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PREPARATION AND EVALUATION OF AQUEOUS PHASE COMPATIBLE MOLECULARLY IMPRINTED POLYMERS FOR SHIKIMIC ACID

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PREPARATION AND EVALUATION OF AQUEOUS PHASE COMPATIBLE MOLECULARLY IMPRINTED POLYMERS FOR SHIKIMIC ACID

By

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PREPARATION AND EVALUATION OF AQUEOUS PHASE COMPATIBLE MOLECULARLY IMPRINTED POLYMERS FOR SHIKIMIC ACID

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Chairperson : Professor Nor Azah Yusof, Ph.D.
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Shikimic acid (SA) is an important component in the production of several important drugs particularly the anti-influenza drug, Oseltamivir. Naturally, SA exists as an intermediate in the plant biosynthesis of aromatic compounds via shikimate pathway. Commercially, SA is extracted from the Chinese star anise or produced through the fermentation process by modified strain of *Escherichia coli* (*E. coli*). Regardless of the method of production, SA needs to be purified before it can be used for the intended purpose. Conventional method in the purification of SA usually involved the use of non-specific adsorbents that are less effective in isolating the SA. Molecularly imprinted polymer (MIP) being one of the latest adsorbents in separation science, offers an alternative technique that is more selective and specific than the conventional adsorption methods.

MIP is known to be not compatible to the aqueous phase with usually low or no selectivity, making the preparation of MIP that work well in aqueous phase a challenge to those in the field. Reported in this thesis are exploratory work carried out to prepare non-covalent imprinted polymer for SA with the aim that the polymer prepared is capable of working in highly aqueous environment in which the raw extract of SA is usually in.

"Trial and error" approach was used as the preliminary tool in searching the right formulation of template:monomer:cross-linker (TMX) ratio that produced a good imprinted polymer judging from the imprinting factor (IF) scores of the polymer in batch rebinding experiments. The optimized TMX ratio finally determined was 1:6:10

in 10 mL methanol and water (4:1, v/v) porogen system. The best template: monomer (TM) ratio was also evaluated using ultraviolet (UV) spectroscopy approach, the results obtained were in agreement with the preliminary "trial and error" results, indicated that TM ratio of 1:6 was the optimal.

The polymer was physically characterized using Fourier transform infrared (FTIR) spectroscopy and scanning electron microscopy (SEM) techniques. Results indicated that complete polymerization was achieved and different morphologies observed between imprinted and control polymers may be used to explain the imprinting effect shown by the SA imprinted polymer. Optimization on the rebinding conditions suggested that the SA imprinted polymer performed best in 100% aqueous environment at pH 4.0.

Binding isotherm study suggested that the binding sites distribution was heterogeneous in nature and it can be well described using Freundlich isotherm model. Study of the polymer's adsorption kinetic concluded that the adsorption process obeyed pseudo second order kinetic with rate constant, **K** of 0.0047 $g \bullet \mu g^{-1} \bullet min$ and the experimental maximum adsorption for SA imprinted polymer was determined as 38.8 $\mu g \bullet g^{-1}$.

Cross-reactivity experiments results showed that the imprinted polymer having good selectivity toward SA and the polymer was packed into cartridge and used for the separation of SA from artificial mixture of SA, methyl shikimate (SE) and gallic acid (GA) in tap water. A clean separation with three isolated peaks as shown in high performance liquid chromatography (HPLC) chromatogram was obtained.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENYEDIAAN DAN PENILAIAN POLIMER CETAKAN MOLEKUL ASID SYIKIMIK SERASI DENGAN FASA AKUEUS

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Asid syikimik (SA) merupakan satu sebatian penting dalam pengeluaran beberapa jenis ubat penting, terutamanya ubat anti-influenza dengan jenama Oseltamivir. Secara semula jadi, SA wujud sebagai sebatian perantaraan dalam proses biosintesis sebatian aromatik dalam tumbuhan yang berlangsung melalui laluan syikimat. Secara komersil, SA diekstrak dari bunga lawang Cina atau dihasilkan melalui proses fermentasi oleh strain *Escherichia coli* (*E. coli*) yang telah diubahsuai. Tanpa mengira kaedah penghasilannya, SA yang dihasilkan perlu melalui proses penulenan sebelum ia dapat digunakan untuk tujuannya. Secara konvensional, penulenan SA dilakukan dengan kaedah yang melibatkan penggunaan penjerap tidak spesifik yang kurang berkesan dalam pemisahan asid syikimik. Polimer cetakan molekul (MIP) merupakan antara penjerap baru dalam bidang Sains Permisahan, yang menawarkan teknik alternatif permisahan sebatian dengan lebih selektif serta spesifik berbanding kaedah penjerapan konvensional.

