
Figure 4.5. Variation in (a) capital cost component, (b) operating cost component at a constant flux of 45 LMH.

The pressure energy depends on the fluid flow and TMP, so it is increased to exert enough force for the feed to pass through the membrane as (i) TMP is increased to maintain constant flux and (ii) additional area is added due to which the recovery of permeate is increased.

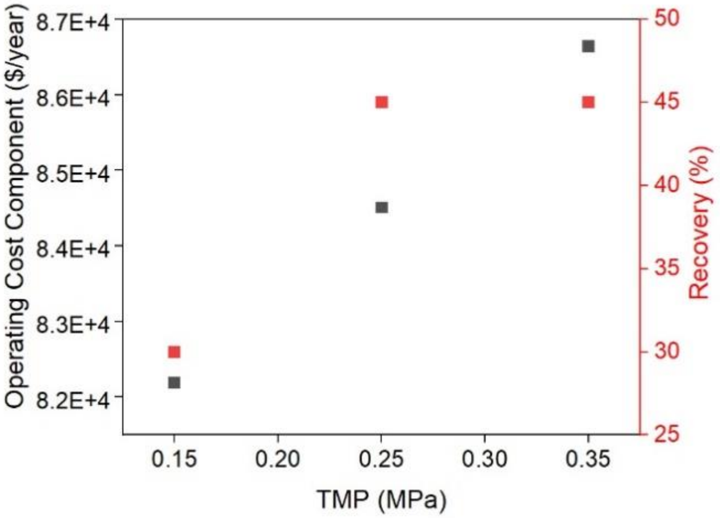
At 45 LMH, the variation of operating cost components with different areas is shown in Figure 4.5 (b). The pressure energy depends on the fluid flow and TMP, so it is increased to exert enough force for the feed to pass through the membrane as (i) TMP is increased to maintain constant flux and (ii) additional area is added due to which the recovery of permeate is increased. When the increase is considered at a particular area, the rise with TMP is solely due to the increase in TMP (fluid flow has no effect). When viewed at a specific TMP, the filtration rate increases due to more area, which increases the fluid flow, so more permeate is recovered, which increases the pressure energy, thereby increasing the operating cost component. The behavior of increase in operating cost component is similar at different membrane areas. To achieve a recovery of 80% at 45 LMH compared to 55 LMH, an additional \$7500 of annual operating cost is expended. Due to the uniform deposition of foulants in case of a constant flux operation, this mode is used in industries widely [73].

4.2.3 Case – 3: Operated at Constant TMP Mode and Constant Membrane Area

In this mode of operation, the flux drops and stabilizes at a specific value. At a constant area of 1500 m^2, the change in recovery with flux is shown in Figure 4.6 (a). The flux drops from an initial value due to fouling and then stabilizes at the final values, shown in Figure 4.6 (b). At a lower TMP of 0.15 MPa, the final stabilized flux is too low at 20 LMH. This means that the amount of permeate produced would be significantly less, and this type of operation is never desired. And at a high TMP of 0.35 Mpa, the stabilized flux is at 30 LMH. But at a higher TMP, rapid fouling takes place, which involves additional costs and is not suggested. So, a moderate TMP of 0.25 Mpa is used in the present study through the stabilized flux is at 30 LMH, the operating TMP is low and causes lower fouling. The capital cost remains the same at \$1.35 million for 1500 m^2. The operating cost at 0.25 Mpa is \$84,508. The flux stabilizes and operates at a final value of 30 LMH recovering only 45% of the feed, which is relatively low. To improve this to the desired recovery of 80%, an additional membrane area is added, discussed in the next section.



