

**SYNTHESIS AND CHARACTERIZATION OF MESOPOROUS
CARBONATED HYDROXYAPATITE FOR DRUG DELIVERY
APPLICATION**

by

NUR FARAHYAH BINTI MOHAMMAD

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LIST OF ABBREVIATIONS

ALP	Alkaline Phosphatase
Alpha-MEM	Alpha-Minimum Essential Medium
ANOVA	One-way Analysis of Variance
ARB	Angiotensin-II Receptor Antagonist
BCP	Biphasic Calcium Phosphate
BET	Brunauer-Emmett-Teller
BG	Biactive Glass
BJH	Barrett-Joyner-Halenda
BMP	Bone Morphogenic Proteins
bFGF	Basic Fibroblast Growth Factor
β -TCP	Beta Tricalcium Phosphate
CHA	Carbonated Hydroxyapatite
CMC	Critical Micelle Concentration
CTAB	Cetyltrimethylammonium Bromide
DDS	Drug Delivery System
DI	Deionized Water
DLC	Drug Loading Capacity
DMF	Dimethylformamide
DPM	Di(ethylenediamineplatinum) Medronate
DR _t	Drug Release
EDX	Energy Dispersive X-ray
EE	Entrapment Efficiency
ELISA	Enzyme-Linked Immunosorbent Assay

FESEM	Field Emission Scanning Electron Microscopy
FBS	Fetal Bovine Serum
FR-DTGS	Recovery Deuterated Triglycine Sulfate
FTIR	Fourier Transmission Infra-Red Spectrometry
FWHM	Full Width Half Maximun
HA	Hydroxyapatite
HRTEM	High Resolution Transmission Electron Microscopy
ICDD	International Centre of Diffraction Data
IUPAC	International Union of Physical and Applied Chemistry
JCPDS	Joint Committee on Powder Diffraction
KBr	Potassium Bromide
MBGs	Mesoporous Bioactive Glasses
MCM-41	Mobil Composition of Matter No. 41
MCM-48	Mobil Composition of Matter No.48
MRTD	Maximum Recommended Therapeutic Dosages
MSNs	Mesoporous Silica Nanoparticles
PBS	Phosphate Buffer Saline
PEO	Polyethylene Oxide
pNP	p-nitrophenol
pNPP	p-Nitrophenyl Phosphate
PPO	Polypropylene Oxide
PSD	Pore Size Distribution
SEM	Scanning Electron Microscopy
SBA-15	Santa Barbara Amorphous

SBF	Simulating Body Fluid
SDS	Sodium Dodecyl Sulphate
SDDs	Sustained Drug Delivery Systems
TEL	Telimisartan
TEM	Transmission Electron Microscopy
TGA	Thermogravimetric Analysis
TGF	Transformation Growth Factor
UV-Vis	Ultraviolet-Visible
VEGF	Vascular Endothelial Growth Factor
XRD	X-Ray Diffraction

LIST OF SYMBOLS

Q	amount of adsorbed drug (mg/g)
C_i	initial concentration (mg/ml)
C_t	residual concentration at time t (mg/ml)
V	volume of the drug (ml)
M	mass of the mesoporous sample (g)
m	mass of the drug that added initially
$C_{t\text{-corr}}$	corrected concentration at time t
C_t	apparent concentration at time t
v	volume of sample taken
V	total volume of dissolution medium
V_{SBF}	volume of the SBF
M_{drug}	total mass of drug in drug carriers
F	percentage/fractional release of drug
k	rate at which drug is released
t	elapsed time
n	release exponent

