# BIOCATALYSTS SYNTHESIS AND DEPOSITION IN MICROFLUIDICS FLOW SYSTEM

FIONA LING WANG MING

DOCTOR OF PHILOSOPHY

UNIVERSITI MALAYSIA PAHANG

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We hereby declare that we have checked this thesis and in our opinion, this thesis is adequate in terms of scope and quality for the award of the degree of Doctor of Philosophy.

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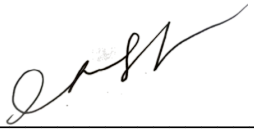

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I hereby declare that the work in this thesis is based on my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously or concurrently submitted for any other degree at Universiti Malaysia Pahang or any other institutions.

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# ABSTRAK

Penghasilan biopemangkin pepejal yang berkesan melalui mengimobilisasi enzim atas pembawa adalah sangat penting dalam applikasi katalisis. Nanopartikel telah diguna secara meluas sebagai pembawa enzim dan sifat permukaan pepejal tersebut (morfologi dan saiz pori) dan saiz partikel memainkan peranan penting dalam menentukan hasil imobilisasi enzim pada pepejal dan mempengaruhi prestasi pemangkin biomangkin yang dihasilkan. Justeru, mensistensis nanopartikel yang mempunyai saiz dan bentuk (taburan saiz sempit) yang dihendaki adalah amat penting. Tambahan pula, syarat semasa proses imobilisasi termasuk masa dan keadaan adalah mustahak bagi menghasilkan biopemangkin yang berkesan tanpa menyebabkan kerosakan tidak dapat dipulihkan kepada enzim. Walau bagaimanapun, kebanyakan proses immobilization melibatkan masa reaksi yang panjang akibat daripada rintangan mass transfer yang tinggi. Teknologi mikrofluidik telah menjadi platform baru dalam sintesis nanopartikel kerana teknologi tersebut dapat mengendali bendalir dengan lebih tepat dalam alat mikrofluidik. Antaranya, keadah emulsi (generasi titisan) dalam alat mikrofluidik mempunyai pelbagai faedah termasuk pencampuran yang berkesan, permukaan yang lebih luas dan pengurangan pencemaran kerana reaktan dapat dienkapsulasi dalam titisan berasingan. Teknologi mikrofluidik dapat meningkatkan kadar pencampuran berkesan justeru menjadi cara baharu dalam immobilize enzim atas pembawa pepejal dan menghasilkan biopemangkin. Kerja ini bertujuan untuk memperkenalkan dan menyiasat kebolehlaksanaan mikroreaktor dalam sintesis nanopartikel silika dan mengimobilisasi lipase untuk menghasilkan mangkin bersaiz nano dan digunakan dalam reaksi pengesteran. Dalam penyelidikan ini, mikroreaktor *polydimethylsiloxane* pertama kali direka menggunakan perisian AutoCAD dan dibuat menggunakan kaedah *direct writing*. Nanopartikel silika disintesis melalui kaedah sol-gel dalam mikroreaktor yang dihasilkan. Kajian ini juga mengkaji kesan sifat fizikal fasa berterusan pada saiz nanopartikel, dengan menambahkan surfaktan Sorbitan Monooleate nonionik dengan kepekatan yang berbeza (1 – 5 vol/vol%) kepada *tetraethyl orthosilicate*. Kaedah sol-gel konvensional dalam skala *batch* juga dijalankan dalam keadaan reaksi yang sama untuk tujuan perbandingan. Nanopartikel silika yang disintesis dicirikan menggunakan *Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), Energy Dispersive X-Ray Analysis (EDX), X-ray diffraction (XRD),* dan *nitrogen physisorption* analisis. *Rhizomucor miehei* lipase kemudian diimobilisasikan atas nanopartikel menggunakan sistem *batch* dan mikroreaktor. Larutan penyangga dikumpul secara berkala dan digunakan untuk analisis activity lipase. Biokatalis dicirikan menggunakan *Fourier-transform infrared spectroscopy* (FTIR). Prestasi pemangkin biopemangkin yang disintesis disiasat melalui esterifikasi fitosterol dan analisis kuantitatif dilakukan dengan menggunakan kromatografi gas untuk mendapatkan tahap esterifikasi. Dari hasil eksperimen, nanopartikel silika yang dihasilkan dari mikroreacktor mempunyai saiz lebih kecil dengan monodispersity yang lebih tinggi dan konfigurasi sfera yang sempurna berbanding dengan bentuk nanopartikel silika yang tidak teratur yang disintesis secara *batch*. Nanopartikel silika yang dihasilkan dalam sistem *bench* dan mikroreaktor yang telah dikalsinasi mempunya saiz purata 1.9 µm dan 480 nm, masing-masing ketika diperhatikan menggunakan SEM. Hasil analisis mengesahkan silika yang dihasilkan dalam sistem mikroreaktor mempunyai ketulenan tinggi dengan saiz partikel yang lebih kecil serta isipadu dan saiz pori yang lebih luas. Hasil eksperimen menunjukkan bahawa lipase mempunyai kapasiti muatan yang lebih tinggi pada nanopartikel silika yang disintesis dalam sistem aliran mikro dan mencapai kadar imobilisasi kira-kira 90%.