(a)



(b)

Figure 4.6. (a) Fall in recovery due to a drop in flux at constant membrane area, (b) change in operating cost component at stabilized flux values for different TMP's is shown. The arrow represents the flux drop in the constant TMP mode. Note that a 10 LMH interval is taken in between the initial and stabilized flux

4.2.4 Case – 4: Operated at Constant TMP Mode and Varying Membrane Area

As the membrane unit is operated at low stabilized fluxes, an additional area is added to improve the recovery of the permeate. At a TMP of 0.25 Mpa, 1200 m^2 of the additional area is added to obtain the desired recovery. And at a lower operating TMP of 0.15 Mpa, 2500 m^2 of the additional area is added to recover 80%. This can be seen in Figure 4.7. So, the unit cannot be operated at a low TMP as the volume of permeate produced will be very low and is undesirable. When the flux falls below a particular value, which is considered low while in operation, either membrane can be cleaned, which incurs additional cleaning cost, or membranes can be replaced, which incurs frequent replacement cost, increasing the expenditure and reducing the profits.

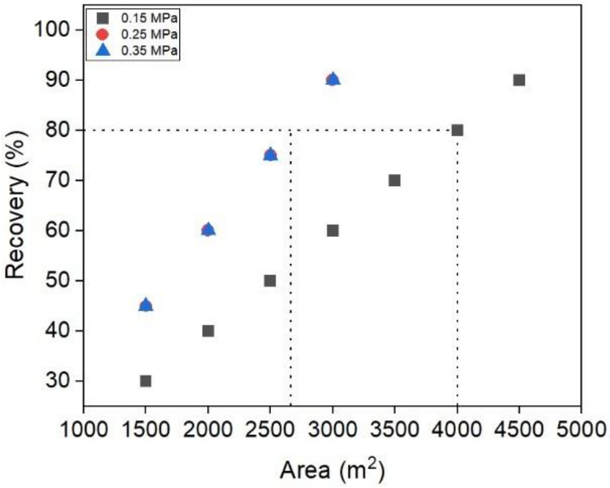
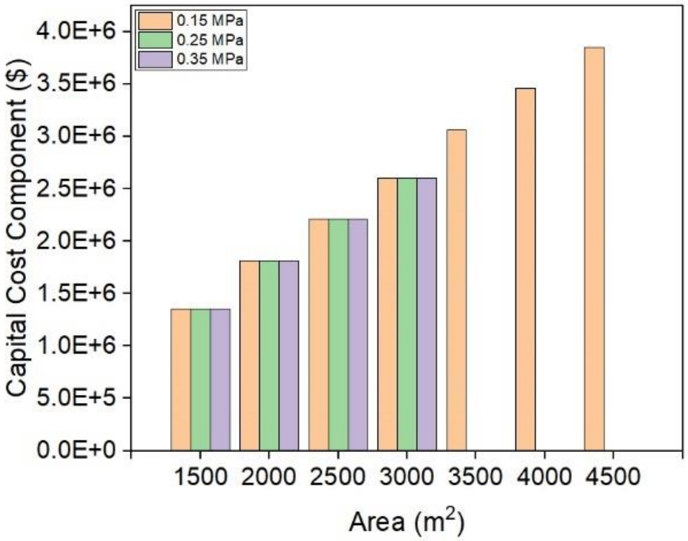
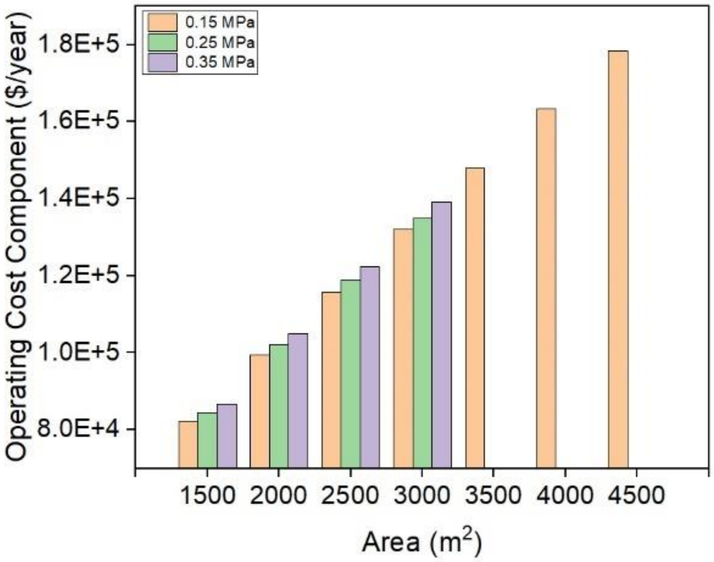