SINTESIS DAN PENCIRIAN HIDROKSIAPATIT BERKARBONAT BERLIANG MESO UNTUK APLIKASI PENGHANTARAN DADAH

ABSTRAK

Hidroksiapatit berliang meso (HA) sebagai pembawa dadah telah dikaji secara meluas tetapi kurang tumpuan diberikan terhadap spesis yang lebih bioserasi iaitu hidroksiapatit berkarbonat (CHA) berliang meso. Pengenalan struktur liang meso dijangka memberikan CHA berliang meso sifat biokeserasian dan profil pelepasan dadah yang lebih baik. Matlamat utama kajian ini adalah untuk menghasilkan CHA berliang meso yang mempamerkan ciri-ciri liang optimum bagi aplikasi penghantaran dadah dan mengkaji sifat-sifat biokeserasian bahan tersebut. Kesan-kesan jenis surfaktan dengan unit polietilena oksida-polipropelena oksida (PEO-PPO) yang berbeza, jenis pelarut basuhan yang digunakan (seperti air ternyahion, etanol dan aseton), kepekatan surfaktan, dan kandungan karbonat terhadap ciri-ciri liang daripada CHA berliang meso telah disiasat. CHA berliang meso telah disintesis dengan kaedah hidroterma menggunakan surfaktan triblok kopolimer bukan ionik sebagai templat untuk mewujudkan liang dalam partikel CHA. Di antara pelbagai pelarut basuhan yang telah dikaji, air ternyahion menjadi pilihan yang lebih utama sebagai pelarut dalam proses basuhan, kerana ia bukan sahaja secara fisiologikalnya lebih bioserasi berbanding etanol tetapi juga menghasilkan luas permukaan yang tinggi ($63 \text{ m}^2\text{g}^{-1}$) berbanding pelarut lain. CHA berliang meso yang disintesis menggunakan P123 ($63 \text{ m}^2\text{g}^{-1}$) mempunyai luas permukaan yang lebih besar berbanding yang dihasilkan menggunakan F127 ($58 \text{ m}^2\text{g}^{-1}$). Gambar-gambar mikroskop penghantaran elektron mengesahkan kewujudan liang-liang meso dalam sampel yang dihasilkan sebagai saluran-saluran liang bertatasusunan. Ciri-ciri

liang optimum (iaitu luas permukaan = $78 \text{ m}^2\text{g}^{-1}$, saiz liang = 27 nm dan isi padu liang = 0.542 nm) CHA berliang meso diperolehi apabila kepekatan surfaktan (1.7 mM) dikekalkan hampir kepada kepekatan kritikal micelle (CMC) 0.0044 mM. Kandungan karbonat pelopor yang tinggi (1 M) menghasilkan CHA berliang meso dengan luas permukaan yang tinggi dan kandungan karbonat adalah dalam julat tulang semula jadi manusia (2-8%). Biokeserasian bahan telah ditentukan dengan menjalankan kajian bioaktiviti *in vitro*, ujian ketoksikan dan ujian alkali fosfatase (ALP) ke atas CHA berliang meso. Keputusan kajian bioaktiviti *in vitro*, ujian ketoksikan dan ujian ALP membuktikan bahawa CHA berliang meso mempunyai biokeserasian yang setanding dengan HA komersil. CHA berliang meso disahkan tidak toksik terhadap sel-sel MC3T3-E1. Bahan ini juga menyokong pembezaan sel-sel pada pelbagai kepekatan ekstrak sehingga 25 mg/ml. Akhirnya, pemuatan dadah dan profil pelepasan dadah CHA berliang meso dinilai menggunakan ibuprofen dan cisplatin sebagai model dadah. Bagi kajian menggunakan ibuprofen, liang-liang meso yang terdapat di dalam CHA membolehkan ia mempunyai kapasiti pemuatan dadah yang tinggi (DLC = 18.9 wt%) dan pemuatan yang lebih efisien (28 wt%) serta jumlah pelepasan (about 39 %) yang lebih tinggi berbanding CHA tidak berliang (DLC = 6.6 wt%, EE = 13.2 wt%, release amount about 10%). CHA berliang meso dengan luas permukaan yang lebih besar menunjukkan sifat pelepasan terkawal yang lebih baik berbanding CHA berliang meso yang mempunyai luas permukaan yang rendah.