Keputusan menunjukkan bahawa kaedah pencampuran bukanlah parameter yang paling ketara dalam proses imobilisasi lipase berbanding dengan sifat pembawa (morfologi dan saiz) itu sendiri. Spektrum FTIR menunjukkan bahawa lipase berjaya dijerap pada nanopartikel silika melalui penjerapan fizikal di mana lipase tidak bergerak menunjukkan semua jalur yang ditunjukkan oleh nanopartikel silika dan lipase bebas. Lipase yang tidak bergerak menunjukkan tahap esterifikasi yang tinggi yang mengesahkan bahawa kadar reaksi dan hasil produk yang tinggi. Lipase yang tidak bergerak menunjukkan tahap esterifikasi maksimum sebanyak 97.3% dalam keadaan reaksi pemuatan pemangkin 2.5 mg/ml; nisbah molar β-sitosterol dan minyak biji bunga matahari: 1:2; 150 rpm; 50 °C; 4 jam. Kajian ini menunjukkan kebolehlaksanaan mikroreaktor dalam mensintesis nanopartikel untuk menghasilkan nanopartikel yang lebih kecil dan seragam yang dapat diterapkan dalam bidang berlainan seperti reaksi dan *drug delivery*.

## ABSTRACT

The production of effective solid biocatalyst through immobilizing the enzymes on a carrier is one of the important applications in catalysis. Nanoparticles are widely used as the support for enzymes where the properties (morphology and pore size) of the solid surface and the particle's size play an important role in deciding the enzymes immobilization yield on the solid which directly affecting the catalytic performance of the produced biocatalyst. Thus, synthesizing nanoparticles with controlled size and shape (narrow particle size distribution) is an important target that large numbers of research works were aiming for. Besides that, the immobilization conditions including the time and the immobilization environment are crucial for obtaining an effective biocatalyst without causing irreversible damage to enzymes. Conventional mixing methods used in nanoparticle synthesis are one of the most effective factors in determining the quality of the nanoparticles themselves. The mass transfer area between the reactants in the conventional production methods is controlled by the mixer design and operation and that will control the reaction time which will affect the produced nanoparticle's quality. A high-precision mixing method is believed to enhance the mass transfer area and nanoparticles quality and provide an excellent platform for enzyme immobilization as well. Microfluidic technology provides a new platform in nanomaterials synthesis due to the precise handling of fluid within the microfluidic devices. Among that, the emulsion method (droplet generation) in microfluidic demonstrated various benefits including effective mixing, larger surface area, and reduction in contamination possibilities as the reactants are encapsulated in segmented droplets. The highly efficient mixing in microfluidic devices also creates a new path in immobilizing lipase on the solid carrier to produce biocatalyst. This present work aims to introduce and investigate the effect of high-precision mixing provided using microfluidics technology on silica nanoparticles synthesis and lipase immobilization for the production of nano-sized catalysts for the esterification reaction. In this work, a polydimethylsiloxane microreactor was first designed and fabricated using the direct writing method. Silica nanoparticles were synthesized in the microreactor adapting sol-gel method by varying nonionic Sorbitan Monooleate surfactant concentrations (1 – 5 vol/vol%), and residence time, and the results were compared with nanoparticles produced from a bench-scale system. The synthesized silica nanoparticles were characterized using Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), Energy Dispersive X-Ray Analysis (EDX), and X-ray diffraction (XRD), and nitrogen physisorption analysis. The nanoparticles were then immobilized with *Rhizomucor miehei* lipase in both batch-scale and microreactor system methods. The buffer solution was collected periodically and brought for lipase activity assay analysis. The biocatalysts were characterized using Fourier-transform infrared spectroscopy (FTIR). The catalytic performance of the synthesized biocatalysts was investigated and validated through the esterification of phytosterol and quantitative analysis was conducted using gas chromatography. From the results, the silica nanoparticles produced from the microflow system were smaller in size with higher monodispersity and perfect spherical configuration compared to the irregular shapes of silica nanoparticles synthesized in bulk. The calcined silica nanoparticles produced in the bench-scale and microflow system had a mean size of 1.9 µm and 480 nm, respectively when observed using SEM. The characterization results confirmed high-quality silica nanoparticles were synthesized with smaller size, higher monodispersity, and larger pore size and volume. The experimental results showed that the lipase had a higher loading capacity on silica nanoparticles synthesized in a microflow system with an

immobilization yield of about 90%. The present work indicates that the mixing method is not the most significant parameter in lipase immobilization compared to the properties of the carriers (morphology and size) themselves. The FTIR spectrum indicated that lipase was successfully immobilized on the silica nanoparticles via physical adsorption where the immobilized lipase showed all the bands demonstrated by silica nanoparticles and free lipase. The immobilized lipase showed a high degree of esterification confirming the high reaction rate and product yield. The immobilized lipase demonstrated a maximum degree of esterification of 97.3% under reaction conditions of 2.5 mg/ml catalyst loading; molar ratio of β-sitosterol to sunflower seed oil: 1:2; 150 rpm; 50 °C; 4 hours. This present work showed the feasibility of microreactors in synthesizing smaller and uniform nanoparticles to be applicable in different fields such as reactions and drug delivery.

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