Figure 4.7. Additional area required to improve recovery to 80% at different operating TMP's. The flux stabilizes at the same value at 0.35 MPa and 0.25 Mpa; hence the area needed to increase recovery is the same, so the points are overlapped.

The variation of the capital cost component with membrane area at various operating TMP's is evaluated. The capital involved with the additional area at a lower TMP is higher, compared to Figure 4.8 (a). At the lower operating TMP of 0.15 MPa, the capital cost component increases by 2.55 times and the operating cost component by 1.98 times due to the recovery of 80% at a larger membrane area of 4000 m^2, relative to a recovery of 30% at 1500 m^2. At 0.25 MPa, the capital cost component increases by 1.73 times and the operating cost component by 1.47 times to get the desired recovery of 80% from a recovery of 45%, shown in Figure 4.7. Thus, for recovery of 80%, the only difference in costs of units operating at 0.25 MPa and 0.35 MPa is that the higher-TMP accounts for an additional $3800 of operating cost in this case.



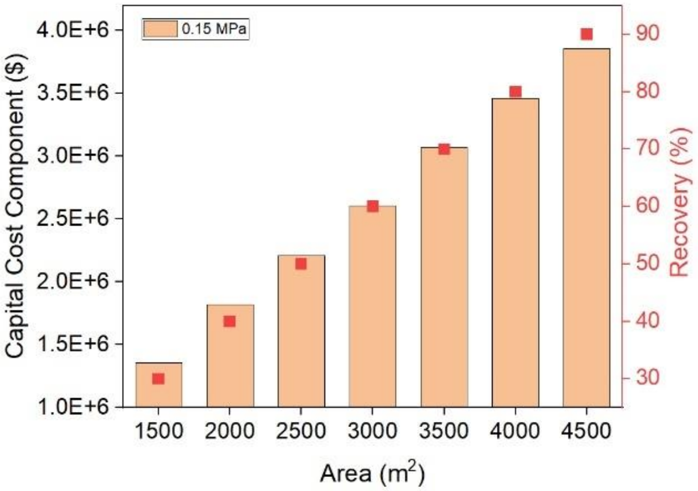
(a)

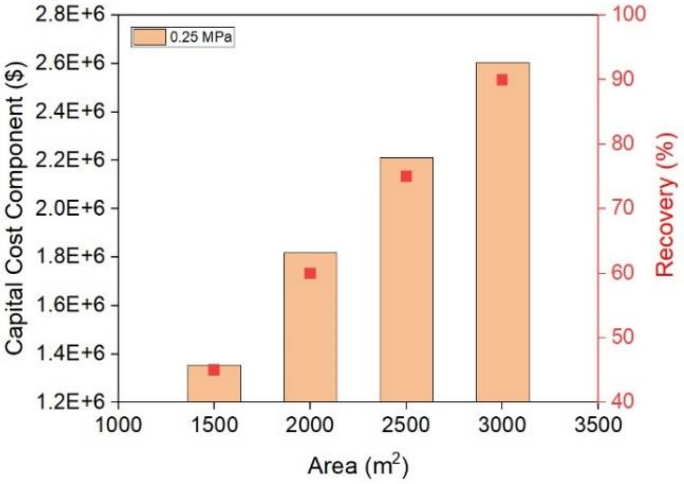


(b)

Figure 4.8. Variation in (a) capital cost component, (b) operating cost components for additional area added at different operating TMP's to achieve the desired recovery. For example, at a lower TMP of 0.15 MPa, the area required to achieve 80% recovery is 4000 m^2, 1350 m^2 higher than that at 0.25 MPa and 0.35 MPa. Hence single bars representing cost components at 0.15 MPa are shown at higher areas.

