ALGINATE BIOFILM AND BEADS INCORPORATED WITH SUPERPARAMAGNETIC IRON OXIDE NANOPARTICLES (SPIONS) FOR BIOMEDICAL APPLICATION

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ABSTRACT

Alginate is a natural polysaccharide with promising properties such as non-toxicity, biocompatible, and biodegradable. Superparamagnetic Iron Oxide Nanoparticles (SPIONs) have extraordinary properties which led to be explore and studies in biomedical applications such as targeted drug delivery, hyperthermia, and tissue repair. Therefore, this study produces alginate biofilm and beads containing SPIONs and characterises their physical and chemical properties. Sodium Alginate (SA) is used to create biofilm and beads of 1 wt. % SA with 0–3.0g SPIONs. SEM, FESEM, EDS, FTIR, XRD, AFM, contact angle measurement, TGA, swelling behaviour, and Kirby Bauer disc diffusion were used to characterise the samples. SEM and FESEM images show the biofilm and beads with smooth and porous microstructures. EDS elemental analysis showed abundant Fe^{2+} ions on the samples, making them appropriate for biological applications such as embolotherapy for cancer treatment. FTIR spectrum study showed that SA and SPIONs interacted due to cross-linking process. XRD peak proves the presence of crystalline structures of SPIONs such as halite, maghemite and magnetite. AFM revealed the biofilms surface were rough due to the formation of peaks and valleys. It was found that the biofilm has hydrophilic properties from contact angle analysis. TGA showed that the beads degraded between 93 – 98%. Swelling investigation found that the surface of the bead able to preserve the shape after absorbing water within 120 minutes in different solutions such as distilled water, PBS pH 7.2 and NaCl Antibacterial studies showed that this research's formulation of SA combined with SPIONs may not be enough to induced antibacterial capabilities. Out of all the parameters, SA incorporated with 2.0g SPIONs shows the best and excellent result from the characterization. However, all the parameters prove to be useful and can be applied to be use a biomedical application depending on the designated applications.

ABSTRAK

Alginat adalah polisakarida semula jadi dengan sifat yang menjanjikan seperti tidak toksik, biokompatibel, dan biodegradasi. Nanopartikel Besi Oksida Superparamagnetik (SPIONs) mempunyai sifat luar biasa yang membolehkan kajian dalam aplikasi bioperubatan seperti penghantaran ubat bersasar, hipertermia dan pembaikan tisu. Oleh itu, kajian ini menghasilkan biofilm dan manik alginat yang mengandungi SPIONs dan mencirikan sifat fizikal dan kimianya. Natrium Alginat (SA) digunakan untuk membuat biofilm dan manik 1 wt% SA dengan 0 – 3.0g SPION. SEM, FESEM, EDS, FTIR, XRD, AFM, pengukuran sudut kontak, TGA, tingkah laku membengkak, dan kaedah Kirby Bauer digunakan untuk mencirikan sampel. Gambar SEM dan FESEM menunjukkan biofilm dan manik dengan struktur mikro halus dan berpori. Analisis elemen EDS menunjukkan banyak ion Fe^{2+} yang banyak pada sampel, menjadikannya sesuai untuk aplikasi biologi seperti emboloterapi untuk rawatan barah. Kajian spektrum FTIR menunjukkan bahawa SA dan SPION berinteraksi kerana hubung silang. Analisis puncak XRD menunjukkan kewujudan struktur kristalin SPION seperti halite, maghemite dan magnetite. AFM mendedahkan permukaan biofilm kasar kerana pembentukan puncak dan lembah. Didapati bahawa biofilm mempunyai sifat hidrofilik. TGA menunjukkan bahawa manik-manik itu merosot antara 93 – 98%. Penyelidikan pembengkakan mendapati bahawa permukaan manik dapat mengekalkan bentuknya setelah menyerap air dalam masa 120 minit dalam larutan yang berbeza seperti air suling, Kajian PBS pH 7.2 dan NaCl. Kajian antibakteria menunjukkan bahawa formulasi penyelidikan SA ini yang digabungkan dengan SPION mungkin tidak cukup untuk mendorong keupayaan antibakteria. Daripada semua parameter, SA yang digabung bersama 2.0g SPION menunjukkan hasil terbaik dari pencirian. Walau bagaimanapun, semua parameter boleh digunakan dalam aplikasi bioperubatan.

