ELECTROSPUN HYDROXYETHYL CELLULOSE NANOFIBROUS SCAFFOLDS FUNCTIONALIZED WITH HYDROXYAPATITE FOR BONE TISSUE ENGINEERING

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SUPERVISOR'S DECLARATION

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 in Advanced Materials

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I hereby declare that the work in this thesis is based on my original work except for quotations and citation 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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Dedicated to

My Grandmother (Nani Maa)

&

My Beloved Parents

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LIST OF SYMBOLS

A	Cross-section area of specimens
d	spacing between atomic planes or lattice spacing (A^o)
E'	Storage modulus scaffolds (MPa)
E''	Loss modulus of scaffolds (MPa)
E^*	Complex modulus
tan δ	Loss factor or loss tangent
ΔE'	Rigidity of polymers (%)
S_R	Swelling ratio (%)
M_R	Mass rate ratio (%)
W_h	Mass of sample after incubation in PBS
W_i	Mass of sample before incubation in PBS
W_s	Mass of swollen sample
W_d	Mass of dry sample

Greek Symbols

λ	X-ray wavelength
ε	Tensile strain
σ	Tensile stress

φ	Diffraction angle (degree)
σ_A	Sinusoidal stress
ε_A	Sinusoidal strain

LIST OF ABBREVIATIONS

ACP	Alternate calcium phosphate soaking method
ANOVA	Analysis of variance
ATR	Attenuated total reflectance
BTE	Bone tissue engineering
CaP	Calcium phosphate
DMA	Dynamic mechanical analysis
DSC	Differential scanning calorimetery
DTG	Differential thermo-gravimetric
ECM	Extra-cellular matrix
EDX	Energy Dispersive X-rays
FESEM	Field emission scanning electron microscopy
FTIR	Fourier transforms infrared spectroscopy
GA	Glutaraldehyde
HEC	Hydroxyethyl cellulose
MTT assay	Colorimetric assay for cell metabolic activity
nHA	Nano-hydroxyapatite
PBS	Phosphate buffered saline
PCL	Poly (caprolactone)
PEO	Poly (ethylene oxide)
PLGA	Poly (lactic-co-glycolic acid)
PLLA	Poly (lactic acid)
PVA	Poly (vinyl) alcohol
SBF	Simulated body fluid
SD	Standard deviations in the mean values

SEM	Scanning electron microscopy
TGA	Thermo-gravimetric analysis
U2OS	Human osteosarcoma cells
UTM	Universal testing machine
UV	Ultra violet light
XPS	X-ray photoelectron spectroscopy
XRD	X-ray diffraction

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ABSTRAK

Kejuruteraan tisu tulang memberi tumpuan kepada penggunaan perancah sebagai pengganti penting bagi menjana semula struktur tulang serta memulihkan fungsi tisu tulang. Pemilihan bahan yang sesuai adalah langkah penting ke arah pembinaan perancah dalam kejuruteraan bioaktif dengan seni bina permukaan sesuai, keserasian bio, penguraian bio dan sifat mekanikal bio yang boleh meniru matriks luar sel tulang asli (ECM). Tujuan utama kajian ini adalah untuk menyediakan perancah yang mempunyai sifat keserasian bio dan penguraian bio berasakan hydroxyethyl selulosa (HEC)dengan menggunakan air sebagai satu-satunya pelarut. Perancah nanogentian yang mempunyai sifat bio mekanikal direka menggunakan HEC polimer dengan polyvinyl alkohol (PVA)dan disediakan melalui teknik elektroputaran. HEC telah dicampur dengan PVA dalam pelbagai kepekatan untuk mendapatkan kelikatan yang sesuai untuk electroputaran. Bagi fungsi nanogentian HEC / PVA, zarah nanohydroxyapatite (NHA) telah disintesis dan kemudian diperkukuhkan dalam perancah HEC / PVA melalui electroputaran. Tambahan pula, bio-mineral perancah HEC / PVA dilakukan dengan menggunakan cecair simulasi badan (SBF) dan alternatif kalsium fosfat proses rendaman (ACP) untuk meniru ECM. Keserasian perancah dengan sel tanpa mineral dan galian telah dinilai secara vitro dalam kajian struktur sel. Pengimbas mikroskop elektron dan imbasan ruang pancaran elektron mikroskop digunakan untuk analisis struktur. Sifat-sifat mekanikal telah dikaji menggunakan mesin ujian Universal. Tenaga serakan X-ray, spektroskopi Fourier transform inframerah, spektroskopi X-ray fotoelektron, X-ray pembelauan, analisis Thermo-gravimetrik, pengimbas calorimetery yang berbeza dan analisis mekanikal dinamik telah digunakan untuk menganalisis sifat kimia dan sifat termal perancah. Perancah nanogentian mempamerkan gambaran struktur yang sangat baik dengan struktur berliang saling berkaitan. Perubahan kepekatan HEC mempunyai pengaruh besar ke atas struktur dan sifat-sifat perancah. Secara dengan peningkatan kepekatan HEC, diameter gentian menurun dan saiz liang meningkat. Diameter perancah electrospun nanogentian diubah dalam lingkungan 379 nm kepada 524 nm dan liang saiz yang berbeza-beza dari 9 mikron ke 6 μm. Ini menunjukkan bahawa perancah HEC / PVA memiliki sifat-sifat mekanikal dan kimia yang baik. Rod seperti zarah Nha dengan komposisi kimia mineral tulang semulajadi telah berjaya disediakan dengan kaedah kimia basah. Keputusan itu mengesahkan pengukuhan partikel nHA dalam HEC / PVA nanogentian electroputaran. Lapisan kristal mineral dijumpai di permukaan perancah selepas bio-mineral. Pemendapan mineral biomimetic meningkat dengan masa rendaman dalam SBF dan Nha dan pemendapan didapati meningkat dengan tinggi kandungan HEC semasa proses rendaman ACP. Pengaruh biomineralisasi diperhatikan dengan baik melalui bioaktiviti dan sifat-sifat mekanik perancah. Peningkatan sifat mineral mungkin disebabkan oleh kehadiran zarah-zarah mineral pada perancah nanofibrous yang membolehkan penembusan dan pemindahan sel dan memberikan kekuatan mekanikal yang baik dengan interaksi kimia yang kuat. Keputusan ini menunjukkan bahawa perancah HEC / PVA adalah bahan bio yang boleh baik untuk digunakan dalam kejuruteraan tisu tulang.

