SYNTHESIS, CHARACTERIZATION AND PHYSICOCHEMICAL INVESTIGATIONS OF CHITOSAN BUILT HYDROGEL FOR CONTROLLED DRUG DELIVERY APPLICATIONS

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1CpMEM	Low molecular weight- chitosan containing hydrogel
2CpMEM	Medium molecular weight- chitosan containing hydrogel
3CpMEM	High molecular weight- chitosan containing hydrogel
^{13}C -NMR	Carbon-13 Nuclear Magnetic Resonance
3-APBA	3-Aminophenylboronic Acid
3D	3-Dimensional
AA	Alginic Acid
AAm	Acryl amide
AFM	Atomic Force Microscopy
AP	4-Aminophenol
APS	Ammonium persulfate
BMA	Butyl methacrylate
C1	Low Molecular-Weight Chitosan
C2	Medium Molecular-Weight Chitosan
C3	High Molecular-Weight Chitosan
CMC	Critical Micelle Concentration
Cond.	Surface Conductivity

$CONH_2$	Amide
COO^-	Carboxylate ion
–COOH	Carboxylic acid
CS	Chitosan
DDS	Drug delivery system
DD	Deionized Distilled
DFT	Density Field Theory
DLS	Dynamic Light Scattering
DNA–	Deoxyribonucleic Acid
DSC	Differential scanning calorimetry
EDC	3-dimethylaminopropyl)-3-ethyl carbodimide hydrochloride
EDA	1,2-Ethylenediamine
EGDMA	Ethylene Glycol Dimethacrylate
Eq	Equation
ESDRDs	Electro-Stimulated Drug Release Devices
FCS	Fluorescence Correlation Spectroscopy
FSAA	Fluorosiloxanyl Alkyl Acrylate
FT-IR	Fourier Transform Infra-Red
GPC	Gel Permeation Chromatography
HEMA	2-hydroxyethyl (methacrylate),
HOMO	Highest Occupied Molecular Orbitals
IPN	Interpenetrating Networks
k_{app}	Rate Constant

LCST–	Lower critical solution temperature
LUMO	Lowest unoccupied molecular orbitals
MAA	Methacrylic acid
MAS	Magic Angle Spinning
MBA	N,N-methylenebisacrylamide
MO	Molecular orbitals
MQ	Multiple-Quantum
M_w	Molecular weight
NaCl	Sodium Chloride
$–NH_2$	Amine
$NH3^+$	Ammonium ion
NOCC	N, O-carboxymethyl chitosan
Ɵ	Theta
^oC	Temperature in Centigrade
–OH	Hydroxyl
P407	Poloxamer407
PAA	Poly (acrylic acid)
PCL	Polycaprolactone
PDEAAm	Poly(*N*,*N*-diethylacrylamide),
PDEAEMA	polydiethylaminoethyl methacrylate
PDI	Polydispersity indices
PDMAEMA	Poly(*N*,*N*-dimethylaminoethyl methacrylate),
PEG	Poly(ethylene glycol),
PEO	Polyoxyethylene,

PEtOz-CHMC	Poly(2-Oxazoline)-Cholesteryl Methyl Carbonate
PF-127	Pluronic,
pK_a	Acid Dissociation Constant
PMAA	Poly (methacrylic acid),
pMEM	poly(ethylene glycol) methyl ether methacrylate)
PNIPAAm	Poly (*N*-isopoprylacrilamide),
Poly (AA)-g-PEG	Poly(acrylic acid)-graft-Poly(ethylene glycol),
Poly(AA)-g-PEG	Poly(acrylic acid)-graft-Poly(ethylene glycol),
PolyHEMA	poly (2-hydroxyethyl methacrylate)
PPO	Polypropylene oxide
PPy	polypyrrole
PVA	Poly vinyl alcohol,
PVAm	Poly(vinylamine),
PVP	Poly(*N*-vinylpyridine)

SINTESIS, PENCIRIAN DAN PENGKAJIAN FIZIKOKIMIA KE ATAS KITOSAN TERBINA HIDROGEL BAGI APLIKASI PENGHANTARAN UBATAN TERKAWAL

