PREPARATION AND CHARACTERISATION OF HYDROGEL FILM AND NANOFIBER FROM CARBOXYMETHYL-BASED CELLULOSE AND SAGO PULP FOR CONTROLLED RELEASE APPLICATION

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By

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Chairman: Norizah Abdul Rahman, PhD
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Carboxymethyl cellulose (CMC)-based hydrogels show great capability in delivering and occupying small particles like drugs and dyes. CMC-based hydrogel could enhance the capability of a hydrogel and benefit the mankind since it has excellent biocompatibility and biodegradable properties to be use in biomedical application. In this study, a series of CMC and carboxymethyl sago pulp (CMSP) blended with poly(ethylene oxide) (PEO) hydrogel in the form of films and nanofibers were fabricated by using citric acid as a cross-linker. The CMSP used was isolated from sago waste, while CMC was purchased from Fluka Company. CMSP derived from sago waste was studied in the place of CMC because it has similar structure and can help to preserve the environment. For the production of hydrogel nanofibers, the nanofibers were prepared by using electrospinning technique prior cross-linking with citric acid. The electrospinning parameters used were concentration of the polymers blend solution, weight ratio of CMC or CMSP to PEO, applied voltage, tip-to-collector distance and the solution flow rate. The average fiber diameter of the CMSP/PEO nanofibers are from 201 to 300 nm and CMC/PEO from 101 to 200 nm. However, the formation of CMC/PEO nanofibers on the collector was very thin even after several hours of electrospinning, and not able to peel off. Thus, it cannot be further study for fabrication of hydrogel and controlled release. The swelling behaviour of the hydrogels film and nanofibers were optimised based on four parameters; ratio of CMC or CMSP to PEO, percentage of citric acid, temperature and curing time. The results show percentage of swelling and thermal property of CMC/PEO and CMSP/PEO hydrogel was improved compared to CMC and CMSP alone. In controlled release study, methylene blue (MB) was chosen as the model drug due to its

hydrophilic nature. The controlled release results show CMSP/PEO hydrogel nanofibers had the highest percentage of MB loading (89.20 ± 0.42%) than CMC/PEO and CMSP/PEO hydrogels film. This can be relates with swelling results that show CMSP/PEO hydrogel nanofibers has the highest percentage of swelling (4366 ± 975%). The MB release study showed that the MB released from CMSP/PEO hydrogel nanofibers was slowly released with pH dependency. The total cumulative percentage release of MB in pH 4.0 (17.04%) and pH 7.34 (19.44%) for CMSP/PEO hydrogel nanofibers are not much different from the CMSP/PEO hydrogel film (pH 4.0 = 14.11% and pH 7.34 = 17.92%), but showed a lower total cumulative percentage release of MB at pH 1.20 (8.91%) and 8.0 (21.21%). The results indicate CMSP/PEO hydrogel nanofibers have a good potential to be used, for example for drug delivery in intestinal area and wound healing.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PENYEDIAAN DAN PENCIRIAN HIDROGEL FILEM DAN NANOFIBER DARIPADA KARBOKSIMETIL BERASASKAN SELULOSA DAN PULPA SAGU UNTUK APLIKASI KAWALAN PELEPASAN