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LIST OF SYMBOLS AND ABBREVIATIONS

wt %	-	Percentage by Weight
g	-	Gram
°	-	Degree symbol
α	-	alpha
γ	-	Sigma
μ	-	Micro
˚C	-	Degree celsius
θ	-	Theta
β	-	Beta
nm	-	Nanometer
ml	-	Mililiter
μl	-	Microliter
ROS	-	Reactive oxygen species
SA	-	Sodium Alginate
SPIONs	-	Superparamagnetic Iron Oxide Nanoparticles
NP	-	Nanoparticles
IONP	-	Iron Oxide Nanoparticles
Fe_2O_3	-	Iron (III) Oxide
H_2O_2	-	Hydrogen Peroxide
SEM	-	Scanning Electron Microscope
FESEM	-	Field Emission Scanning Electron Microscope
EDS	-	Energy Dispersive Spectroscopy
XRD	-	X – Ray Diffraction
FTIR	-	Fourrier Transform Infrared Spectroscopy
AFM	-	Atomic Force Microscopy
TGA	-	Thermalgravimetric Analysis

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CHAPTER 1

INTRODUCTION

1.1 Background Study

The human body is a complex, highly structured structure composed of individual cells that collaborate to perform the essential processes for life. The skin is the biggest organ in the human body. The skin protects the body's outermost layer and consists of seven layers of tissues that shield the bone, muscles, ligaments, capillaries, and other internal organs. In addition to safeguarding the body, the skin also defends against pathogenic organisms (Chen et al., 2018; He et al., 2021). Microorganisms can get into the body through wounds in the skin. These pathogens may have caused damage and sickness not just to human tissues and organs but also to human body systems, particularly the lymphatic system. The inability of the body to protect itself against invading germs and diseases may have resulted from damage to the lymphatic system. The human body cannot correctly auto-regenerate most of its significant tissues and organs if medical illnesses involving tissue dysfunction or pathogenic infections severely compromise the integrity of the original tissue. Faced with an ever-increasing burden of injuries, congenital anomalies, and degenerative diseases, tissue engineering, and regenerative medicine hold the potential to generate new biological treatments to cure a variety of incurable diseases (Chen & Liu, 2016).

Due to the advancement of technologies in the medical field, the increasing demand for bio–based materials are attracting more attention, especially in the biomedical areas that are rapidly evolving, such as tissue engineering, wound healing, and targeted drug delivery. Biomaterials are widely used in the biomedical field, especially in surgical and medical, and are easy to obtain either naturally or synthetically. Polysaccharides, long-chain biopolymeric carbohydrate molecules primarily formed of monosaccharide units, are bio-based materials that combine enormous promise in biomedical applications with the distinctive advantageous properties of natural polymers, as opposed to synthetic polymers. Cellulose, chitin, and alginate are commonly used natural-based biopolymers among polysaccharides (Seddiqi et al., 2021).

Alginate is a naturally occurring polysaccharide derived from algae that have been extensively investigated and utilized in food and healthcare purposes. Alginate has garnered considerable interest due to its powerful hydration and antifouling properties towards oils (Sánchez-Fernández et al., 2020). Alginates can be soluble in water, but divalent cations, such as calcium ions, form a persistent alginate gel in the presence of divalent cations. Calcium ions bind alginate's G acid sites, while the M acid sites are inactive. Alginates' structural and biocompatibility properties depend on their G/M ratio and purity. Alginate is shear-thinning, and pure alginate with a high G acid content (G/M = 66/34) demonstrates optimal strength and injectability. Wound healing, medication delivery, and tissue engineering are applications where alginate hydrogels are particularly advantageous. They have been formed into microspheres and filled with thrombin for embolization of the blood vessels. In addition, alginate gels can be generated in situ by sequentially administering sodium alginate (SA) and calcium chloride solution for endovascular occlusion (Jiang et al., 2022).

Researchers have become interested in synthesizing nanoparticles and investigating their peculiar features recently. Since their magnificent properties, such as mechanical, chemical, electrical, optical, magnetic, electro-optical, and magneto-optical, are distinct from their bulk properties and depend on particle size, nanoparticles have considerable interest. Nanoparticles' introduction to the medical sector sparked substantial optimism for the early diagnosis and treatment of catastrophic diseases such as cancer (Laurent & Mahmoudi, 2011). Superparamagnetic iron oxide nanoparticles (SPIONs, Fe_3O_4, magnetite) are nanocrystals of iron oxides covered with hydrophilic polymers. SPIONs are now employed as a contrast agent for magnetic resonance imaging (MRI) created for clinical applications with high spatial-resolution MR sequences (Kang et al., 2009).