For additional clarity in the variation of capital cost with membrane areas at three different TMP's, Figures 4.9 & 4.10 can be referred to. Figure 4.9 shows the individual variation in capital cost component and recovery with the addition of membrane area in the constant TMP mode at three different operating TMP's. Figure 4.10 shows the individual variation in operating cost component and recovery with the addition of membrane area in the constant TMP mode at three different operating TMP's.





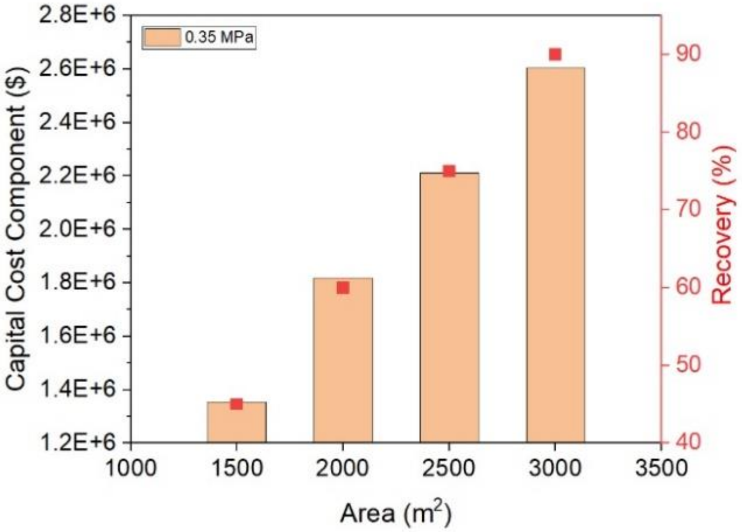
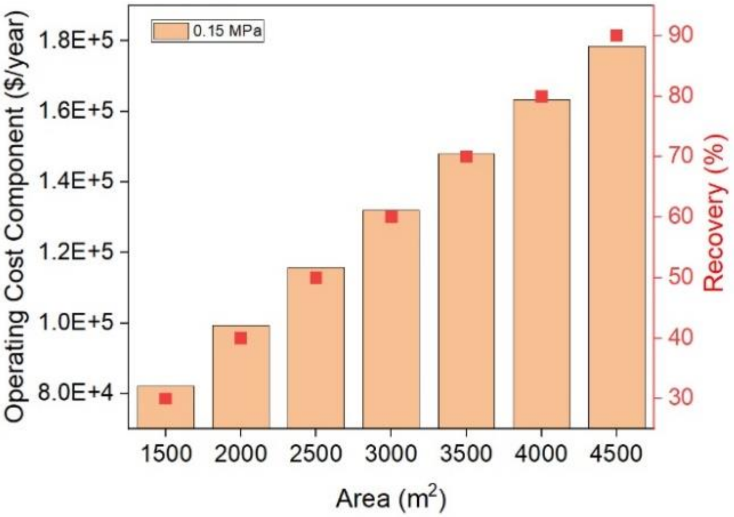
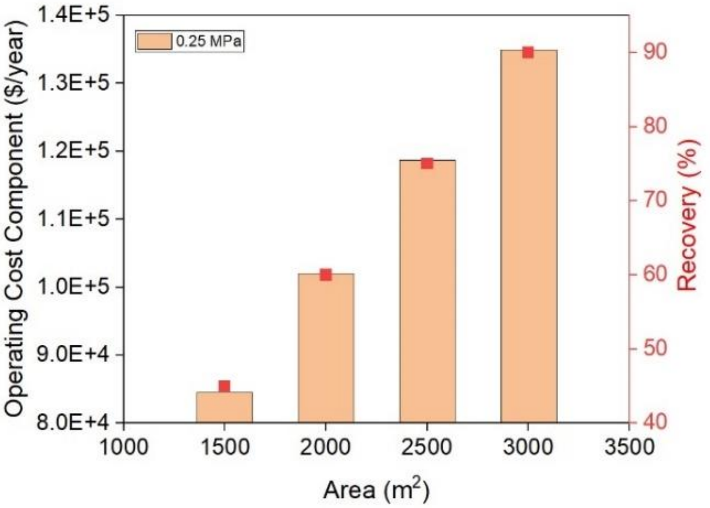


Figure 4.9. Detailed variation in capital cost component on the primary axis and the change in recovery on the secondary axis is shown with membrane area at three different TMP's.


