THE DEVELOPMENT OF AN INNOVATIVE THERMAL MIXING TECHNIQUE FOR THE FABRICATION OF LARGE SCALE POLYMETHACRYLATE MONOLITHS

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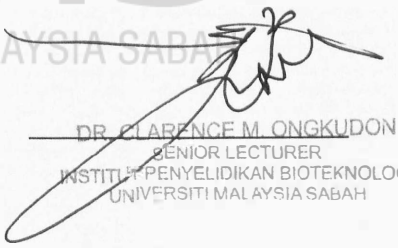

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ABSTRACT

The upsurge of monolith technology has redefined the limit of bioseparation sciences that was previously established by packed-bed column. Polymethacrylate monolith features large pores that are interlinked and give form to continuous pore channels which enable mass transport to transpire under convection manner. To date, there have been many successful attempts in the application of monolith for biomolecules separation using small-scale monoliths. However, the production and application of large-scale monoliths have not received much attention due to challenges pertaining to thermal escalation and wall channeling. The objective of this project is to investigate and elucidate the hurdles in monolith up-scaling and come out with possible solutions to overturn the persisting challenges. In regards to this, polymethacrylate monolith was fabricated through thermal-initiated free radical polymerization for subsequent analysis. A novel strategy involving the use of SEM on partitioned monolith coupled with temperature profiling and pore size distribution modality curves was used to determine the effect of porogen content (%) and thermal expansion on the pore morphology of varied scales of monoliths. Moreover, the effect of mold internal dimension on the magnitude of heat build-up was investigated by fabricating 70 % porogen-containing monoliths in columns that comes with various dimensions. The results showed that pore morphology differs with different monomer concentrations while the intensity of thermal build-up is inversely proportional to the porogen content (%). Also, the homogeneity of monoliths was observed to be directly proportional to porogen content (%) and inversely proportional to thermal build-up. The column internal diameter (i.d) analysis revealed that thermal escalation ceased beyond 8 cm i.d monolith while the changes of pore morphology and uniformity remained unchanged from 5 cm i.d onwards. However, the increased column diameter resulted in poorer heat transfer and was clearly illustrated by the large peak width of 17.0 cm i.d. The effect of thermal build-up on pore morphology and homogeneity was attributed to fixated differences in porogen content (%). In conclusion, the significant disparity of pore size distribution profile of various sections was not observed albeit improvement was recognized with reduced heat accumulation. Based on the preliminary studies conducted, thermal minimization method was devised as the countermeasure to reduce the heat escalation. The effectiveness of thermal mixing strategy was validated by successful fabrication of an intact monolith under 70 % porogen content, 5 cm i.d and 150 ml with negligible heat build-up. To improve on its applicable column size range, monolith reactor was designed and built which involved channeling water intermittently in between hot and cold water in accordance with the temperature of core region. In addition, three loop controllers were designed and put into test via fabrication of 17.0 cm i.d, 3.9 L monolith by using the reactor. The results have revealed the 3rd loop variant as the most optimal controller by managing to fabricate an intact 17.0 cm i.d monolith up to 3.9 L whereby the highest T_{max} recorded was 74.63 ^{o}C as compared to 124.95 ^{o}C and 122.28 ^{o}C achieved by the other two controllers respectively. The success of this method will pave the way for the future through which mass production of therapeutic drugs with monolith of liter scale is practically feasible.