SPIONs are considered one of the most promising possibilities for developing novel cancer treatment techniques due to their unique magnetic features. Numerous research employed SPIONs for magnetically mediated hyperthermia, a concept based on the observation that the survival of malignant cells is decreased at temperatures above 41°C compared to non-cancerous cells. Applying an external alternating magnetic field allows SPIONs to be accumulated directly at the tumour location and heated. The unusual magnetic features of SPIONs, such as high magnetization values and superparamagnetic, make them particularly useful as hyperthermia agents. By simultaneously delivering anticancer medications or physiologically active substances, the efficacy of such a treatment could be enhanced (Reczyńska et al., 2020).

1.2 Problem Statement

Polymer microcapsules have been used as carriers for drugs and growth factors due to their in-vivo and in-vitro capacity to monitor and target areas. Previously, among the materials used in the manufacture of microcapsules were synthetic polymers such as chitosan, dextran, PVA (Poly (Vinyl Alcohol), PVP (Poly (Vinyl Pyrrolidine) and poly (ethylene glycol) (PEG). That is because of its versatility and strong mechanical, chemical, and transport characteristics. The processing of synthetic polymer-based microcapsules typically requires harsh environments, such as non-physiological pH or temperature, and poisonous and mammalian cell harmful organic solvents. The problem can be addressed if the beads are fabricated from natural polymers, which are healthy for living cells and tissues. Many scientists have also recently been involved in polymer microcapsules SPIONs. The synthesis of SPIONs has undergone significant advancements, driven by both scientific curiosity and a wide range of technological applications. These applications encompass magnetic storage media, biosensing applications, and medical uses like targeted drug delivery, contrast agents in magnetic resonance imaging (MRI), and magnetic inks for jet printing. SPIONs consist of iron oxide cores that may be manipulated to specific locations using external magnetic fields. The use of nanoparticles has witnessed a significant rise in several domains such as research, medicine, and industry, owing to the continuous advancements in nanomaterials. These tiny particles are now being extensively employed in areas including cosmetics, microelectronics, and as carriers for pharmaceutical drugs. Among the various types of produced nanoparticles (NPs), SPIONs stand out as particularly noteworthy and captivating. They possess numerous practical biological uses, including targeted delivery of chemicals, tracking of stem cells, magnetic resonance imaging (MRI), hyperthermia, tissue restoration, and in vivo cell tracking. The magnetic polymer microcapsules were found to be suited in biomedical applications such as embolic agents for anti-cancer embolotherapy, targeted drug delivery, hyperthermia, and cell therapy. Thus, in this study, alginate is selected and manufactured as biofilm and beads through solution casting and manual syringe method. Both biofilm and beads are fabricated with SA as the primary substance and incorporated with SPIONs with different weight ratios for biomedical applications to be study the effective and compatibility of both materials to be considered as a biomedical application.

1.3 Objectives

The main objectives of this research are:

1) To produce biofilm and beads based on SA incorporated with superparamagnetic iron oxide nanoparticles (SPIONs).
2) To characterize the physical and chemical properties of SA incorporated with SPIONs in the form of biofilm and beads.
3) To evaluate the antibacterial properties of SA incorporated with SPIONs.

1.4 Scope of Study

The research scopes of the study are as follows:

1) Fabrication of 1 wt % of SA incorporated with different mass composition of SPIONs at 0 g, 0.5 g, 1.0 g, 2.0 g, and 3.0 g.
2) Fabrication of SA incorporated with SPIONs biofilm via solution casting method.
3) SA incorporated with SPIONs beads were fabricated through manual syringe pump method.
4) The microstructure arrangement of the biofilm and beads was analyzed using Scanning Electron Microscopy (SEM) and Field Emission Scanning Electron Microscope (FESEM).
5) The elemental composition of the biofilm and beads was analyzed by emitting a focused scanning electron beam through Energy Dispersive X–Ray Spectroscopy (EDS).
6) The physiochemical properties of biofilm were examined via Fourier transform infrared spectroscopy (FTIR).
7) The crystallography structure of the biofilm was examined by Xray Powder Diffraction analysis (XRD).
8) The surface roughness of the biofilm was examined with an atomic force microscope (AFM).
9) The bio-composite film's hydrophilicity was investigated using contact angle estimation (Goniometer).
10) The thermal properties of beads were examined by thermogravimetric analysis (TGA).
11) The structural integrity of the beads was tested by swelling testing.
12) The antibacterial property of the bio composite film was assessed by the disc diffusion method (Kirby–Bauer test).