0.15 MPa
Operating Cost Component ($/year)
8.0E+4
1.0E+5
1.2E+5
1.4E+5
1.6E+5
1.8E+5
Recovery (%)
30
40
50
60
70
80
90
1500
2000
2500
3000
3500
4000
4500
Area (m^2)


0.25 MPa
Operating Cost Component ($/year)
8.0E+4
9.0E+4
1.0E+5
1.1E+5
1.2E+5
1.3E+5
1.4E+5
Recovery (%)
40
50
60
70
80
90
1000
1500
2000
2500
3000
3500
Area (m^2)

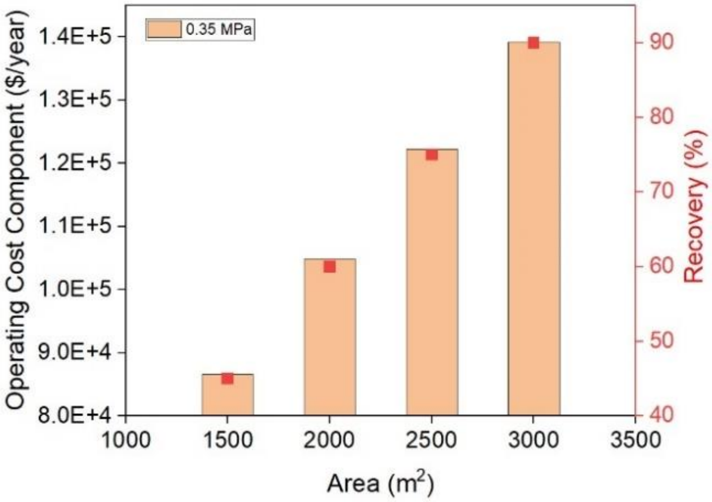


Figure 4.10. Detailed variation in operating cost component on the primary axis and the change in recovery on the secondary axis is shown with membrane area at three different TMP's.

4.2.5 Comparison: Constant Flux Mode vs Constant TMP Mode

Finally, it was observed that in a constant TMP mode, many additional areas are needed to get the desired recovery which increases the capital cost. Among the TMP values for operating at constant TMP, balancing is necessary between the higher capital cost due to the greater membrane area associated with low TMP and the higher operating cost due to the higher-pressure energy associated with high TMP. Among the flux values for operating at constant flux, a lower flux requires more membrane area and thus higher capital cost and operating cost, and a higher flux suffers worse membrane fouling and, therefore, higher maintenance cost.

But when operated at a constant flux mode at a moderate flux (much higher fluxes causes intensive fouling, which increases maintenance and membrane replacement costs), the area needed would be less, reducing the capital investment. The cost components for obtaining the desired recovery of 80% for different modes of operation are shown in Table 4.4. Therefore, it can be inferred from the table that constant flux mode at a moderate flux is economically beneficial. Also, when the membrane area is increased, the number of spiral wound modules increases, increasing cross-sectional area, thereby reducing the crossflow velocity. So, fouling increases with adding additional area [90]. This leads to very high fouling in the case of constant TMP mode (more area requirement). Therefore, it is suggested to use a constant flux mode in industries due to its economic viability. Finally, when the unit is operated at a constant flux mode, the cost is minimal when the unit is operated at a flux of 55 LMH and 1500 m^2 and a TMP above 0.22 Mpa (to keep flux constant) to get around 80% recovery for 100,000 L/hr of input.