ABSTRAK

PEMBANGUNAN TEKNIK CAMPURAN HABA INOVATIF UNTUK PENGHASILAN MONOLIT POLIMETAKRILAT BERSKALA BESAR

Kewujudan teknologi monolit telah mengubah definisi had sains bio-pemisahan yang dahulunya hanya didominasi oleh kolum penapis termampat. Monolit polimetakrilat mempunyai struktur liang besar yang saling bersambung dan ini mewujudkan saluran liang berterusan yang membolehkan pengangkutan jisim berlaku melalui proses perolakan. Sehingga kini, terdapat banyak kejayaan dalam penggunaan monolit skala kecil untuk pemisahan biomolekul. Walau bagaimanapun, penghasilan dan penggunaan monolit berskala besar tidak mendapat banyak perhatian disebabkan beberapa cabaran terutama sekali yang berkaitan dengan peningkatan haba dan saluran dinding. Objektif projek ini adalah untuk mengkaji dan menjelaskan cabaran-cabaran yang dihadapi dalam penghasilan monolit berskala besar sekaligus mencari kaedah-kaedah penyelesaian. Dalam hal ini, monolit polimetakrilat telah dihasilkan melalui pempolimeran radikal bebas yang diaktifkan oleh haba untuk analisis seterusnya. Strategi novel yang melibatkan penggunaan SEM pada monolith yang telah dibahagikan, pemprofilan suhu, dan lengkungan modaliti taburan saiz liang telah digunakan untuk menentukan kesan kandungan porogen (%) dan pengembangan haba pada morfologi liang monolit berbeza skala. Selain itu, kesan dimensi acuan pada magnitud penghasilan haba telah dikaji dengan menggunakan monolit yang mengandungi 70 % porogen dalam kolum yang berlainan dimensi. Hasil kajian menunjukkan bahawa morfologi liang yang terhasil berbeza pada kepekatan monomer yang berlainan, manakala intensiti pembentukan haba adalah berkadar songsang dengan kandungan porogen (%). Selain itu, keseragaman monolit didapati berkadar langsung dengan kandungan porogen (%) dan berkadar songsang dengan pembentukan haba. Analisis diameter dalaman kolum (i.d) mendedahkan penemuan baru dimana peningkatan haba berhenti pada 8 cm i.d monolit manakala perubahan morfologi dan keseragaman liang kekal tidak berubah dari 5 cm i.d dan seterusnya. Walau bagaimanapun, penambahan diameter dalaman kolum menyebabkan masalah pemindahan haba secara berkesan dan jelas digambarkan pada kolum berkelebaran maksima, 17.0 cm i.d. Kesan peningkatan haba kepada morfologi dan kehomogenan liang adalah disebabkan oleh perbezaan kandungan porogen (%). Kesimpulannya, tidak ada perbezaan yang ketara dalam analisis profil taburan saiz liang di antara semua bahagian monolit tetapi ianya bertambah baik dengan pengurangan haba terkumpul. Berdasarkan kajian awal yang dijalankan, kaedah pengurangan haba telah dipilih sebagai langkah untuk mengurangkan peningkatan haba. Keberkesanan teknik campuran pemanasan dan penyejukan berjaya dibuktikan apabila monolit tanpa rekahan yang mempunyai diameter 5 cm dan isipadu 150 ml berjaya dihasilkan dengan kesan pembentukan haba berlebihan minima. Untuk meningkatkan saiz monolit yang boleh dihasilkan menggunakan cara ini, reaktor monolit telah direka dan dibina dimana ianya melibatkan pengaliran air panas dan sejuk setara dengan suhu pusat monolit. Di samping itu, tiga jenis sistem kawalan telah direka dan diuji melalui fabrikasi monolit 17.0 cm i.d, 3.9 L dengan menggunakan reaktor tersebut. Keputusan ujikaji telah mendedahkan bahawa sistem kawalan jenis ketiga sebagai kaedah paling

optimum dengan kejayaan yang dicapai melalui penghasilan monolit tanpa rekahan yang mempunyai diameter 17.0 cm dan isipadu 3.9 L. Sistem ini juga berjaya mengurangkan pembentukan haba kepada suhu 74.63 °C berbanding 124.95 °C dan 122.28 °C yang dicapai oleh dua sistem kawalan lain. Keberkesanan kaedah ini akan membolehkan pengeluaran besar-besaran ubat teraputik dengan monolit berskala liter di masa depan lebih praktikal.

