THE SYNTHESIS AND CHARACTERISATIONS OF POROUS THIOAMIDE-
SULFONATED-MODIFIED POLY (ACRYLONITRILE-CO-DIVINYLBENZENE-
80) AS POTENTIAL SORBENT TO CAPTURE POLAR ANALYTES

FARHANA SYAKIRAH ISMAIL

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

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THE SYNTHESIS AND CHARACTERISATIONS OF POROUS THIOAMIDE SULFONATED-MODIFIED POLY(ACRYLONITRILE-CO-DIVINYLBENZENE-80) AS POTENTIAL SORBENT TO CAPTURE POLAR ANALYTES

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July 2019

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Pharmaceuticals contain biologically active components that can pollute watercourses as a result of excretion from individuals and the uncontrolled release of residues from chemical plants. Pharmaceutical residues can persist at low concentrations in the environment, and thus may be potentially harmful to aquatic animals and humans. The control and monitoring of such residues are therefore of prime interest by, for example, solid-phase extraction using solid sorbents to purify and preconcentrate the residues prior to their chemical analysis. In the present work, poly(acrylonitrile-co-divinylbenzene-80) (poly(AN-co-DVB-80)) sorbents were synthesised by varying the comonomer feed ratios under precipitation polymerisation conditions to deliver a family of porous polymer microspheres. Acrylonitrile confers polar character onto the sorbents, and the acrylonitrile-derived nitrile groups can be chemically transformed via polymer-analogous reactions into thioamide and sulphonyl functional groups which make the sorbents even more suitable for the capture of polar analytes, including pharmaceuticals. In the present study, the Fourier transform infrared (FTIR) spectroscopy results confirmed the chemical modification of poly(AN-co-DVB-80) (P33) to form thioamide-modified poly(AN-co-DVB-80) (TP33) and sulphonation thioamide-HSO₃-modified poly(AN-co-DVB-80) (TP33-HSO₃) due to the presence of strong peaks at ~1050 cm⁻¹ and ~1154.47 cm⁻¹ that were assigned to the stretching vibrations of C=S group and SO₃H group in TP33 and TP33-HSO₃, respectively. The Brunauer-Emmett-Teller (BET) data demonstrated that the specific surface area of P33 had decreased significantly from 565.0 m²g⁻¹ (P33) to 330.0 m²g⁻¹ (TP33) and 5.9 m²g⁻¹ (TP33-HSO₃) after the chemical modifications were carried out with thiourea and sulphuric acid, respectively. The scanning electron microscopy (SEM) analysis proved that the morphologies structure of the copolymers was retained after chemical modification and sulphonation.
The TP33 had 4.3% of sulphur content due to the chemical modification of the P33 with thiourea, while the amount of sulphur in TP33-HSO₃ was the highest (6.5%) due to the sulphonation with sulphuric acid. The performance of the porous thioamide-sulphonated (TP33-HSO₃) sorbents was demonstrated via the dispersion-solid phase extraction of mefenamic acid (MA), salicylic acid (SA), and diclofenac (DCF) from aqueous medium.

It was found that the highly functionalised TP33-HSO₃ has better extraction compared to the TP33 despite its low specific surface area. Meanwhile, the extraction of pharmaceuticals by using TP33 was better compared to the extraction by using P33, although the specific surface area (SSA) of TP33 is 330.0 m²g⁻¹ and SSA of P33 is 565.0 m²g⁻¹. This finding showed that in addition to the role of SSA that influenced the extraction process; the presence of active functionalised groups also contributed to the extraction efficiency of the sorbents to extract polar pharmaceuticals. It was found that the maximum extraction for TP33 for MA, SA and DCF were 93.88 mg.g⁻¹ (78.23%), 80.07 mg.g⁻¹ (66.72%) and 70.70 mg.g⁻¹ (58.91%), respectively, while maximum extraction for TP33-HSO₃ were 96.88 mg.g⁻¹ (80.73%), 97.15 mg.g⁻¹ (80.96%) and 69.51 mg.g⁻¹ (57.93%), respectively.
Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master sains

SINTESIS DAN KARAKTERIA POROS POLI PENGUBAHSUAIAN TIOAMIDA-SULFONATED (ACRYLONITRIL-KO-DIVINILBENZANA-80) SEBAGAI POTENSI SORBEN UNTUK ANALISIS KUTUB

