

PREPARATION AND CHARACTERIZATION
OF CHITOSAN/POLY LACTIC ACID
NANOFIBERS USING ELECTROSPINNING
PROCESS FOR DRUG DELIVERY
APPLICATIONS

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DOCTOR OF PHILOSOPHY

UNIVERSITI MALAYSIA PAHANG



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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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DELIVERY APPLICATIONS

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ABSTRAK

Serat nano merupakan bahan baru yang sangat penting dalam bidang bioperubatan, manakala sistem electrospinning menggunakan wayar merupakan salah satu teknologi yang berkebolehan untuk pengeluaran lapisan serat nano secara berterusan dan besar-besaran. Kitosan merupakan polimer bio yang mudah diperolehi, mesra alam dan bioserasi. Walau bagaimanapun, pengeluaran serat nano daripada kitosan adalah sukar kerana penggunaan medan elektrik yang tinggi semasa electrospinning mencetuskan daya tolakan antara kumpulan ionik dalam struktur molekul polimer, menyebabkan penghasilan serat nano bermanik bukannya serat nano yang sekata. Di samping itu, kelarutan kitosan yang rendah dalam pelarut menyukarkan penghasilan serat nano kitosan. Dalam kajian ini kitosan yang mempunyai berat molekul tinggi telah dipecahkan kepada kitosan yang mempunyai berat molekul rendah melalui kaedah pendeasetilan. Pelbagai tahap pendeasetilan menghasilkan kitosan yang berat molekul rendah yang berbeza. Kitosan ini seterusnya dicampur dengan larutan poli (laktik) asid (PLA) dalam diklorometana untuk memudahkan proses electrospinning. Campuran kitosan-PLA melalui proses electrospinning menggunakan wayar bebas untuk menghasilkan serat nano yang kemudiannya diperiksa sifat permukaannya menggunakan microscopy imbasan elektron (SEM) dan analisis sudut sentuhan. Manakala, struktur kimia dalam serat nano dianalisis menggunakan spektroskopi inframerah transformasi Fourier (FTIR) dan kalorimetri imbasan kebezaan (DSC). Pencirian mekanikal dan fizikokimia juga telah dijalankan bagi serat nano yang dihasilkan. Serat nano yang mempunyai kualiti yang terbaik kemudiannya diubahsuai untuk aplikasi penyampaian ubat dengan memuatkan drug model, iaitu Diclofenac Sodium (DNA), ke dalam serat nano yang seterusnya dianalisis menggunakan pelbagai teknik pengesanan unsur dan fizikokimia. Potensi serat nano direka untuk aplikasi penyampaian ubat telah disahkan melalui kajian pelepasan drug secara *in vitro* serta kinetik pelepasan drug. Hasil kajian menunjukkan bahawa pendeasetilan 25% kitosan 15 kDa dan 7.5 kDa menghasilkan serat nano lebih berkualiti berbanding dengan berat molekul yang tinggi (30 kDa) chitosan. Serat nano yang dihasilkan menunjukkan sifat-sifat mekanikal lebih baik berbanding dengan nanofibers chitosan yang dilaporkan sebelum ini. Malah, kekuatan tegangan (3 MPa), modulus Young (1.5 MPa), dan% Pemanjangan (10%) adalah setanding dengan nilai yang dilaporkan sebelum ini bagi serat nano yang biasa digunakan untuk aplikasi penyampaian ubat. Sebaliknya, pembelauan sinar-X (XRD) dan X-ray spektroskopi fotoelektron (XPS) keputusan mendedahkan bahawa DNA tersimpan sekata dalam serat nano. Kajian pembebasan drug menunjukkan bahawa serat nano kitosan-PLA yang disediakan dengan menggunakan 25% kitosan (15 kDa) boleh digunakan untuk menyampaikan model drug (DNA) mengikut cara pelepasan terkawal selama 96 h dengan pelepasan letusan kira-kira 25%, dan kinetik pelepasan mengikut difusi Fickian. Oleh itu, serat nano yang dihasilkan dalam penyelidikan ini mempunyai ciri-ciri hidrofilik dan hidrofobik yang sangat baik untuk penyampaian durg yang mempunyai pelbagai darjah kecutuban.

