DEVELOPMENT OF DESIGN ADVISOR TOOL FOR SEPARATION PROCESS OF BIOPHAMACEUTICAL PRODUCTION

Nurulhuda Binti Abdul Latif and Syazana Mohamad Pauzi

Faculty of Chemical Engineering, Universiti Teknologi Mara

Abstract— **Effective manufacturing productions are crucial as the demand of biopharmaceutical products are high and in need of scale up from laboratory based to financially feasible processes. The purpose of this study is to develop a decision support tools should provide a user friendly interface between the user and the tool platform, focusing on separation processes in biopharmaceutical productions.**

As for this research of designing advisor tool for the separation process of biopharmaceutical products, the software tool is programmed in MATLAB and the user interacts by means of a Graphical User Interface(GUI) which allows editing the parameters used for simulations in a friendly way. Included processes such as centrifugation and filtration process with two modes of filtration. This computer aided should be able to help achieving the goal of changing in process capacity and formulate the models at different scale thus able to reduce the time involve in the process separation

***Keywords*- biopharmaceutical, separation, filtration, centrifugation, GUI**

I. INTRODUCTION

The separation and purification of biopharmaceuticals are the ones with high cost and time consuming downstream processes. (Sekhon, 2010). In the downstream processing of biopharmaceutical production, the separation process involves separation of biomass which is separating the biomass basically by centrifugation and ultrafiltration. In this study, an advisor tool that can provide the outlook or the simulation of the process of the separation itself is very important to be able to choose the best ways and less costly productions. The advisor tools can be a mini simulation that can provide an evaluation of process and options from the process perspective. As for the reference to current technology and place for us, the advisor tools are not readily available and it is expensive. This advisor tool is not really focusing on the scaling up of the processes thus it is my focus on this study which is focusing on the scaling up of the separation process of the downstream process. Simulation tools that are developed by the previous developer are that the produced simulation tool that aid in the evaluation of manufacturing alternatives

With the advisor tools, one can consider from various option with respect to the type of separation process needed to remove either bacteria cells or mammalian cells with the use of centrifuge or a filter- where the same job would be done but it would really differ the in the efficiency.

For centrifugation process, there are several types of centrifuges such as tubular and decanter centrifuge and they possess the same requirement for scaling up process which is the sigma factor. It depends on centrifuge design geometry and properties of the suspended particles itself. Both disk and tubular centrifuges have been used for separation of microbial cells or bacteria, yeast, and mammalian cells, especially in biopharmaceutical production. Centrifugation uses the sigma concept and Leung number where it is an amplified relation between the machine performance, total flow rate Q and index of the centrifuge size, **Σ**. (Wakeman, 2005)

Membrane filtration may be a proficient and economical method for dividing components in the fluid stream. Type of membrane filtration is based on membrane pore sizes. There are two modes of filtration that is dead-end filtration and cross flow filtration. The basic dead-end filtration usually involve accumulation of matter on the filter as the feed flow is forced through the membrane. Fine particles with permeation rates less than 1 m^3/m^{-2} h^{-1} is usually removed with dead-end mode filters with usually filters maximum diameter of 293 mm and feed is forced to pass through the filter surface via an applied pressure.

(Galka, April 2007) The particle develop will bring about increased resistant on filtration and inevitably makes decrease in saturate flux and the example of this mode is diafiltration.The average flux for each concentration and diafiltration step can be estimated from the optimization data and combined with the desired volumes to be processed. The estimated required membrane area could afterward be calculated for both scale of manufacturing scale-down runs.

Feed solution passes along the membrane surface for another type of membrane filter which is cross flow filtration. Two basic filter configurations are generally used is cartridge filters also often called as the membrane forms a set of parallel hollow fibers. It is characterized in terms of number of fibers, diameter and length and lastly the pore size. The ability to scale a transform from the lab on manufacturing is crucial factor in development of process. Reasonable scale-up increments are typically 5 to 20 times (Leung, 2007). Scaling up a process involves increasing the filter area in order to handle larger volumes of starting material without significantly changing process conditions.

When scaling a process, cartridge housing diameter is increased in order to maintain constant volume to area ratio. Starting volume is checked whether it is suitable for the target process time with the estimation of flux. Also, the essential factors that is important to monitor a cross-flow filtration process are liquid pressure and flow rates. Two differential pressure measurements are generally used, ΔP and transmembrane pressure (TMP). (Gosling, Sept 2003)

Flux is commonly expressed in units of liters per m2 of membrane per hour (LMH). This value is scalable, meaning that it can be kept constant when the process is scaled up. (Wakeman, 2005)

There are certain criteria that should be followed as reference to type of application and the cell type as shown below:

Table 1: Reference data for certain cell types

Cell type	Typical concentration factor	Path length (cm)	Fiber lumen diame-ter	Nominal pore size(NMWC)
E.coli	5x	30 or 60	1.0	0.1 µm 500kD 750kD
Yeast	2x	30	1.0	0.1 µm 0.2 µm 750kD
Mammalian	7-10x	30 or 60	0.75 to 1.0	o.2 µm 0.45 µm 0.65 µm

Recommended starting point for process conditions:

Bacterial cells (For removal of cells)	Mammalian cells (Removal of cells an optimal recovery of target protein)
Average flux 25 LMH	Flux flow control at 30 LMH
Filter pore size: 0.1µm	Filter pore size: 0.2 to 0.65 µm

Permeate flow control that contain a high cell mass and a large target molecule in the feed stream, testing should begin with the permeate flow control set as low as 10 to 20 LMH. When working with cross flow filtration such as ultrafiltration membranes, the TMP should be gradually increased to see if there is a proportionate and stable increase in flux. This value is scalable, meaning that it can be kept constant when the process is scaled up.

The design advisor tool will simulate several series of process used in a production where it will be a tool that act as preliminary study of the process and it will help

in decision-making for further action for separation processes.

II. METHODOLOGY

A. Development of design advisor tool

First method is to create a Graphical User Interface (GUI) that interact with the equation for solving needed parameters of involved separation equipment. Firstly all the related equations have to be solved in the MATLAB program creating the database for the process to link with the GUI for the usage of the user. Calculation of the design then translated into command to produce the output value for the design advisor tool. In this section, equations that are involved in the calculation of the design are translated into commands to produce the value that is needed for the design advisor tool.

B) Creating Graphical User Interface

In the GUI template, icon selected such as the 'edit text', 'pop-up menu', 'callback button' and many other used and changed the characteristic of it by editing the 'Properties Inspector'. There are several panel column on the GUI made for the centrifugation and filtration where different panels are filled with the needed data user have so they can obtained the value needed for further action. 'Edit text' icon were used for the results to be displayed after the calculation is run in the Matlab in the 'Editor' section For the usage of the tool, user had to have the data they needed related to the process and several data that are constant through the simulation is maintained.

The steps involve in the calculations are:

1) For filtration

a) Retentate volume

b) Membrane area

c) Flux rate

d) Shear rate

2) For centrifuge

a) Sigma value

b) New production flow rate (for scale up)

C)Design of Centrifuge unit operation

Sigma factor

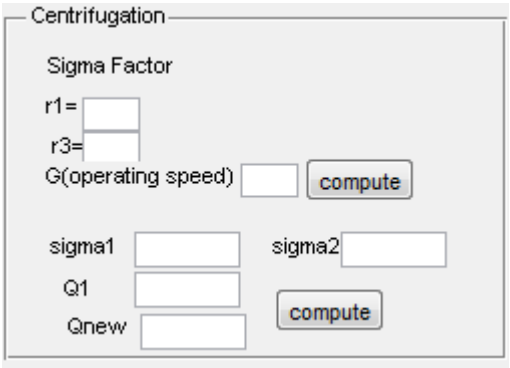
Sigma factor used in scale up in particle separation for similar design machines. The value of the sigma of a centrifuge is equal to the cross-sectional area of a gravity settling tank (R. K. Sinnott, 2003).

$$\Sigma \simeq \frac{\omega^2}{g}\pi L\left(\frac{3}{2}r_3^2+\frac{1}{2}r_1^2\right)$$

and

$$\frac{\Sigma_1}{Q_1}=\frac{\Sigma_2}{Q_2}$$

The sigma value obtained used for scale up between similar design centrifuges, where the feed rate for Q1 with Σ1 is related to feed rate Q2 with Σ2.



The GUI for centrifuge process

D)Design of Filtration unit operation

Dead end filtration

Manufacturing scale volumes should be determined first by the user by inserting value of:

1) Feed volume

2) End concentration

Vr=Feed volume/End concentration

Calculating optimum feed flow (Cross-flow filtration)

The required membrane area with the required pump rate at each of the two feed flow conditions:

Membrane Area [m2] = Process Volume [L] / (Flux [LMH] x Process Time [h])	Pump feed rate [L/min] = Feed flux [L/min/m2] x Area [m2].

