FACILITATIVE RECOVERY OF CYCLODEXTRIN GLUCANOTRANSFERASE USING CHROMATOGRAPHIC STRATEGIES

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IB 2014 22

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By

MAGARET A/P SIVAPRAGASAM

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

January 2014

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DEDICATION

To my family

who taught me hard work and perseverance is the key to success

Praise to God Almighty, the spiritual author

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

FACILITATIVE RECOVERY OF CYCLODEXTRIN GLUCANOTRANSFERASE USING CHROMATOGRAPHIC STRATEGIES

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January 2014

Chairman : Associate Professor Norhafizah Abdullah, PhD
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Cyclodextrin glucanotransferase (CGTase), are monomeric enzymes that are secreted extracellularly which catalyzes transglycosylation reactions via its glucosyl residues and are used as an acceptor in forming cyclodextrins (CD). CD's, are widely used in the pharmaceutical, medicine, food, textile, agriculture and the cosmetic industries. Purifying CGTase is often a complicated task due to its heterogeneity, complexity and instability. To harness, it requires a set of downstream processing which typically consist of a cascade of recovery steps. The CGTase used in this study originated from *Bacillus sp* G1, which was successfully cloned and expressed in *E.coli* BL21. Recombinant CGTase was found to be growth related with maximum enzyme production at 167 U/mL after 10 hours of culture at 37^0C in an orbital shaker with constant speed of 175 rpm. A series of pre purification strategies were carried out to determine the best method to concentrate the enzyme for subsequent purification procedures. Ammonium sulphate precipitation (70% saturation point) and dialysis tubing (SnakeSkin and flat tubing-with MWCO 3.5k) were investigated for concentrating the CGTase from *E.coli* culture. Results showed dialysis using SnakeSkin method to be superior to ammonium sulphate precipitation with CGTase yield of 148 U/mL and 19 U/mL respectively. Adsorbents used were mixed mode (of hydrophobic and ion exchange) ion exchangers, and immobilised metal affinity chelating. These adsorbents packed in a Tricorn 10/50 column, were screened for their suitability to purify CGTase by buffer optimization, frontal analysis and static binding evaluations. Purification yields using mixed mode chromatography were observed by using the mixed mode resin, PPA HyperCel which obtained 97% of CGTase enzyme recovery. Recovery performance were compared with other chromatography methods which is the ion exchange chromatography at 78% recovery and immobilised metal affinity chromatography at 87% recovery.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PEMULIHAN DIPERMUDAHKAN SIKLODEKSTRIN GLUKANOTRANFERASE MENGGUNAKAN STRATEGI KROMATOGRAFI

Oleh

MAGARET A/P SIVAPRAGASAM

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Siklodekstrin glukanotransferase (CGTase) merupakan satu kelas enzim monomerik yang dirembeskan di luar sel yang memangkinkan tindakbalas pentransglikosilan melalui sisa glukosilnya yang bertindak sebagai penerima dalam pembentukan siklodekstrin (CD). CD digunakan secara meluas di dalam industri farmaseutikal, perubatan, makanan, tekstil, pertanian dan kosmetik. Penulenan CGTase adalah satu tugas yang sukar disebabkan oleh kepelbagaian, kerumitan dan ketidakstabilannya. Untuk mendapatkannya, ia memerlukan satu set pemprosesan hiliran yang biasanya terdiri daripada satu rantaian langkah-langkah pemulihan. CGTase yang digunakan dalam kajian ini berasal daripada *Bacillus sp*. G1, yang telah berjaya diklon ke dalam *E.coli* BL21. CGTase rekombinan didapati berkait rapat dengan kadar pertumbuhan dan pengeluaran enzim maksimum adalah sebanyak 167 U/mL selepas 10 jam pengkulturan pada 37°C di dalam penggoncang orbital dengan kelajuan malar 175 putaran per minit. Sebagai enzim luar sel, satu siri pra-penulenan telah dilakukan bagi menentukan kaedah yang terbaik untuk memekatkan enzim dalam prosedur penulenan yang berikutnya. Pemendakan ammonium sulfat (70% tahap tepu) dan tiub dialisis (*SnakeSkin* dan tiub pipih dengan potongan berat molekul 35000) telah diuji untuk pemekatan CGTase dari kultur *E.coli*. Keputusan menunjukkan dialisis menggunakan kaedah *SnakeSkin* adalah lebih baik berbanding pemendakan ammonium sulfat dengan hasil CGTase, masing-masing sebanyak 148 U/mL dan 19 U/mL. Penjerap yang digunakan terdiri daripada mod campuran (hidrofobik dan pertukaran ion), penukar ion, dan pengkelatan afiniti logam tersekat gerak. Penjerap ini dipadatkan di dalam turus Tricorn 10/50 dan telah disaring untuk kesesuaian bagi penulenan CGTase dengan mengoptimumkan penimbal, analisis depan dan keupayaan pengikatan statik. Hasil penulenan terbaik telah diperoleh melalui resin mod campuran, PPA HyperCel, dengan 97% pemulihan CGTase. Prestasi kadar pemulihan telah dibandingkan dengan kaedah kromatografi yang lain seperti kromatografi penukaran ion dengan rekoveri 78% dan pengkelatan afiniti logam tersekat dengan kadar rekoveri 87%.