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LIST OF ABBREVIATIONS

DNA	-	Deoxyribonucleic acid
ROI	-	Return of investment
PEG	-	Polyethylene glycol
HPLC	-	High performance liquid chromatography
BSA	-	Bovine serum albumin
IEX	-	Ion Exchange
IgG	-	Immunoglobulin G
NAD^+	-	Nicotinamide adenine dinucleotide
TMOS	-	Tetramethoxysilane
PEO	-	Polyethylene oxide
PEEK	-	Polyether ether ketone
HSA	-	Human serum albumin
GMA	-	Glycidyl methacrylate
EDMA	-	Ethylene dimethacrylate
µm	-	Micrometer
CIM	-	Convective interaction media
AIBN	-	Azobisisobutyronitrile
CDI	-	Carbonyldiimidazole
DSC	-	Disuccinimidyl carbonate
cm	-	Centimeter
mm	-	Milimeter
Na_2CO_3	-	Sodium carbonate
CO_2	-	Carbon dioxide
SC-CO_2	-	Supercritical carbon dioxide
PSI	-	Per square inch
TMPTMA	-	Trimethylolpropane-trimethacrylate
BMA	-	Butyl methacrylate
EGDMA	-	Ethylene glycol dimethacrylate
i.d	-	Internal diameter
mL	-	Mililiter

nm	-	Nanometer
ROMP	-	Ring-opening metathesis polymerization
NBE	-	Norborn-2-ene
$RuCl_2(PCy_3)_2(CHPh)$	-	First-generation Grubbs initiator
UV	-	Ultraviolet
RTILs	-	Room temperature ionic liquids
kGy	-	Kilogray
PAN	-	Polyacrylonitrile
DMSO	-	Dimethyl sulfoxide
TIPS	-	Thermally induced phase separation
^oC	-	Degree celcius
m^2	-	Square meter
g	-	Gram
TEOS	-	Tetraethyl orthosilicate
TBOF	-	Tetrabutyl ammonium fluorid
m^2g^{-1}	-	Square meter per gram
cm^3g^{-1}	-	Cubic centimeter per gram
Wt%	-	Percentage by weight
Hr	-	Hour
PFA	-	Polyfurfuryl alcohol
mL g^{-1}	-	Mililiter per gram
PEGDA	-	Polyethylene (glycol) diacrylate
PPO	-	Poly(propylene)glycols
NaOH	-	Sodium hydroxide
HIPE	-	High internal phase emulsion
ϕ	-	High internal phase volume ratio
SEM	-	Scanning electron microscope
PVA	-	Polyvinyl alcohol
CTAB	-	Hexadecyltrimethylammonium bromide
SDS	-	Sodium dodecyl sulfate

RAFT	-	Reversible addition-fragmentation chain transfer
kbp	-	Kilobase pairs
T_{poly}	-	Polymerization temperature
T_{max}	-	Maximal temperature
pH	-	Potential Hydrogen
FRP	-	Free radical polymerization
R^2	-	Coefficient of determination
T_{sp}	-	Temperature setpoint for chiller/ waterbath
NGC	-	Next generation chromatography
VBA	-	Visual basic for application
L	-	Liter
w/w	-	
ΔT_{max}	-	Differential maximum temperature value recorded in between two monoliths
ΔT_{core}	-	Differential maximum temperature value recorded at core region in between two monoliths
$T_{waterbath}$	-	Temperature of waterbath
≈	-	Approximate
<	-	Less than
$T_{chiller}$	-	Temperature of chiller
CAD	-	Computer aided design
$T_{forecast}$	-	Predicted temperature
$T_{present}$	-	Present/Current/Live temperature value
$T_{previous}$	-	Previous temperature value
$T_{surface}$	-	Temperature measured at surface of monolith
V_{pore}	-	Volume of pore fraction
W_{wet}	-	Weight of wet adsorbent fragment
W_{Dry}	-	Weight of dry adsorbent fragment

g/cm^3	-	Density
V_{Mold}	-	Volume of clay mold
$V_{Adsorbent}$	-	Volume of adsorbent fragment
SOP	-	Standard operating procedure