ABSTRACT

Nanofibers are considered as a new class of highly important materials in the biomedical field, whereas free surface wire electrospinning system is one of the most versatile technologies for the continuous and mass production of nanofibrous layers. On the other hand, chitosan is a bio-derived, biodegradable and biocompatible polymer. However, the production of chitosan nanofibers is considered difficult because the application of high electric field during electrospinning triggers the repulsive forces between the ionic groups within the polymer backbone, resulting into formation of beads instead of continuous fibers. In addition, the low solubility of chitosan is another major limitation for the production of chitosan nanofibers. In this study high molecular weight chitosan was converted to low molecular weight chitosan with subsequent deacetylation, to produce low molecular weight chitosan with different degrees of deacetylation. These were further blended with a solution of poly(lactic) acid (PLA) in dichloromethane to facilitate the spinning process. The chitosan-PLA blend was electrospun using the free surface wire electrospinning process and the produced nanofibers were characterized for their surface properties using scanning electron microscopy (SEM) and contact angle analysis. In addition, the structural properties were determined through fourier transforms infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). Furthermore, mechanical and physicochemical characterizations were conducted using different techniques. Fibers with the best performance were then modified for drug delivery applications by loading a model drug, Diclofenac Sodium (DNa), into the nanofibers, after which it was characterized accordingly using different elemental and physicochemical techniques. Then, the potential of the fabricated nanofibers for drug delivery applications was verified through in vitro release studies as well as drug release kinetic studies. Results showed that 25% fully deacetylated chitosan of 15 kDa and 7.5 kDa produces better quality nanofibers compared with the higher molecular weight (30 kDa) chitosan. Significantly, the produced nanofibers showed improved mechanical properties compared with the previously reported chitosan nanofibers prepared using the high molecular weight chitosan. In fact, the tensile strength (3 MPa), Young's modulus (1.5 MPa), and %Elongation (10%) are comparable to the previously reported values of nanofibrous mats produced using different polymers and used for drug delivery applications. On the other hand, X-ray diffraction (XRD) and X-ray photoelectron spectroscopy (XPS) results reveal that the incorporated DNa is distributed within the nanofibers. Notably, release results showed that chitosan-PLA nanofibers prepared using 25% chitosan (15 kDa) could be used to deliver the model drug (DNa) in a controlled release manner for 96 h with burst release of about 25%, and release kinetics follow the Fickian Diffusion kinetics. Therefore, the nanofibers produced herein can open up a new type of nanofibers with both hydrophilic and hydrophobic properties which are highly desirable for the delivery of drugs with various degrees of polarity.

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LIST OF SYMBOLS

η	Intrinsic viscosity
η_{rel}	Relative viscosity
η°	Solvent viscosity
η_{sp}	Specific viscosity
λ	Lambda
κ	Kappa
ι	Iota
K, a	Mark-Houwink constants
n	Fickian rate constant
K_0	Zero order rate constant
K_1	First order rate constant
K_H	Higuchi dissolution constant
K	Fickian diffusion constant

LIST OF ABBREVIATIONS

AcAc	Acetic Acid
CR	Controlled release
CRDD	Controlled release drug delivery
DCM	Dichloromethane
DDA	Degree of deacetylations
DLS	Dynamic light scattering
DNa	Diclofenac sodium
DSC	Differential scanning calorimetry
EDTA	Ethylenediaminetetraacetic acid
EDX	Energy disoersive X-ray
FDA	Food and drug administration
FDUV	First derivative ultra violet spectroscopy
FTIR	Fourier transform infrared
FSD	Fiber size distribution
Gm	Gram
HA	Hyaluronic acid
HCl	Hydrochloric acid
HMWC	High molecular weight chitosan
HNMR	HNuclear Magnetic Resonance
hr	Hour
kDa	Kilo Dalton
LMWC	Low molecular weight chitosan
Mn	Number average molecular weight
Mv	Viscosity average molecular weight
Mw	Weight average molecular weight
Mt	Amount of drug released at time t
M ∞	Amount of drug released at time ∞
NaOH	Sodium Hydroxide
NSAID	Nonsteroidal anti-inflammatory drugs
PCL	Poly caprolactone
PEO	Polyethylene oxide

PET	Polyethylene terephthalate
PLA	Polylactic acid
PLGA	Poly lacticco-glycolic acid
ppm	Parts per million
PVA	Polyvinyl alcohol
PVP	Poly-vinylpyrrolidone
S1	15%CS 30kDa nanofiber
S2	15%CS 15kDa nanofiber
S3	15%CS 7.5kDa nanofiber
S4	25%CS 30kDa nanofiber
S5	25%CS 15kDa nanofiber
S6	25%CS 7.5kDa nanofiber
S7	PLA nanofiber nanofiber
SEM	Scanning electron microscopy
STDEV	Standard deviation
Tc	Crystalization temperature
Tg	Glass transition temperature
Tm	Melting temperature
TM	Tensile modulus
TS	Tensile strength

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