NUR ARIFAH BINTI ISMAIL @ MOHD ISMAIL DOCTOR OF PHILOSOPHY 2019

FABRICATION AND CHARACTERIZATION OF GELLAN GUM FILMS INCORPORATING NANOSTRUCTURED TITANIUM DIOXIDE FOR WOUND DRESSING APPLICATIONS

NUR ARIFAH BINTI ISMAIL @ MOHD ISMAIL

DOCTOR OF PHILOSOPHY
UNIVERSITI MALAYSIA TERENGGANU

2019

FABRICATION AND CHARACTERIZATION OF GELLAN GUM FILMS INCORPORATING NANOSTRUCTURED TITANIUM DIOXIDE FOR WOUND DRESSING APPLICATIONS

NUR ARIFAH BINTI ISMAIL @ MOHD ISMAIL

DOCTOR OF PHILOSOPHY
UNIVERSITI MALAYSIA TERENGGANU

2019

FABRICATION AND CHARACTERIZATION OF GELLAN GUM FILMS INCORPORATING NANOSTRUCTURED TITANIUM DIOXIDE FOR WOUND DRESSING APPLICATIONS

NUR ARIFAH BINTI ISMAIL @ MOHD ISMAIL

Thesis Submitted in Fulfillment of the Requirement for the Degree of Doctor of Philosophy in the Faculty of Science and Marine Environment

Universiti Malaysia Terengganu

2019

DEDICATION

Dedicated to:
My Prime Love, Allah the Almighty
My initiator, His Messenger
My endless love, parent and siblings
My precursor, Dr Mohd Hasmizam Razali, Assoc Prof Dr Khairul Anuar Mat Amin and Prof Dr Fadzilah @ Adibah Abd Majid
My support system, relatives and friends

"My success can only come from Allah.
In Him I trust, and unto Him I look"
[Hud:88]

LIST OF PUBLICATIONS

Publications

1. **Nur Arifah Ismail**, Khairul Anuar Mat Amin, Fadzilah @ Adibah Abdul Majid, and Mohd Hasmizam Razali. (2019). Gellan Gum Incorporating Titanium Dioxide Nanoparticles Biofilm as Wound Dressing: Physicochemical, Mechanical, Antibacterial Properties and Wound Healing Studies. *Materials Science and Engineering: C*. Under review. (Q1, IF: 5.08).
2. **Nur Arifah Ismail**, Khairul Anuar Mat Amin, and Mohd Hasmizam Razali. (2018). Novel Gellan Gum Incorporated TiO_2 Nanotubes Film for Skin Tissue Engineering. *Materials Letters*, 228, 116–120. (Q1, IF: 2.687).
3. Mohd Hasmizam Razali, **Nur Arifah Ismail**, Mohd Farhan Azly Mohd Zulkafli, and Khairul Anuar Mat Amin. (2018). 3D Nanostructured Materials: TiO_2 Nanoparticles Incorporated Gellan Gum Scaffold for Photocatalyst and Biomedical Applications. *Materials Research Express*, 5, 035039. (Q1, IF: 1.597).
4. Mohd Hasmizam Razali, **Nur Arifah Ismail**, Uwais Al-qarni Osman, and Khairul Anuar Mat Amin. (2018). Mechanical and Physical Properties of Gellan Gum (GG) Biofilm: Effect of Glycerol. *ASM Science Journal Special Issue 2018 (1) AIMS2018*, 158-165. (Q4, SJR: 0.12).
5. **Nur Arifah Ismail**, Khairul Anuar Mat Amin, and Mohd Hasmizam Razali. (2018). Preparation of Gellan Gum (GG) Film: The effect of GG, Calcium Chloride ($CaCl_2$), Glycerol Concentration and Heat Treatment. *IOP Conference Series: Materials Science and Engineering*, 440, 012006. (SJR: 0.2).
6. **Nur Arifah Ismail**, Mohd Hasmizam Razali, and Khairul Anuar Mat Amin. (2017). Characterization of Nanostructured Titania and Titanate Materials Synthesized by Simple Hydrothermal Method. *Materials Science Forum*, 889, 229-233. (Q3, SJR: 0.18).
7. Mohd Hasmizam Razali, **Nur Arifah Ismail**, and Khairul Anuar Mat Amin. (2017). Nanostructured TiO_2 Materials: Preparation, Properties and Potential Applications (3P's). *Solid State Phenomena*, 266, 84-89. (Q4, SJR: 0.16).

8. **Nur Arifah Ismail**, Mohd Hasmizam Razali, and Khairul Anuar Mat Amin. Mechanical and Physicochemical Properties Study on Gellan Gum Thin Film Prepared using Film Casting Method. (2017). *3rd Electronic and Green Materials International Conference 2017 (EGM 2017) AIP Conference Proceeding*, 1885, 020045.
9. Mohd Hasmizam Razali, **Nur Arifah Ismail**, and Khairul Anuar Mat Amin. (2016). Study on Phase Transition of Hydrothermally Synthesized 1-D Titanate into Titania (TiO_2) as a Potential Nanobiomaterials. *International Journal of Applied Chemistry*, 12, 629-634. (Q4, SJR: 0.12).