MIP sememangnya diketahui tidak serasi dengan fasa akueus dan biasanya menunjukkan selektiviti yang rendah ataupun tidak menunjukkan selektiviti, ini menyebabkan penyediaan MIP yang berfungsi baik dalam keadaan akueus suatu cabaran kepada mereka yang menceburi bidang ini. Tesis ini melaporkan hasil kerja penyelidikan awal tentang penyediaan polimer cetakan tidak kovalen bagi SA dengan matlamat polimer cetakan yang terhasil boleh berfungsi dalam persekitaran berkandungan akueus yang tinggi, iaitu persekitaran di mana SA pada kebiasaannya wujud.

Kaedah “cuba-jaya” telah digunakan sebagai kaedah awal dalam menentukan rumusan nisbah templet:monomer:penyilang (TMX) yang sesuai untuk menghasilkan polimer

cetakan SA yang bagus, dinilai melalui skor cetakan (IF) polimer berkenaan dalam ujian penjerapan semula secara kelompok. Rumusan TMX 1:6:10 dalam 10 mL porogen campuran metanol-air (4:1, v/v) telah ditentukan sebagai rumusan optimum. Nisbah templet:monomer (TM) yang optimum juga dinilai dengan menggunakan kaedah spektroskopi ultraungu (UV), di mana keputusan yang diperolehi bersetuju dengan keputusan awal dalam kaedah "cuba-jaya", yang menunjukkan nisbah TM 1:6 adalah optimum.

Pencirian secara fizikal menggunakan spektroskopi transformasi inframerah Fourier (FTIR) dan mikroskopi elektron pengimbasan (SEM) telah dilakukan ke atas polimer yang dihasilkan. Keputusan pencirian menunjukkan bahawa proses pempolimeran telah berlangsung dengan lengkap, pemerhatian tentang perbezaan morfologi antara polimer bercetak dan polimer rujukan mungkin boleh digunakan bagi menerangkan prestasi penjerapan yang ditunjukkan polimer cetakan SA. Pengoptimuman keadaan penjerapan semula menunjukkan polimer cetakan SA menunjukkan prestasi penjerapan semula terbaik apabila ia berada dalam keadaan akueus 100% pada pH 4.0.

Kajian isoterma penjerapan menunjukkan taburan titik jerapan pada polimer cetakan adalah heterogen secara asasnya, dan model isoterma Freundlich adalah sesuai untuk menjelaskan keadaan ini.

Kajian kinetik proses penjerapan pada polimer cetakan SA yang dihasilkan menyimpulkan bahawa proses penjerapan adalah mengikut hukum kinetik pseudo tertib kedua dengan pemalar kadar, **K** iaitu 0.0047 $g \bullet \mu g^{-1} \bullet min$ dan penjerapan maksimum secara eksperimental bagi polimer cetakan asid syikimik adalah 38.8 $\mu g \bullet g^{-1}$.

Keputusan eksperimen reaktiviti bersilang menunjukkan polimer cetakan yang dihasilkan menunjukan selektiviti yang baik terhadap SA. Polimer ini telah dipek dalam katrij dan digunakan dalam pemisahan SA dari campuran tiruan SA, metil syikimat (SE) dan asid galik (GA) dalam air paip. Permisahan bersih yang memberikan tiga puncak berasingan seperti yang ditunjukkan dalam kromatogram kromatografi cecair berprestasi tinggi (HPLC) telah diperolehi.

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For any errors or inadequacies that may remain in this work, of course, the responsibility is entirely my own.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
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LIST OF ABBREVIATIONS

^{1}H NMR	Proton nucler magnetic resonance
4VP	4-vinylpyridine
AAM	Acrylamide
ACN	Acetonitrile
ACVA	4,4-azobis-4-cyanovaleric acid
B	Concentration of template in its bound form during equilibrium in rebinding experiment
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DVB	Divinylbenzene
EGDMA	Ethylene glycol dimethacrylate
F	Concentration of template in its free form during equilibrium in rebinding experiment
FI	Freundlich isotherm
FTIR	Fourier transform infrared spectroscopy
GA	Gallic acid
IF	Imprinting factor
LA	Lauric acid
LI	Langmuir isotherm
MAA	Methacrylic acid
MeOH	Methanol
MIP	Molecular imprinted polymer
NIP	Non-imprinted polymer (Control polymer)
SA	Shikimic acid
SE	Methyl shikimate
SEM	Scanning electron microscope
TGA	Themal gravimetric analysis
THF	Tetrahydrofuran
TM ratio	Template:Monomer ratio
TMX ratio	Template:Monomer:Cross-linker ratio
TRIM	Trimethylolpropane trimethacrylate
UV-Vis	Ultraviolet-visible