Oleh

NAFEESA BINTI MOHD KANAFI

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Hidrogel berasaskan CMC menunjukkan keupayaan yang hebat dalam penghantaran dan dipenuhi zarah-zarah kecil seperti dadah dan pewarna. Hidrogel berasaskan CMC boleh meningkatkan keupayaan hidrogel dan memberi faedah kepada manusia memandangkan ia mempunyai ciri-ciri bioserasi dan biodegradasi yang bagus untuk digunakan dalam aplikasi bioperubatan. Dalam kajian ini, satu siri CMC dan karboksimetil pulpa sagu (CMSP) yang dicampurkan dengan poli(etilena oksida) (PEO) dalam bentuk filem-filem hidrogel dan nanofiber direka dengan menggunakan asid sitrik sebagai sambung-silang. CMSP yang digunakan telah diasingkan daripada pulpa sagu, manakala CMC dibeli daripada syarikat Fulka. CMSP yang berasal daripada sisa buangan sagu semulajadi telah dikaji bagi menggantikan tempat CMC kerana ia mempunyai struktur yang sama dan boleh membantu memelihara alam sekitar. Untuk penghasilan nanofiber hidrogel, nanofiber disediakan menggunakan teknik elektrospinning sebelum disambung-silang menggunakan asid sitrik. Parameter-parameter elektrospinning yang digunakan adalah kepekatan cecair campuran polimer, nisbah berat CMC atau CMSP kepada PEO, voltan yang digunakan, jarak dari hujung jarum ke pengumpul dan kadar alir cecair. Purata diameter fiber untuk nanofiber CMSP/PEO adalah daripada 201 hingga 300 nm dan nanofiber CMC/PEO pula adalah daripada 101 hingga 200 nm. Walau bagaimanapun, pembentukan nanofibers CMC/PEO pada pemungutnya sangat nipis walaupun selepas beberapa jam elektrospinning dan sukar untuk dikupas. Jadi, ia tidak boleh diteruskan untuk kajian pelepasan dadah dan pencirian. Tingkah laku bengkak hidrogel filem dan nanofibers dioptimumkan berdasarkan empat parameter, nisbah CMC atau CMSP kepada PEO, peratusan asid sitrik, suhu dan masa pemadatan. Keputusan menunjukkan peratusan pembengkakan dan

sifat terma bagi hidrogel CMC/PEO dan hidrogel CMSP/PEO menunjukkan peningkatan yang baik berbanding CMC dan CMSP sahaja. Dalam kajian pelepasan kawalan, metilena biru (MB) dipilih sebagai model dadah kerana sifat hidrofiliknya. Keputusan pelepasan kawalan menunjukkan nanofiber hidrogel CMSP/PEO mempunyai peratusan tertinggi memuat MB (89.20 ± 0.42%) berbanding hidrogel CMC/PEO dan hidrogel CMSP/PEO. Ini boleh dikaitkan dengan keputusan pembengkakan yang menunjukkan nanofiber hidrogel CMSP/PEO mempunyai peratusan pembengkakan yang tertinggi (4366 ± 975%). Kajian pelepasan MB menunjukkan MB yang terlepas daripada nanofiber hidrogel CMSP/PEO adalah merupakan pelepasan yang perlahan dengan kebergantungan kepada pH. Jumlah peratusan kumulatif MB dalam pH 4.0 (17.04%) dan pH 7.34 (19.44%) untuk nanofiber hidrogel CMSP/PEO agak sama dengan hidrogel CMSP/PEO (pH 4.0 = 14.11% and pH 7.34 = 17.92%) tetapi menunjukkan jumlah peratusan kumulatif pelepasan MB yang lebih rendah pada pH 1.20 (8.91%) dan 8.0 (21.21%). Hasil keutusan ini menunjukkan bahawa nanofiber hidrogel CMSP/PEO mempunyai potensi yang baik untuk digunakan dalam penghantaran dadah di kawasan usus dan penyembuhan luka.

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LIST OF ABBREVIATIONS

CA	Citric acid
CMC	Carboxymethyl cellulose
CMSP	Carboxymethyl sago pulp
CMSS	Carboxymethyl sago starch
CONH	2˚ amide
$CONH_2$	1˚ amide
DSC	Differential scanning calorimetry
ECM	Extracellular matrix
ECH	Epichlorohydrin
FTIR	Fourier transform infrared
GI	Gastrointestinal
GPC	Gel permeation chromatography
HPMC	Hydroxypropyl methylcellulose
IVD	Intervertebral disc
MB	Methylene blue
$NaClO_2$	Sodium chlorite
PAA	Poly(acrylic acid)
PBS	Phosphate-buffered saline
PEO	Poly(ethylene) oxide
PVA	Poly(vinyl alcohol)
Q	Percentage of swelling
SEM	Scanning electron microscopy

SO_3H	Sulfonic acid
TGA	Thermogravimetric analysis
US FDA	United State Food and Drug Administration
UV-Vis	Ultraviolet-visible
XRD	X-ray diffraction