ACKNOWLEDGEMENTS

I would like to express my deepest appreciation to my advisor, Dr. Norhafizah, for her excellent guidance and for patiently correcting my writing. To my co supervisor, Prof Raha for her insightful comments and support.

My family, without who this effort would have been worth nothing. Your love, support and constant patience have taught me so much about sacrifice, discipline and compromise.

In my daily work I have been blessed with a friendly and cheerful group of fellow lab mates who provided me my daily dose of laughter and moral support throughout this five years; who I am forever grateful for.

This thesis would have remained a dream had it not been for God. All praise and thanks due.

I certify that a Thesis Examination Committee has met on 9th January 2014 to conduct the final examination of Magaret a/p Sivapragasam on her thesis entitled "Facilitative Recovery of Cyclodextrin Glucanotransferase using Chromatographic Strategies" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of **Doctor of Philosophy** The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

BSA	bovine serum albumin
CIP	cleaning-in-place
EBA	expanded bed adsorption
HEA	hexylamine
FBA	fluidized bed adsorption
PBA	packed bed adsorption
PPA	phenylpropylamine
IEC	ion exchange chromatography
HIC	hydrophobic interaction chromatography
AC	affinity chromatography
SEC	size exclusion chromatography
RPC	reversed phase chromatography
MMC	mixed-mode chromatography
IgG	immunoglobulin G
MW	molecular weight
IMAC	immobilized metal affinity chromatography
BPER	Bacterial Protein Extraction Reagent
MWCO	Molecular weight cut off
q^*	concentration of the adsorbent phase to the adsorbent per unit volume of settled adsorbent
q_m,	maximum adsorption capacity of adsorbent
C^*	equilibrium concentration of protein in bulk solution
K_d	dissociation constant for the mixture with the adsorbent.
K	Constant, refers to the capacity of the adsorbent for the adsorbate
$1/n$	Constant, measures the strength of adsorption
x	mass of adsorbate
m	mass of adsorbent
p	the equilibrium pressure of adsorbate
v	volume of gas adsorbed at STP (0°C, 760 mmHg)
c	constant related to the heat of adsorption
v_m	volume of monomolecular layer of gas adsorbed at STP
P_o	vapor pressure of adsorbate at test temperature
$C_{U\,O}$	initial solute concentration in the feed solution
$C_{B\,O}$	initial solute concentration in the adsorbent
S	quantity of feed solution
A	quantity of adsorbent
N	number of theoretical plate
t_R	retention time
σ_t	standard deviation of chromatographic peak
d	peak width at half height expressed in units of time, volume or measured distance on chromatogram
L	column length (in units of cm)
t	retention value of acetone or NaCl peak expressed in volume, time or measured distance on chromatogram
N	number of theoretical plates
t_R	retention time

w_h	peak width at half height (in units of time)
a	the distance from the leading edge of the peak to the mid-point of the peak
b	the distance from the mid-point of the peak to the trailing edge

CHAPTER 1

INTRODUCTION

1.1 Background Study

Product recovery involves processing steps in which product such as proteins are captured, concentrated and purified from biological feedstock such as bacteria, yeast, fungal or mammalian cells culture. Purifying protein is often a complicated task due to proteins' heterogeneity, instability and complexity, in particular when not in their native environment. For process engineers, the challenges are not only associated with the task to recover protein in its active form, but also to achieve high yields that are expressed intrinsically at low concentration of feedstock containing many components of host organism and culture medium. This challenge is addressed in different approaches, such as the use of multi-steps process and integration of two or more techniques. For example, combining clarification steps (involving centrifugation and filtration) followed by product concentration steps (via ultrafiltration/diafiltration) and finally purification step, achieved typically via forms of chromatography techniques.