CHAPTER 1

INTRODUCTION

1.1 Shikimic Acid and Molecularly Imprinted Polymer

Shikimic Acid (SA) is the main raw material for the production of several important drugs used in the treatment of influenza and chemotherapy. Currently, commercial production of SA is achieved via the extraction from Chinese star anise or the biosynthesis process by modified strain of microorganisms. Although there are other reported sources for the extraction or synthesis of SA, all those methods are found to be not economically viable at this point in time. Recently, there was a report on the discovery of SA in the aqueous waste stream from the palm oil milling process (Ravigadevi *et al.*, 2011), this new discovery has triggered research to look into the possibility of extracting SA as an alternative to the two commercial routes mentioned above. Regardless of the method of production, crude SA always contain impurities that need to be removed, otherwise it will affect the quality and final usage of the product.

The enrichment of active components from natural source is a complicated process. The problem is doubled if the desired active components are present in trace quantities. Currently, the common methods to separate and enrich these active components involve the use of non-specific adsorbent such as silica gel (including the modified one), alumina oxide and meso- or macro-porous resin. The modes of separation usually relying on the polarity of the feed materials, polar components will be retained longer if the adsorbents are polar and when hydrophobic adsorbents are used, non-polar components will be retained. Another mode of separation is based on charge, the components having different charges from the adsorbent will be retained and those neutral or having the same charge as the adsorbent will be released. Molecular sizes can also be utilized in the separation and enrichment of active components in natural products. The adsorbents are usually resin with a narrow range of porosity which, during elution, will either allow or refuse the penetration of the components of interest. Through the differences in the elution profile, components of interest are separated.

Molecular imprinted polymers (MIP) are highly cross-linked polymeric materials that are formed during the polymerization process in the presence of template molecules. During polymerization, template molecules and functional monomers undergo self-assembly process as a result of bonding interactions such as covalent bonding, hydrogen bonding, van der Waals interaction, $\pi - \pi$ interaction and others. Output from the self-assembly process is the formation of a polymer with the functional monomers framing the template molecules. Upon removal of the template molecules, the polymers now have voids in them in the shape of the template molecules. These voids are the sites which are capable of rebinding with the specific template or its analogue.

Although the effectiveness of MIP as the adsorbent in the separation or enrichment of chemical compounds is well known and proven (Chen and Shi, 2013, Pardo *et al.*, 2012), there are several challenges need to be overcome before MIP technique can really be used extensively as routine mode of separation. One of these challenges is the incompatibility of MIP in aqueous phase. This is especially true if the MIP interactions are mainly based on hydrogen bonding.

1.2 Problem Statement

It is well-known that the poor ability of imprinted polymer to bind selectively in the aqueous phase is one of the issues that need to be addressed in the field of MIP preparation. Unfortunately, many target molecules of interest are only present in aqueous media such as body fluids, wastewater and river. SA is a compound that has a very high solubility in water (18 g•L^{-1}), due to its high medicinal value, the research in the area of SA production and purification has become one of the hottest topics in the respective fields. It is the aim of this study to develop a good formulation for the preparation of SA imprinted polymer that can work in a solvent with a high aqueous content, preferably close to 100%. Other aspects of MIP preparation such as rebinding condition optimization, polymer characterizations, binding sites evaluations and subsequently the application of the prepared MIP in the separation of SA from its analogue compounds are also the interest of this study.

1.3 Objectives of the Study

The following objectives are set for this study:-

a) To prepare SA imprinted polymers that are compatible in aqueous phase.

b) To identify the most suitable functional monomer to be used in the preparation of aqueous phase compatible SA imprinted polymers.

c) To optimize the formulation of the SA imprinted polymers in term of Template: Monomer: Cross-linker (TMX) ratio and types of porogens.

d) To optimize the rebinding conditions and to evaluate the aqueous compatibility of the prepared SA imprinted polymers.

e) To characterize the prepared SA imprinted polymers.

f) To use the prepared SA imprinted polymers in the enrichment of SA from artificial mixture of SA and its analogues.

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