Awards and Achievements

1. Student Research Day, Universiti Malaysia Terengganu (2019). Biocompatible and Biodegradable GG+TiO_2-NTs Film for Rapid Wound Healing. Participant.
2. 3 Minutes Thesis Competition, Universiti Malaysia Terengganu (2019). Advanced Bio-Nanocomposite Films for Rapid Wound Healing. Participant.
3. 3 Minutes Thesis Competition, School of Fundamental Science, Universiti Malaysia Terengganu (2019). Advanced Bio-Nanocomposite Films for Rapid Wound Healing. 1st runner up.
4. Travel Grant Award (XVIIIth Congress of the International Society for Animal Clinical Pathology (ISACP 2018), Tokyo, Japan).
5. 3 Minutes Thesis Competition, School of Fundamental Science, Universiti Malaysia Terengganu (2018). Advanced Bio-Nanocomposite Films for Rapid Wound Healing. Participant.
6. Citra Award, School of Fundamental Science, Universiti Malaysia Terengganu (2018).
7. Silver Medal Award (Minggu Penyelidikan dan Inovasi 2018). 2-D Nanostructured Materials for Wound Dressing Application.
8. 3 Minutes Thesis Competition, School of Fundamental Science, Universiti Malaysia Terengganu (2017). Advanced Bio-Nanocomposite Thin Films for Rapid Wound Healing. Participant.

9. Citra Award, School of Fundamental Science, Universiti Malaysia Terengganu (2017).
10. Silver Medal Award (Minggu Penyelidikan dan Inovasi 2017). GT-MED: Advanced Nanocomposite Thin Films for Rapid Wound Healing.

Conferences Attended

1. XVIIIth International Society for Animal Clinical Pathology Congress (ISACP 2018), Nippon Veterinary and Life Science University (NVLU), Tokyo, Japan. 4-8 August 2018. Bio-Nanocomposite Films of Titanium Dioxide Nanoparticles Incorporated Gellan Gum (GG+TiO_2-NPs) for Wound Healing.
2. 1st International Fundamentum Science Symposium 2018 (IFUNSS 2018). Primula Beach Hotel, Terengganu, Malaysia. 25–26 June 2018. Preparation of Gellan Gum (GG) Film: The effect of GG, $CaCl_2$, Glycerol concentration and heat treatment.
3. 3rd International Conference on Green Design and Manufacture 2017 (IConGDM 2017). Krabi, Thailand. 29-30 April 2017. Mechanical and Physicochemical Properties Study on Gellan Gum Thin Film Prepared Using Film Casting Method.
4. 7th International Conference on Postgraduate Education (ICPE-7 2016). Dewan Agung Tuanku Canselor, UiTM Shah Alam. 1st December 2016. Study on Phase Transition of Hydrothermally Synthesized 1-D Titanate into Titania (TiO_2) as a Potential Nanobiomaterials.
5. 5th International Conference on Engineering and Innovative Materials (ICEIM 2016). INTEKMA Resort & Convention Centre, Kuala Lumpur, Malaysia. 10-12 September 2016. Characterization of Nanostructured Titania and Titanate Materials Synthesized by Simple Hydrothermal Method.

Abstract of thesis presented to the Senate of Universiti Malaysia Terengganu in fulfillment of the requirements for the degree of Doctor of Philosophy

FABRICATION AND CHARACTERIZATION OF GELLAN GUM FILMS INCORPORATING NANOSTRUCTURED TITANIUM DIOXIDE FOR WOUND DRESSING APPLICATIONS

NUR ARIFAH BINTI ISMAIL @ MOHD ISMAIL

2019

Main Supervisor : Mohd Hasmizam Razali, Ph.D
Co-Supervisor : Associate Professor Khairul Anuar Mat Amin, Ph.D
Professor Fadzilah @ Adibah Abdul Majid, Ph.D
School : Faculty of Science and Marine Environment

Titanium dioxide (TiO_2) nanostructures, which are nanoparticles, nanorods and nanotubes, were successfully synthesised by using the hydrothermal method. These TiO_2 nanostructures were incorporated into gellan gum (GG) film. Good film was produced by using 1.00 g GG with a 5 mM $CaCl_2$ cross-linker and 50% w/w glycerol as a plasticiser dried at 50 °C for 24 h. GG incorporating TiO_2 nanoparticles (GG+TiO_2-NPs), nanorods (GG+TiO_2-NRs) and nanotubes (GG+TiO_2-NTs) was produced via the evaporative casting method. GG+TiO_2-NTs film shows the best mechanical properties, a high swelling ability and moderate water vapour transmission rates attributed to the chemical interaction between GG and TiO_2 nanotubes. GG+TiO_2-NTs film also shows antibacterial properties with 10 ± 0.38 mm, 12 ± 0.06 mm, 11 ± 0.06 mm and 10 ± 0.12 mm inhibition zone was obtained against *Staphylococcus aureus*, *Streptococcus*, *Escherichia coli* and *Pseudomonas aeruginosa*, which are as good as control samples (penicillin). This is due to the ability of TiO_2 nanotubes to generate reactive oxygen species, mainly hydroxyl (•OH) radicals, to decompose organic compounds in bacterial cells and deactivated the bacteria. The high antibacterial activity of GG+TiO_2-NTs films support their good performance for wound healing tested *in vitro* and *in vivo* on *Sprague Dawley*