ABSTRACT

Bone tissue engineering focuses on using scaffolds as vital substitute to regenerate the bone structure and therefore recover the function of bone tissue. Selection of the suitable material is an important step towards the construction of bioactive engineered scaffolds with appropriate surface architecture, biocompatibility, biodegradability and biomechanical properties that can mimic the natural bone extracellular matrix (ECM). The main aim of this research is to prepare bio-compatible and biodegradable scaffolds based on hydroxyethyl cellulose (HEC) using water as the only solvent. The biochemically and functionally designed nanofibrous scaffolds of HEC polymer with polyvinyl alcohol (PVA) were prepared by electrospinning technique. HEC was blended with PVA in various weight concentrations to get a suitable viscosity for electrospinning. For functionalization of HEC/PVA nanofibers, the nanohydroxyapatite (nHA) particles were synthesized and then reinforced in HEC/PVA scaffolds through electrospinning. Furthermore, bio-mineralization of HEC/PVA scaffolds was performed using simulated body fluid (SBF) and alternate calcium phosphate (ACP) soaking process to mimic ECM. The cytocompatibility of unmineralized and mineralized scaffolds was evaluated by in-vitro cell culture studies. Scanning electron microscopy and Field emission scanning electron microscopy were used for structural analysis. Mechanical properties were investigated by Universal testing machine. Energy dispersive X-ray, Fourier transform infrared spectroscopy, X-ray photoelectron spectroscopy, X-ray diffraction, Thermo-gravimetric analysis, Differential scanning calorimetery and Dynamic mechanical analysis were used to analyse chemical, and thermal properties of scaffolds. The prepared nanofibrous scaffolds exhibit excellent morphology with interconnected porous structure. Changing HEC concentration had great influence on the structure and properties of the scaffolds. With increasing HEC concentration, the fiber diameter decreased and pore size increased. The diameters of electrospun nanofibrous scaffolds varied in the range of 379 nm to 524 nm and the pore sizes varied from 9 μm to 6 μm.The results revealed that the biocompatible HEC/PVA scaffolds possess good mechanical and chemical properties. The rod like nHA particles with chemical composition of natural bone minerals was successfully prepared by wet chemichal method. The results confirmed the reinforcement of nHA patricles in HEC/PVA electrospun nanofibers. Coating of mineral cystals was found on the surface of scaffolds after bio-mineralization. The deposition of biomimetic minerals increased with time of immersion in SBF and nHA deposition was found to increase with high content of HEC during ACP soaking process. The influence of biomineralization was observed with improved bioactivity and mechanical properties of the scaffolds. The enhancement in properties after mineralization could be due to the presence of mineral particles on nanofibrous scaffolds which allows the penetration and migration of cells and provides good mechanical strength with strong chemical interaction. These results suggest that the HEC/PVA scaffolds are promising biomaterials for bone tissue engineering.

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LIST OF PUBLICATIONS

1) **Sugandha Chahal**, Fathima Shahitha Jahir Hussain, Anuj Kumar, Mohammad Syaiful Bahari Abdull Rasad., Mashitah Mohd Yusoff. 2016. Fabrication, characterization and in vitro biocompatibility of electrospun hydroxyethyl cellulose/poly (vinyl) alcohol nanofibrous composite biomaterial for bone tissue engineering. *Chemical Engineering Science*, **144**: 17-29.

2) **Sugandha Chahal**, Fathima Shahitha Jahir Hussain, Anuj Kumar, Mohammad Mashitah Mohd Yusoff, Mohammad Syaiful Bahari Abdull Rasad. 2015 .Electrospun hydroxyethyl cellulose nanofibers functionalized with calcium phosphate coating for bone tissue engineering. *RSC Advances*, **5**(37):.29497-29504.