1.5 Significant of Study

The finding of this research rebound to the benefit of the future development of biopolymer and bio composite films in the medical field. This research can help to be proven in the clinical trials and, if successful, would significantly contribute to the technology and application of biomedical in sustaining better protection of the human body. Natural biopolymer has a much better approach and benefits in application, cost, and environmental aspects than synthetic biopolymer. Biomedical engineering is a growing sector parallel to the growth and advancement of technology, leading toward a more frugal and sustainable lifestyle in engineering. Therefore, not only could this research reduce the cost of medical treatment in biomedical applications such as wound healing, targeted drug delivery, and therapeutic embolization, but it also has the properties of biodegradability as it is made of natural biopolymer instead of the synthetic-based biopolymer, which could ensure the sustaining and more conserving life in the future.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

This chapter outlines the literature review for nomenclature (including consideration of specific and previous) and keywords related to research. Data from the current study consists of publications such as journals, books, blogs, research papers, and web posts. Definition and clarifying biopolymers, biopolymer groups, Sodium Alginate, Superparamagnetic Iron Oxide Nanoparticles (SPIONS), Sodium Alginate Incorporated with SPIONs, and anti-bacterial properties are listed in this section of the literature review.

2.2 Biopolymers

Polymers are constructed from long sequences of identical molecules. The resulting products display distinct characteristics depending on the molecular shapes bound and the connections made. Elastic polymers include rubber and polyester. Epoxy and glass are two others that come to mind; they are more challenging and wear-resistant. It is possible to create larger macromolecules called polymers by covalently linking several smaller molecules called monomers. The regularity, relative orientation, and visual appearance of different monomers within the same polymer molecule can differ significantly, as can the total amount of monomers present. The ability to precisely determine the number of monomers or the degree of polymerization in various synthetic and natural polymers allows for modifying their properties (Gad, 2014). Figure 2.1 depicts the polymerization process, which involves the transformation of monomers into larger molecules.

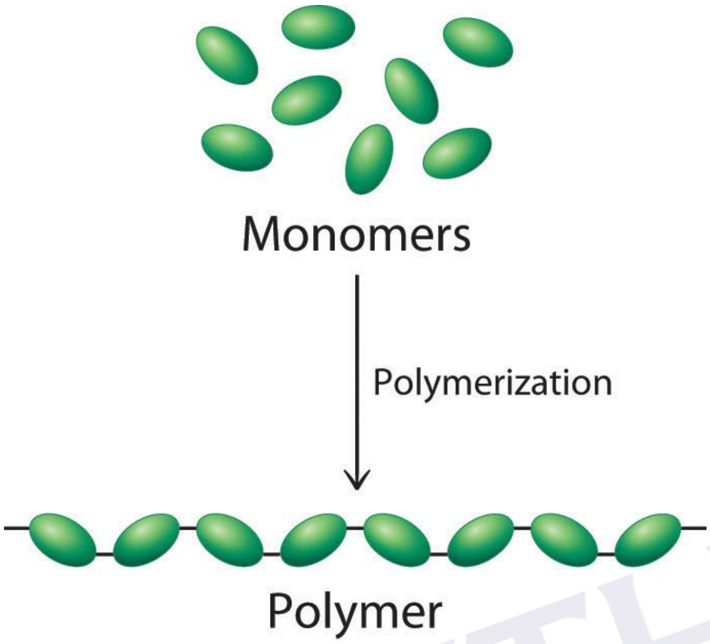

Figure 2.1: Polymerization Process (https://www.livescience.com/60682-polymers.html, 2017)

Table 2.1 contains a list of natural and artificial polymers. Polymers can use to treat several health conditions, including chronic wounds, cell development, antimicrobial, and antifouling uses. They are non-toxic, biodegradable, and biocompatible, making them ideal candidates for green product manufacturing in biological applications. Both polymers are derived chemically from biological molecules or are manufactured by living creatures from natural sources. Polymers exhibit a wide range of utility in various applications, most notably in long-term pharmaceutical and biological applications. The advantages and disadvantages of using natural or synthetic polymers in biomedicine are summarised in Table 2.2. Nonetheless, the numerous health programs that may be marketed have concluded. Due to their low cost and recycled content, biopolymers have become a substantial and growing demand in the pharmaceutical and biomedical sectors. According to IUPAC terminology, "polymer" refers to materials composed of macromolecules with a high relative molecular mass (International Union of pure and applied chemistry). However, this phrase can refer to polymer compounds, polymer blends, or polymers. Polymers also encompass a diverse spectrum of chemicals categorized according to their source, use, composition, thermal activity, polymerization method, or production methodology (Colmenares & Kuna, 2017).