Table 4.4. Cost components for obtaining the desired recovery of 80% in different operating modes

Operation mode	Cap cost (in million $)	Operating cost (in thousand $)
Constant Flux 45 LMH	1.58	94.27
Constant Flux 55 LMH	**1.35**	**85.60**
Constant TMP 0.35 MPa	2.34	128.05
Constant TMP 0.25 MPa	2.34	124.25
Constant TMP 0.15 MPa	3.46	163.34

This analysis provides the variation in cost components with either TMP or flux and the added membrane area to improve recovery. However, the revenue of the obtained permeate is not estimated as the product's value is unknown. Also, the membrane unit can be placed as a separator at any location, either downstream or upstream. And the permeate produced may not be the final product to be sold in the market and generate revenue. So, the revenue generated by-product cannot be calculated as there is a possibility that other additives are added in further process steps to the product to improve its final quality (product from the current unit) that alters the product's value. Hence the profit is not calculated here.

4.3 Variation of the Cost Components with Stage Configuration

The respective cost components, recovery, and purity of the specific configuration, along with the change in membrane areas, are shown in Table 4.5. The equations and parameters mentioned in Tables 3.1, 3.2, and 4.1 were used to evaluate. There is a trade-off between product recovery, purity, and expenditure—the cost expenditure increases due to increased membrane area. The two-stage configuration shown in Figure 3.5(b) is beneficial if less pure permeate is required. But in the pharmaceutical industry, purity is of the highest importance. So, either configuration shown in Figures 3.5(c) or 3.5(d) can be used in the biocatalyst separation unit, which has higher purity. In the configuration shown in Figure 3.5(c), the purity of the product improved drastically. But the final recovery of permeate decreases from the desired recovery. So, it is suggested that the three-stage configuration be used in the biocatalyst separation unit in pharmaceutical industries as the recovery and purity of the permeate are higher. The capital and annual operating costs increased by 2.1 and 1.7 times, respectively, compared to the single-stage configuration. The improvement in the purity and recovery compromises this increase in expenditure due to the additional stages. Finally, Table 4.6 shows the final proposed configuration and the various quantities of the UF unit for biocatalyst separation.

Table 4.5. Different metrics of the various stage configurations are mentioned in Figure 3.5. The basis is the constant feed flow of 100,000 L/hr

Figure	Capital Cost (in million $)	Annual Operating cost (in thousand $)	Membrane area (m^2)	Recovery	Purity
3.5 (a)	1.35	85.6	1500	80%	Low
3.5 (b)	1.63	94.28	1745	96%	Low
3.5 (c)	2.42	128.03	2618	64%	High
3.5 (d)	2.82	145.77	3142	93%	High

Table 4.6. The final proposed setup and values involved for the biocatalyst separation in the pharmaceutical industry. Refer to Table 3.2 and Table 4.3 for the conditions used in the evaluation

Quantity	Type/Value
Configuration	3.5(d)
Mode	Constant Flux
Flux	55 LMH
Final Recovery	93%
Capital Cost	$2,826,328
Annual Operating Cost	$145,777

4.4 Variation of the Cost Components with Change in pH

According to the study, Figure 4.11 shows the change in flux and rejection of BSA, a model biocatalyst with the change in pH as explained in the article [86], it was concluded from the experiments that the flux decreases with a decrease in pH. The decrease was slight, around 1.8 LMH for a change in pH, as shown in Figure 4.11. But it can be seen that the rejection decreased with an increase in the pH. This change in flux or rejection is not too drastic. It can be observed from Figure 4.12 (a) the variation in operating cost components with TMP at different pH, which is due to the changes in flux with pH. The change in the operating cost with pH at higher TMP is more when compared to that at lower TMP is due to the higher difference in fluxes at higher TMP's. Since the membrane area is constant, the cost depends only on change permeate flow at fixed TMP. For a stable pH, the change in operating costs for two different areas is shown in Figure 4.12 (b).