Flux calculation

$$J = \frac{Q_p}{A_m}$$

Where:

J = flux, L/hr/m^2 (gal/d/ft^2) or Lmh (gfd)

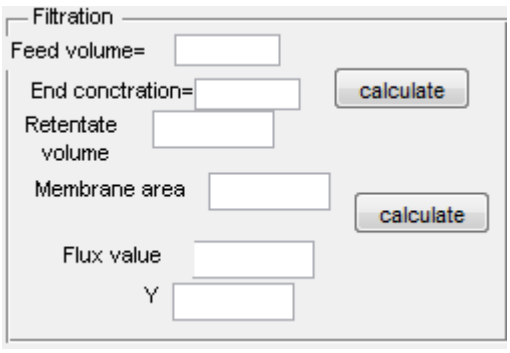
Q_p = filtrate flow rate through membrane, L/hr (gal/d)

A_m = surface area of membrane, m^2 (ft^2)

For hollow fiber filters, the cross flow rate through the fiber lumen is often expressed as the shear rate1 in units of s-1, which is a function of the flow rate per fiber and the diameter of the fiber lumen. Shear rate is calculated as:

$Y = 4q/\pi R3$

Y = shear rate (s-1)
q= volume flow through the fiber lumen, cm3 /s per fiber
R= fiber radius (cm)



The GUI for filtration process

III. RESULTS AND DISCUSSION

The sigma concept allows the centrifugation values related more flexible and complete, but to get the better values and efficiency, deeper theoretical concept should be apply. Sigma factor allows comparison between the performances of geometrically and hydro dynamically similar centrifuges operating on the same feed material. However, this type of scale up factor is not sufficient enough to consider reliable enough to be practiced unless many more other factors are being considered present below is the example of results that obtained from the sigma factor calculations. From the sigma value, new production flow rate can be calculated with the relation as stated before.

Data	Small scale	Large scale
Density	20 000 rev/min	15 000rev/min
Viscosity	0.001Ns/ m^2	0.001Ns/ m^2
Throughput	8 x 10-^{6} m^3/s	8 x 10^{-6} m^3/s
Length	0.2m	0.734m
R3	0.0220m	0.0521m
R1	0.0110m	0.0226m
Σ	221 m^2	2510 m^2

From the new Q value obtained, user can get to know settling velocity the cut size of the centrifuge of the scale up process the try to verify. The comparison with settling velocity that in the most efficient values which is in the range 5 x 10 -8 to 5 x 10-7m s -1 can be done .

For dead end filtration, the value of the retentate can be obtained through the use of this advisor tool and relating to the pore size of the membrane.

Membranes area can be calculated in the tool where in scaling process, the diameter of the fiber filter is

increased for stability between volume to area ratio. Thus the membrane area calculation helps in determining the scability of the process using the filter the user intended to use. Flux rate is also useful in determining whether the starting volume the user intended to use for scaling up is suitable for the targeted process time.

IV. CONCLUSION

The objectives of this research project is to develop an advisor tool focusing on separation process in biopharmaceutical production. The advisor tool developed was focusing on the parameters that sizing of the design but more toward the parameters that needed in the scaling up process and help in further decision-making. The comparison between this advisor and readily available tools is not displayed in this research paper since readily available tool such as SuperPro is complex and give more details that the user can also custom define the details, however for future studies, equations involved for the unit equipment should be expanded focusing on the objectives to design the unit equipment with the sizing details. The tool's database has to be expanded for it to be more reliable tool that can help user to get the values needed for their requirement. However this advisor tool helps in determining the several data needed for scaling up the unit operation. In conclusion, the objectives of this advisor tools is achieved and it can be improved with more input in the database for it to be considered as a well-functioning and complete advisor tool.

V. ACKNOWLEDGEMENT

Special thank you to my supervisor Pn Syazana Mohamad Pauzi for the encouragement and support and constant help throughout conducting this research project and also my research project friends that help me completing this research by guiding me with the software involved.

VI. REFERENCES

[1]A. V. Gothoskar, S. M. (2005). Biopharmaceutical classification of drugs. *Pharm. Rev*.

[2]G. georges, L. A. (2011). Separation science is the key to successful biopharmaceuticals.

[3]Geankoplis, C. J. (2003). Transport Processes & Separation Process Principles. Pearson.

[4]Gosling, I. (Sept 2003). Process Simulation and Modeling Strategies for Biotechnology Industry. *Optimizing Productivity in Multiproduct Batch Facilities*, 1-8.

[5]Leung, W. W.-F. (2007). Centrifugal Separations in Biotechnology.

[6]Madhu Sachidanand, J. E. (2016). Discrete Event Simulation Modelling for Dynamic Decision Making in Biopharmaceutical Manufacturing.

[7]Rader, R. A. (July,2008). Redefining Biopharmaceutical. *Nature Biotechnology ,Volume 26, Number 7*.

[8]Sekhon, B. S. (2010). Biopharmaceuticals: an overview. *Thai J. Pharm. Sci. 34*, 1-19.

[9]Shanklin, T. R. (2001). Selection of bioprocess simulation software for industrial applications. *Biotechnology and Bioengineering*.

[10]Wakeman, R. ,. (2005). Solid/Liquid Separation.

[11]Wallace Wong, F. L. (2007). *Centrifugal Separation in Biotechnology.*