3) **Sugandha Chahal**, Fathima Shahitha Jahir Hussain, Mashitah Mohd Yusoff. 2014. Biomimetic growth of bone-like apatite via simulated body fluid on hydroxyethyl cellulose/polyvinyl alcohol electrospun nanofibers. *Bio-Medical Materials and Engineering*, **24**(1537):.799-806.

4) **Sugandha Chahal**, Fathima Shahitha Jahir Hussain, Mashitah Mohd Yusoff, 2013. Characterization of modified cellulose (MC)/poly (vinyl alcohol) electrospun nanofibers for bone tissue engineering. *Procedia Engineering*, **53**:.683-688. (Scopus)

5) **Sugandha Chahal**, Fathima Shahitha Jahir Hussain, Mohammad Syaiful Bahari Abdull Rasad, Mashitah Mohd Yusoff, Anuj Kumar. 2016: Nano-hydroxyapatite coated hydroxyethyl cellulose electrospun scaffolds and their cellular response. ***International Journal of Polymeric Materials and Polymeric Biomaterials***. (**DOI: 10.1080/00914037.2016.1190926**)

6) Farah Hanani Zulkifli, Fathima Shahitha Jahir Hussain, Mashitah Mohd Yusoff, Nurul Nadiah Hamidon, **Sugandha Chahal**. 2013. Cross-linking effect on electrospun Hydroxyethyl cellulose/poly(vinyl) alcohol nanofibrous scaffolds. *Procedia Engineering*, **53**:.689-695. (Scopus)

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1) **Sugandha Chahal**, Fathima Shahitha Jahir Hussain, Mashitah Mohd Yusoff. 2012. Characterization of modified cellulose (MC)/poly (vinyl alcohol) electrospun nanofibers for bone tissue engineering. Malaysian Technical Universities Conference on Engineering & Technology (MUCET). **2nd Best Paper Award in Science Category.**

2) **Sugandha Chahal**, Farah Hanani Binti Zulkifli, Fathima Shahitha Jahir Hussain, Mashitah binti Mohd Yusoff. 2012. Characterisation of HEC/PVA blend nanofibers produced by electrospinning. National conference for Postgraduate research (NCON). **3rd Best Poster Award.**

3) Farah Hanani Zulkifli, Fathima Shahitha Jahir Hussain, Mashitah Mohd Yusoff Nurul Nadiah Hamidon, **Sugandha Chahal**. 2012. Cross-linking effect on electrospun Hydroxyethyl cellulose/poly(vinyl) alcohol nanofibrous scaffolds. Malaysian Technical Universities Conference on Engineering & Technology (MUCET).

4) **Sugandha Chahal**, Fathima Shahitha Jahir Hussain, Mashitah Mohd Yusoff. 2013. Biomimetic growth of bone-like apatite via simulated body fluid on hydroxyethyl cellulose/polyvinyl alcohol electrospun nanofibers. The 2nd International Conference on Biomedical Engineering and Biotechnology (iCBEB 2013), held in Wuhan, China on 11–13 October 2013.

5) **Sugandha Chahal**, Fathima Shahitha Jahir Hussain,Mashitah Mohd Yusoff, Farah Hanani Zulkifli. 2013. Bone-like apatite coating on electrospun hydroxyethyl cellulose/polyvinyl alcohol nanofibers for bone tissue engineering. Conference on Industry - Academia Joint Initiatives in Biotechnologoly (CIA: Biotech 13).

EXHIBITIONS

1) Dr. Fathima Shahitha, Prof. Mashitah Binti Mohd Yusoff, Farah Hanani Binti Zulkifli and **Sugandha Chahal**. 2012. Scaffolds from chemically modified cellulose for bone tissue engineering. Biomalaysia. **Silver Award**.

2) Dr. Fathima Shahitha, Prof. Mashitah Binti Mohd Yusoff, Sugandha Chahal and Farah Hanani Binti Zulkifli. 2013. Nanofibrous scaffolds from water soluble polymers for bone growth. Creation, Innovation, Technology and Research Exposition (CITREX). **Bronze Award**.

3) Dr. Fathima Shahitha, Prof. Mashitah Binti Mohd Yusoff, Farah Hanani Binti Zulkifli and **Sugandha Chahal**. 2012. Scaffolds from chemically modified cellulose for bone tissue engineering. Creation, Innovation, Technology and Research Exposition (CITREX). **Silver Award**.

4) Dr.Fathima Shahitha Jahir Hussain, **Sugandha Chahal**, Mashitha Binti Mohd Yusoff, Sasikala A/P Appalasuwami, Mohammad Syaiful Bahari Bin Abdull Rasad, Anuj Kumar. 2014. Calcium phosphate coating on electrospun hydroxyethyl cellulose nanofibers for bone tissue engineering. Creation, Innovation, Technology and Research Exposition (CITREX). **Gold Award**.