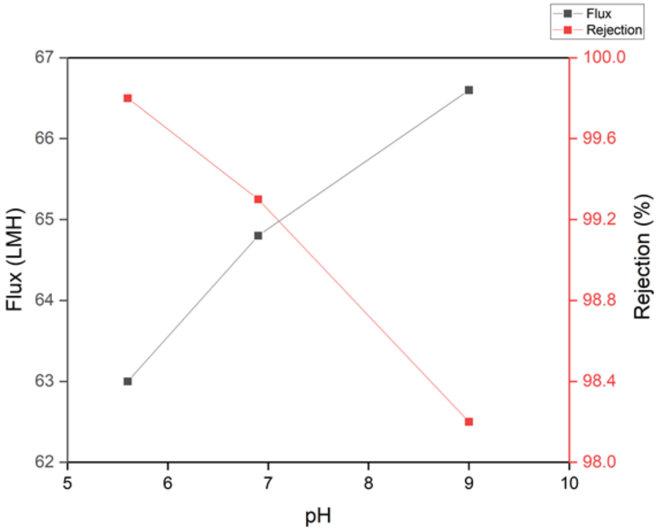
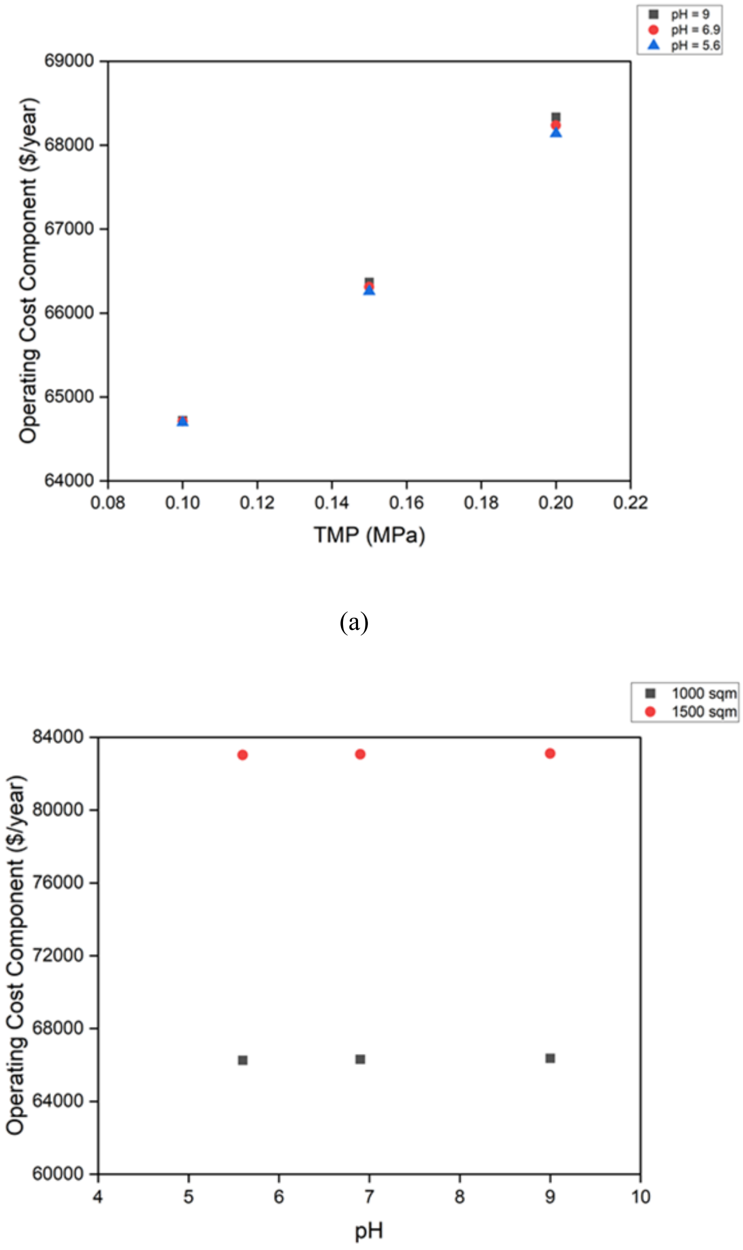


Figure 4.11. Variation of flux and rejection of model biocatalyst (BSA) with change in pH



(a)

(b)

Figure 4.12. Change in operating cost component with (a) TMP at various pH, (b) pH for different membrane areas.