Table 2.1: List of Natural and Synthetic Polymers (Kumar et al., 2014)

Synthetic Polymers	Natural Polymers
Cellulose Derivatives	Tragacanth
Polycarbophil	Sodium Alginate
Poly (Ethylene Oxide)	Karaya Gum
Poly (Vinyl Pyrrolidone)	Guar Gum
Poly (Vinyl Alcohol).	Gelatin
Poly (Hydroxyethyl Methyl acrylate)	Chitosan
Hydroxyl Propyl Cellulose	Soluble Starch

Table 2.2: Advantages And Disadvantages of the Biomedical Use of Natural Or Synthetic Polymers (Bhatia, 2016)

Natural Polymers	Synthetic Polymers
High Biocompatibility	Low biocompatibility
Suitable mechanical characteristics	Better mechanical properties
Low stability	High stability
Produced from a biological process	Produced from a chemical process
Easy to degrade by biological process	Hard to degrade by biological process

2.2.1 Synthetic Based Biopolymers

Synthetic polymers have a few significant benefits over natural polymers in bioengineering procedures. They enable desired alternatives for controlling the shape, architecture, and chemistry of ECM systems that replicated or controlled their material activities. Synthetic polymers are human-made duplicates of polymers synthesized using abiotic chemical pathways. Specific synthetic polymers have been synthesized, including polysaccharides, glycoproteins, peptides, proteins, polyhydroxyalkanoates, and polyisoprene. Numerous synthetic polymers, including PLGA, PEG, PCL, poly-acrylic, polyvinyl, and polyvinylpyrrolidone, have a broad range of biomedical applications due to their biomimetic micro/nanoscale, appealing manufacturing, and bio compatible, including ECM-like fibres. While synthetic polymer biomaterials are designed to create textiles with totally linked pores, they

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APPENDIX W

LIST OF PUBLICATION

1. **W. A. M. A Zakhi,** M. I. Idris, (2022) "Fabrication And Characterization Of Alginate/Iron (Iii) Oxide Beads And Biofilm For Biomedical Applications." Key Engineering Materials, 908, 177-182.
2. S. S. N. A. Bakil, M. I. Idris, **W. A. M. A. Zakhi**, M. A. Selimin, L. T. Chuan, H. Z. Abdullah, (2023) "Sodium alginate membrane/film as wound dressing applications: A review." AIP Conference Proceedings 2530, 110014.
3. N. Z. Hassan, M. N. M. Hatta, N. A. Badarulzaman, **W. A. M. A. Zakhi**, M. R. Fauzi (2023)" The comparison of reinforcement used on carbon foam between graphite and carbon whisker on mechanical and physical properties." AIP Conference Proceedings 2530, 110004

VITA

The author's place of birth is Alor Setar, Kedah, Malaysia. He attended SMK Dato' Syed Omar, located in Alor Setar, Kedah, Malaysia, for his secondary education. The individual initially registered and subsequently undertook a one-year foundation program in science at Universiti Teknologi MARA (UiTM) Kampus Dengkil, located in Malaysia. Following the successful completion of his foundation in science, the individual proceeded to do his undergraduate studies, ultimately obtaining a Bachelor of Engineering with Honors in Mechanical and Manufacturing Engineering in the year 2020 from Universiti Tun Hussein Onn Malaysia (UTHM), located in Malaysia. Following his graduation, he promptly matriculated into the Master of Mechanical Engineering program at UTHM in the same calendar year. The individual in question held the position of a graduate research assistant within the Bioactive Material Research Group (BioMa), which was funded by the Fundamental Research Grant Scheme (FRGS) administered by the Ministry of Higher Education (MOHE) in Malaysia. Between the years 2020 and 2023, the author has achieved notable success by publishing a total of three papers in the subject of biomaterials and carbon foam. Additionally, two papers are currently in the process of publication. The individual possesses a comprehensive knowledge in the areas of material science, biofilm and beads manufacturing, and the utilization of biopolymers in biomedical applications. In addition to his areas of research, the author actively engages in non-governmental organizations and advocates for the United Nations' 17 sustainable development goals (SDGs).