rats. At a higher concentration of TiO_2 nanotubes incorporated into GG film, GG+TiO_2-NTs (10% w/w) films increase the tensile strength and Young's modulus. However, their swelling and water uptake were reduced because of the dense macromolecular chain of cross-linked networks of the films. The antibacterial property of the film was enhanced and thus promoted cell growth and proliferation. GG+TiO_2-NTs (10% w/w) films provide adequate moisture to reduce the risk of dehydration and thus fasten the wound healing process. The wound was found to be fully recovered on day 14 without any scarring. Inflammation was suppressed and reduced and re-epithelialisation was activated in the treated wound by using GG+TiO_2-NTs (10% w/w) films. However, at a higher concentration of TiO_2-NTs incorporated into GG, GG+TiO_2-NTs (15% w/w) and GG+TiO_2-NTs (20% w/w) films show a toxicity effect towards cells, thereby slowing the healing process.

Abstrak tesis yang dikemukakan kepada Senat Universiti Malaysia Terengganu sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

PEREKAAN DAN PENCIRIAN FILEM GELLAN GUM DIGABUNGKAN DENGAN TITANIUM DIOKSIDA BERSTRUKTUR NANO UNTUK APLIKASI PEMBALUT LUKA

NUR ARIFAH BINTI ISMAIL @ MOHD ISMAIL

2019

Penyelia Utama : Mohd Hasmizam Razali, Ph.D
Penyelia Bersama : Profesor Madya Khairul Anuar Mat Amin, Ph.D
Profesor Fadzilah @ Adibah Abdul Majid, Ph.D
Pusat Pengajian : Fakulti Sains dan Sekitaran Marin

Titanium dioksida (TiO_2) struktur nano iaitu partikelnano, rodnano dan tiubnano telah berjaya disintesis dengan menggunakan kaedah hidroterma. TiO_2 strukturnano ini dimasukkan ke dalam filem gellan gum (GG). Filem yang baik dihasilkan menggunakan 1.00 g GG dengan 5 mM $CaCl_2$ rangkai-silang dan 50% w/w gliserol sebagai bahan pelentur dikeringkan pada 50 °C selama 24 jam. GG menggabungkan TiO_2 partikelnano (GG+TiO_2-NPs), rodnano (GG+TiO_2-NRs) dan tiubnano (GG+TiO_2-NTs) dihasilkan menggunakan kaedah penyejatan. Filem GG+TiO_2-NTs menunjukkan ciri-ciri mekanikal yang terbaik, keupayaan penyerapan yang tinggi dan kadar penghantaran wap air sederhana disebabkan oleh interaksi di antara GG dan TiO_2-NTs. Filem GG+TiO_2-NTs juga menunjukkan sifat antibakteria iaitu 10 ± 0.38 mm, 12 ± 0.06 mm, 11 ± 0.06 mm dan 10 ± 0.12 mm zon perencatan diperolehi terhadap *Staphylococcus aureus*, *Streptococcus*, *Escherichia coli* dan *Pseudomonas aeruginosa* setanding dengan sampel kawalan (penisilin). Ini adalah kerana keupayaan TiO_2 tiubnano untuk menghasilkan spesies oksigen reaktif, terutamanya radikal hidroksil (•OH), untuk mengurai sebatian organik dalam sel-sel bakteria dan menyahaktifkan bakteria. Aktiviti antibakteria yang tinggi filem GG+TiO_2-NTs menyokong prestasi baik mereka untuk penyembuhan luka yang diuji secara *in vitro*

dan *in vivo* pada tikus *Sprague Dawley*. Pada kepekatan yang lebih tinggi TiO_2 tiubnano yang dimasukkan ke dalam filem GG, filem GG+TiO_2-NTs (10% w/w) meningkatkan kekuatan tegangan dan *Young's modulus*. Walau bagaimanapun, penyerapan dan pembebasan air dikurangkan disebabkan oleh rantaian makromolekul padat rangkaian rentas filem. Ciri-ciri antibakteria filem itu dipertingkatkan, oleh itu meningkatkan pertumbuhan sel dan percambahan. GG+TiO_2-NTs (10% w/w) filem menyediakan kelembapan yang mencukupi untuk mengurangkan risiko dehidrasi dengan itu mempercepatkan proses penyembuhan luka. Luka itu didapati pulih sepenuhnya pada hari ke-14 tanpa sebarang parut. Keradangan dikurangkan dan epitelialisasi diaktifkan semula pada luka yang dirawat menggunakan filem GG+TiO_2-NTs (10% w/w). Walau bagaimanapun, pada kepekatan TiO_2-NTs yang lebih tinggi yang dimasukkan ke dalam GG, GG+TiO_2-NTs (15% w/w) and GG+TiO_2-NTs (20% w/w) menunjukkan kesan ketoksikan pada sel, dengan itu melambatkan proses penyembuhan.