These variations could be considered almost negligible as the cost components are evaluated annually. Even for a higher membrane area used in this section, the change in cost components is insignificant, unlike the area of 8.05 m^2 used in the article from which this flux data is taken. A significant observation in the current evaluation is that the value of the cost component is minimum at a lower pH of 5.6 owing to lower flux. This is because the flow across the unit impacts the total cost directly. So, keeping the pH low would be somewhat economically beneficial when the membrane area and recovery are constant.

CHAPTER 5. Conclusion

A cost evaluation of an ultrafiltration membrane unit in the downstream processing of API has been performed initially to determine the viability of the separation process. In addition, the effect of mode of operation and stage configuration on the cost expenditures was analyzed. It was found that a capital expenditure of $1.35 million and an annual operating expenditure of $85.6 thousand are needed to install a new ultrafiltration unit for a yearly production of 640 million litres.

Following conclusions could be derived from the results obtained in all the sections to attain a considerate recovery of 80% for a unit operating with a feed input of 100,000 L/hr. First, while operating at a constant flux mode, for a lower flux, a higher additional area should be added to obtain the desired recovery, which increases the capital cost, for a higher flux membrane gets fouled rapidly, increasing the replacement and maintenance costs. So, this study suggests using a moderately higher flux industrially from an economic point of view. While the unit is operated at a constant TMP mode, the stabilized flux is low at a lower operating TMP and is not suggested, at a higher TMP, the membrane is susceptible to fouling, incurring additional expenditure. Also, in this mode, due to the larger additional area required to improve recovery, the rise in expenditure is very high when compared to the constant flux mode, and hence this mode is not suggested. The main reason (apart from cost) why constant flux mode is preferred over constant TMP mode is: In constant TMP mode, the flux tends to drop over time due to fouling, and the unit tends to operate with much higher membrane area (due to drop in flux) than the designed area (at a design flux value). This higher area requires installing additional stages which are practically difficult amidst the operation and also involve higher cost. Whereas in the case of constant flux mode, the unit can be operated at a designed flux (the area is fixed) just by varying the TMP, which is less tedious from an industrial point of view. Finally, for the variation of the expenses for a change in the stage configuration to maximize recovery and purity, it was found that three-stage configuration is highly beneficial to improve the recovery and purity of the product but at the expense of capital and operating expenditure which almost doubled when compared to the unit operated with a single-stage configuration. Since purity is of higher importance in pharmaceutical products, the three-stage configuration with an operating flux of 55 LMH can be used for biocatalyst separation.

The pharmaceutical industry could use the analysis and trends presented in this study to assess and make changes to the operating conditions by having adequate knowledge on the variation of cost. Future studies can be conducted by analyzing further downstream, that is the diafiltration unit and the final concentration unit, to estimate the whole downstream separation plant. Also, varying the current assumptions to suit a specific industry will lead to other potential results.

CHAPTER 6. Challenges

Fouling is the biggest challenge that makes the flux decline leading to the reduction in permeate produced. Also, the purity of the product is critical in the pharmaceutical industry, which gets affected due to the fouling phenomena. As the flux and purity get reduced, the product's final value falls or additional expenditure is needed to recover further or purify the product as seen by adding further stages. So, from an economic perspective, the fouling of membranes must be reduced drastically to benefit from the revenue generated from the product. The protein concentration in feed affects the membrane fouling, which changes the flux, which in turn changes the economics. In future work, the effect of the feed concentration on economics could be studied.

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