CHAPTER 1

INTRODUCTION

1.1 Background of study

In Sarawak, Malaysia, the largest sago-growing areas, sago palms (*Metroxylon sago*) are found in tropical lowland forest and swampy areas in which estimated 54,000 hectares in 2013 by Sarawak agriculture statistics (Bujang & Hassan, 2013; V Pushpamalar et al., 2006). The main product of sago palm, sago starch was exported mainly to Peninsular Malaysia, Japan, Singapore and other countries with total about 48,000 tons in 2013 (Sarawak agriculture statistics, 2013). To isolate sago starch, several mechanical processes involving debarking, rasping, sieving, settling, washing and drying need to go through and at the end of the process, starchy fibrous by-product, sago waste was produced at approximately 7 tons daily from a single processing mill.

Sago waste is light brown in color and still maintains the woody structure as shown in Figure 1.1. It is a lignocellulosic biomass that consist of cellulose, hemicellulose and lignin (Bujang & Hassan, 2013; Veeramachineni et al., 2016). Cellulose is a long and linear polysaccharide polymer which consist of many glucose units that linked to each other by beta 1,4-glycosidic bonds. It has received tremendous attention from researchers nowadays and had been focuses on cellulose derivatives, such as carboxymethylcellulose (Pushpamalar et al., 2006), hydroxypropyl methylcellulose (HPMC) and methylcellulose (Frenot et al., 2006). Since isolation of sago starch requires large amount of water, thus, the residues are mixed with wastewater and easily washed off into nearby streams without proper treatment or deposited in the factory's compound (Bujang & Hassan, 2013). These actions will lead to serious environmental problems in future. To prevent this circumstance, sago waste can become a very economical source of cellulose to the industries due to cheapest, biodegradable and availability of all renewable natural polymers existing in Malaysia. Sago fiber is used to provide bulk for rumen fermentation, sago pith used as animal feed stuff and in livestock industry and sago frond used in pulp and paper industry (Chew et al., 1999). However, the utilization of sago waste should be further explored. Investigating the potential application CMC nanofibers from sago waste drug delivery in this research will not open a new potential application sago waste but also will help to recycle and solve disposal problem of sago waste.

Figure 1.1: Sago waste

Sago pulp is the result of purification of sago waste that is white in color as shown in Figure 1.2. It was reported that 57% w/w sago pulp was successfully isolated from sago waste (V Pushpamalar et al., 2006). The pre-product, sago pulp that consist of cellulose is then been transformed into functionalised cellulose which can be used in various applications such as pharmaceutical excipient and industrial products (V Pushpamalar et al., 2006; Veeramachineni et al., 2016). The purpose of purification of sago waste into sago pulp is to remove the lignin (Veeramachineni et al., 2016).

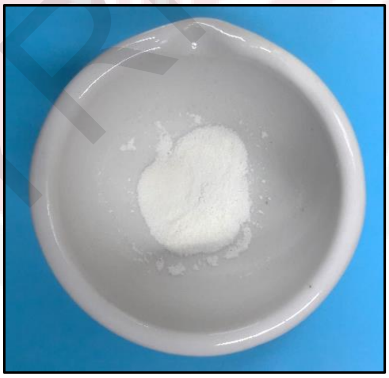

Figure 1.2: Sago pulp powder (delignified sago waste)

Hydrogel is a smart three-dimensional polymeric network structure that capable to hold a lot of water or biological fluids beyond its dry weight without dissolution in water prepared by either chemical or physical cross-linking method (Shen et al., 2016; Tan et al., 2016). Holding capacity of hydrogel is depends on the degree of cross-linking. Hydrophilic groups such as, -OH, -CONH, $-CONH_2$, and $-SO_3H$ that present in the formulation polymers of hydrogel structure are the reason of the ability of hydrogel to absorb water (Khan & Ranjha, 2014).