In this present study, a protein called cyclodextrin glucanotransferase (CGTase) is used. CGTase belongs to the α-amylase enzyme family which catalyzes the degradation of starch via cleavage of α-1,4-glysocidic bonds to form saccharides such as maltose, glucose and cyclodextrin (CD). With the increasing interest and application of cyclodextrin- the product of CGTase catalyzed reaction, there are great demands for its production for food and biotechnology industries at large. Hence creating a demand for the production of CGTase at a reasonable, economic value. CGTase is expressed natively as extracellular metabolites by variety of alkalophilic, mesophilic and hermophilic *Bacillus* genus bacteria (Letsididi et al., 2011; Alves-Prado et al., 2007). The cloning of CGTase gens into bacterial expressing host has been made in recent years, from which its expression and stability was improved significantly (Tesfai et al., 2012; Kweon et al., 2004).

1.2 Problem statement

The current strategy for the purification of CGTase incorporates a many-step procedure that is tedious and time-consuming. Typically, cascades of unit operations involving precipitation, filtration and different mode of adsorption chromatography are employed (Mirka et al., 2012; Savergave et al., 2008). It has been estimated that the overall cost of downstream processing is closely correlated to the number of purification steps employed (Spalding, 1991) and in fact, it represents the most significant expense in protein manufacturing by accounting for 40-65% total manufacturing cost (Orr et al.,

2012). Hence it is essential for the development of purification strategies tailor-made for CGTase, aiming at maximizing the yield, maintaining its biological properties, while minimizing the time and cost of production without compromising the final product purity.

The general approach for any protein purification is usually via exploitation of their physicochemical differences and interactions in charge, hydrophobicity, size or affinity with different separation technique employed (Kweon et al., 2004). The use of combination of more than one type of interaction, also known as mixed-mode has also been used in the past. The fundamental understanding of these interactions is necessary for the development of protein purification with a good industrial compliance. This includes investigation on the static adsorption and desorption behavior with the adsorbents of choice, dynamic behavior during protein loading, washing and elution in the column operation as well as the product integrity (activity, purity and yield).

1.3 Research objectives

The research objectives are listed as follows;

i) To develop a mixed mode chromatographic process for CGTase recovery.
ii) To develop an ion exchange chromatographic process for CGTase recovery.
iii) To develop an affinity chromatographic process for CGTase recovery.
iv) To compare and select the most suitable chromatographic process for CGTase recovery.

1.4 Thesis Layout and Research Strategy

The thesis is organized into eight chapters which conclude with the conclusion and recommendations for future research. This chapter (Chapter 1) highlights the background study of the current purification phenomenon, the problem statements and research objectives. Chapter 2 reviews the background of protein purification, purification and pre-purification strategies as well as various modes of adsorption chromatography. Also thoroughly reviewed are the enzyme CGTase, its origin, sources, applications and current purification strategies which are currently employed. Chapter 3 introduces general methodology used throughout the study. Chapter 4 includes purification of CGTase using mixed mode ligands upon which its suitability was tested with buffer optimizations and column adsorption conditions. Chapter 5 focuses on the purification of CGTase using affinity chromatography method in which a pseudo-type affinity (immobilized metal affinity chromatography) was assessed in its suitability to purify the protein CGTase. Chapter 6 investigates the efficiency of an anion exchanger to stand as a one-step chromatography purification scheme for CGTase recovery. Chapter 7 ties all methods together and concludes the efficiency of all the methods as a

one-step chromatography technique for the successful purification of the enzyme CGTase.

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BIODATA OF STUDENT

The student was born on the 6th of February 1985 at Hospital Besar Taiping, in Perak. She obtained her primary school education at Sekolah Rendah Kebangsaan Kepong Baru and pursued her secondary school at Sekolah Menengah Kebangsaan Kepong Baru before continuing her matriculation at the Asian Institute of Medicine, Science and Technology (AIMST) for a period of 1.5 years. Upon which the author continued her degree in Biotechnology (with Hons) in AIMST and completed her tertiary education in 2008. She then completed her industrial training of 6 months at the Veterinary Research Institute (VRI), Petaling Jaya. Subsequently, she begun her Master in Bioprocess Engineering in UPM and converted her MSc into a PhD (Bioprocess Engineering) in 2009.

LIST OF PUBLICATION

1) "Cell disruption strategies for the release of intracellular Glutathione S-Transferase (GST) from *E.coli* homogenate" - Proceeding in National Symposium of Fermentation Technology 2009, UniKL, (MiCET), Melaka

2) Sivapragasam, M. & Abdullah, N. (2014) "Purification of Glutahione *S*-transferase using mixed mode chromatography", February, vol. 3 issue 2, International Journal of Engineering Research and Technology.