ABSTRAK

Kajian ini bertujuan untuk menjelaskan kesan kepada kepekaan yang terinduksi ke atas struktur, fiziokimia, kuantiti ubat dan profil pembebasan kitosan terbina hidrogel bagi aplikasi penghantaran ubatan terkawal. Pelbagai siri hidrogel berdasarkan radikal bebas pengkepolimeran kitosan dengan poli(etilena glikol) metil eter metakrilat, akrilamida-ko-asid metakrilik dan asid alginik disintesis dan difungsikan melalui misel yang terinduksi, kepekaan glukosa dan hidrofilik untuk lanjutan antara muka dengan larutan ubat. Keseluruhan hidrogel dicirikan dengan menggunakan pelbagai teknik seperti FTIR, ^{13}C-NMR, SEM, AFM, TGA, DSC, DLS and UV-Vis Spektroskopi. Kesan kepada pelbagai rangsangan (pH, glukosa, suhu, kekuatan ionik, uria) terhadap sifat-sifat fiziokimia dan kuantiti ubat dalam vitro melawan profil pembebasan oleh pelbagai model ubat-ubatan daripada matrik hidrogel dikaji pada keadaan fisiologi. Keputusan dicadangkan adalah berat molekul kitosan tidak memberi kesan kepada kepekatan misel kritikal (CMC) dan suhu bawah pelarutan kritikal (LCST). Morfologi hidrogel yang dianalisa menggunakan SEM dan AFM menyebabkan hidrogel dengan kawasan permukaan dalaman yang tinggi membenkan rintangan penyebaran yang rendah. Model ubatan Fluorescein, Rhodamine and Bromocresol green dengan 75.94%, 65.63% dan 76% profil pembebasan diperoleh dan lanya disebabkan oleh elektrostatik kompleks dan lanjutan antara muka ligan terpilih dengan larutan ubat. Pelepasan ubat di dapati

disebabkan oleh kepekatan cerunan, teras ke permukaan dan permukaan ke medium berair melalui penyebaran dan dikesan secara spektroskopik. Pekali penyebaran (n~0.7) dicadangkan mekanisma Bukan Fikian oleh pelepasan ubat melalui penyebaran air dan relaksasi hidrogel. Degradasi in-vitro ole 20% dan 38% dpenoleh untuk hidrogel dengan hidrofilik di dalam gastrik yang disimulasikan dan cecair usus selama 400 jam (2 minggu) melalui hakisan pukal. Oleh itu, kajian ini menyumbang kepada pengetahuan mengenai kitosan terbina hidrogel sebagai bahanbio berpretasi tinggi khususnya dalam aplikasi penghantaran ubat terkawal.

SYNTHESIS, CHARACTERIZATION AND PHYSICOCHEMICAL INVESTIGATIONS OF CHITOSAN BUILT HYDROGEL FOR CONTROLLED DRUG DELIVERY APPLICATIONS

ABSTRACT

This study attempted to clarify the influence of induced sensitivity on the structural, physicochemical, drug loading and release profiles of chitosan built hydrogel for controlled drug delivery applications. Different series of hydrogel based on free radical copolymerization of chitosan with poly (ethylene glycol) methyl ether methacrylate, acrylamide-co- methacrylic acid and alginic acid were synthesized and functionalized with induced micellization, glucose sensitivity and hydrophilicity for extended interfaces with drug solutions. The overall hydrogel were characterized by using different techniques as FT-IR, ^{13}C-NMR, SEM, AFM, TGA, DSC, DLS and UV-Visible spectroscopy. The effect of various stimuli (pH, glucose, temperature, ionic strength, urea) on physicochemical properties and the in vitro drug loading versus release profiles of various model drugs from the hydrogel matrices was investigated at physiological conditions. The results suggested that the molecular weight of chitosan does not effect the Critical Micelle Concentration (CMC) and Lower Critical Solution Temperature (LCST). The morphology of hydrogel Analyzed by SEM and AFM analysis revealed hydrogel with high internal surface areas resulted with low diffusional resistance. The model drugs Fluorescein, Rhodamine and Bromocresol green with 75.94%, 65.63% and 76% release profiles were obtained due to electrostatic complexation and extended interfaces of selective ligands with drug solutions. The drug release was observed due to concentration gradient, core to surface and surface to aqueous medium by diffusion and were

detected spectroscopically. The diffusion coefficeint ($n \approx 0.7$) suggested Non- Fickian mechanism of drug release through water diffusion and hydrogel relaxation. In vitro degradation of 20% and 38% was achieved for hydrogel with induced hydrophilicity in simulated gastric and intestinal fluids for 400 h (2 weeks) through bulk erosion. Therefore, this study contributes to the knowledge of chitosan built hydrogel as high performance biomaterials designed for controlled drug delivery applications.