The water uptake and release occur when the protonable groups respond to external stimuli such as change in pH, ionic strength, or temperature (Barbucci et al., 2000). The swollen state of hydrogel has a soft, flexible and tissue-like physical properties make it applicable in most biomedical applications. Moreover, hydrogel is sensitive to environment stimuli when there are changes such as pH, temperature, presence of enzyme and glucose (Patel & Mequanint, 2009). To apply hydrogel in drug delivery application, non-toxic and biocompatible materials should be the choices in making the formulation of hydrogel as well as new way to improve the properties of hydrogel in drug delivery application.

Nowadays, widespread of knowledge on the techniques of manufacturing nanomaterial had lead researchers around the world to focus on the preparation of nanomaterial for various applications including biomedical (Haider, Haider, & Kang, 2015a). The focus on nanomaterials specifically nanofibers is because of the special characteristics such as low density, large surface area, high pore volume and tight pore size (Rathinamoorthy et al., 2012). Electrospinning, a highly versatile method is one of the techniques for the fabrication of nanofibers. In biomedical application, electrospun nanofibers have been widely studied for drug and therapeutic agent delivery, wound dressings and tissue engineering using natural or synthetic polymers (Abrigo et al., 2014; Haider, Haider, & Kang, 2015b; Teck, 2017).

1.2 Problem statement

Abundance of sago waste produced daily and cellulose is second major components in sago palm (V Pushpamalar et al., 2006). During isolation of sago starch, sago waste was easily washed off into nearby streams or deposited in the factory’s compound (Bujang & Hassan, 2013). These actions can lead to serious environmental problems in future. Sago waste consists of biopolymers such as lignin, cellulose and polysaccharide that can be used for many applications. Cellulose is second major components in sago waste (V Pushpamalar et al., 2006). Apart from that, in the preparation of biopolymer hydrogel, epichlorohydrin was commonly used as cross-linker, however, it can caused carcinogenic by-products and can harm to human. Mostly in electrospinning process, toxic organic solvents are used as the solvent that might leave trace in the nanofibers produced and caused toxicity. In making hydrogel for biomedical application, all carcinogenic by-products and toxic materials need to avoid to ensure only safe materials can enter the human body.

1.3 Hypothesis and significance of study

Natural polymers underwent a re-evaluation as a result of natural biodegradable properties and availability from renewable resources compared to synthetic alternatives. Thus, utilizing the cellulose from sago waste (also known as sago pulp) into valuable product such as carboxymethyl sago pulp (CMSP) could help in preserving the environment as well as benefit the mankind. CMSP also are more cost effective since there are abundance of sago waste available. Moreover, CMSP is a biopolymer that safe to be used for human and suit the requirement in biomedical applications that demanding for non-toxic materials. In this study, CMSP was used to study for drug delivery application in hydrogel form with citric acid as the cross-linker. Citric acid was chosen to replace of commonly used toxic cross-linker such as epichlorohydrin due to its non-toxic property and no toxicity produced even after cross-linking reaction. Recently, the use of nanofibers loaded with drugs for biomedical application has awaken much interest and there were no studies on CMSP-based hydrogel in the form of nanofibers yet. Previous study by Pushpamalar et. al, had shown CMSP hydrogel has good swelling property at different pH media (Vengidesh Pushpamalar et al., 2013). However, to the best of our knowledge, there is no study conducted on the CMSP nanofibers yet. Therefore, CMSP will be electrospun into nanofibers in order to increase the surface area the hydrogel and could improve the delivering and encapsulating of drugs. CMSP will be electrospun into nanofibers by using electrospinning technique. In this study, water was used as a solvent for electrospinning process, which is an ideal solution in biomedical application despite all the toxic organic solvents.

1.4 Objectives

Various studies have been done focusing on economical, safe, and biocompatible materials in building drug delivery system. To accomplish similar aims, a renewable natural polymer from waste (sago pulp) was used in this study in order to open a new potential application sago waste but also will help to recycle and solve disposal problem of sago waste. The objectives of this study are:

i. To isolate sago pulp and prepare CMSP by using carboxymethylation reaction
ii. To prepare and optimise cross-linked CMC/PEO and CMSP/PEO films and nanofibers
iii. To investigate and evaluate the control release of MB for the hydrogel films and nanofibers

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