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Farmaseutikal mengandungi komponen aktif secara biologi yang dapat mencemar kualiti air akibat daripada pembuangan sisa daripada individu dan pelepasan sisa yang tidak terkawal dari industri kimia. Sisa-sisa farmaseutikal yang dilepaskan secara berterusan pada kepekatan rendah di alam sekitar, berpotensi membahayakan haiwan akuatik dan manusia. Oleh itu, kawalan dan pemantauan sisa-sisa perlu diberi kepentingan utama. Contohnya, pengekstrakan fasa pepejal menggunakan sorben pepejal untuk membersihkan dan mengawal kewujudan sisa. Dalam kajian ini, sorben poli(akrilonitril-ko-divinilbenzena-80) poli(AN-ko-DVB-80) disintesis dengan mengubah nisbah suapan komonomer di bawah keadaan pempolimeran pemendapan untuk menghasilkan polimer berliang yang berbentuk mikrosfera. Akrilonitril memberi karakter kutub ke dalam sorben, dan kumpulan nitril yang diperolehi daripada akrilonitril boleh diubah secara kimia melalui tindak balas polimer-analogi ke dalam kumpulan fungsi tioamida dan sulfonat yang menjadikan sorben lebih sesuai untuk menangkap analit kutub, seperti farmaseutikal. Dalam kajian ini, spektroskopi Fourier transform infrared (FTIR) mengesahkan pengubahsuaian kimia poli(AN-ko-DVB-80) (P33) untuk membentuk tioamida terubahsuaui poli(AN-ko-DVB-80) (TP33) dan tioamida-HSO3 terubahsuaui poli(AN-ko-DVB-80) (TP33-HSO3) disebabkan oleh kehadiran puncak kuat pada ~1050 cm^{-1} dan ~1154.47 cm^{-1} yang dirujuk kepada getaran regangan kumpulan C=S dan kumpulan SO3H dalam TP33 dan TP33-HSO3. Data Bruneaur Emmett-Teller (BET) menunjukkan kawasan permukaan spesifik P33 menurun dengan ketara dari 565.0 m^2 g^{-1} (P33) hingga 330.0 m^2 g^{-1} (TP33) dan 5.9 m^2 g^{-1} (TP33-HSO3) hasil pengubahsuaian yang dilakukan dengan tioure dan asid sulfurik. Analisis mikroskopi pengimbasan elektron (SEM) membuktikan bahawa struktur morfologi kopolimer dikekalkan
selepas pengubahsuaian kimia dan sulfonasi. TP33 mempunyai 4.3% kandungan sulfur kerana pengubahsuaian kimia P33 dengan tiourea, manakala jumlah sulfur dalam TP33-HSO₃ adalah yang tertinggi (6.5%) disebabkan oleh sulfonasi dengan asid sulfurik. Prestasi sorben tioamida tersulfat (TP33-HSO₃) poros dibuktikan melalui pengekstrakan penyerakan-fasa pepejal terhadap asid mfenamik (MA), asid salisilik (SA) dan diklofenak (DCF) daripada media akueus.

TP33-HSO₃ telah didapati mempunyai pengekstrakan yang lebih baik berbanding pengekstrakan TP33 walaupun mempunyai kawasan permukaan spesifikasi yang rendah. Sementara itu, pengekstrakan farmaseutikal menggunakan TP33 lebih baik berbanding pengekstrakan dengan menggunakan P33, walaupun kawasan permukaan spesifik (SSA) TP33 adalah 330.0 m²g⁻¹ dan SSA P33 adalah 565.0 m²g⁻¹. Dapatkan ini menunjukkan bahawa, di samping peranan SSA yang mempengaruhi proses pengekstrakan; kehadiran kumpulan yang berfungsi secara aktif juga menyumbang kepada kecekapan pengekstrakan untuk mengekstrak farmaseutikal kutub. Didapati bahawa pengekstrakan maksimum oleh TP33 untuk MA, SA dan DCF adalah 93.88 mg.g⁻¹ (78.23%), 80.07 mg.g⁻¹ (66.72%) dan 70.70 mg.g⁻¹ (58.91%), manakala pengekstrakan maksimum oleh TP33-HSO₃ adalah 96.88 mg.g⁻¹ (80.73%), 97.15 mg.g⁻¹ (80.96%) dan 69.51 mg.g⁻¹ (57.93%).
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I certify that a Thesis Examination Committee has met on 26-July-2019 to conduct the final examination of Farhana Syakirah on her thesis entitled “The synthesis and Characterisation of Porous Thioamide-Sulphonated-Modified Poly(AN-co-DVB-80) as Potential Sorbent to Capture Polar Analytes” in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master's Degree.

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LIST OF ABBREVIATIONS

AN  Acrylonitrile
DVB-80  Divinylbenzene-80
BPO  Benzoyl Peroxide
PAN  Polyacrylonitrile
P29  Poly(DVB)
P35  Poly(AN)
P30  Poly(AN-co-DVB-80) (0.20:0.80)
P31  Poly(AN-co-DVB-80) (0.25:0.75)
P32  Poly(AN-co-DVB-80) (0.4:0.60)
P33  Poly(AN-co-DVB-80) (0.50:0.50)
P34  Poly(AN-co-DVB-80) (0.80:0.20)
TP33  Thioamide-modified poly(AN-co-DVB-80)
TP33-HSO₃  Thioamide-HSO₃-modified poly(AN-co-DVB-80)
FTIR  Fourier Transform Infrared
BET  Brunauer-Emmett-Teller
SEM  Scanning electron microscope
MA  Mefenamic Acid
SA  Salicylic acid
DCF  Diclofenac
NSAID  Nonsteroidal anti-inflammatory drug
STP  Sewage treatment plant
dSPE  Dispersive solid-phase extraction
HPLC  High-performance liquid chromatography
CNTs  Carbon nanotubes
NaOH  Sodium hydroxide
LiAlH₄  Aluminum hydride
TG  Thermogravimetric
TG-DTG  Thermogravimetry-derivative thermogravimetry
API  Active pharmaceutical ingredients
CHAPTER 1

INTRODUCTION

1.1 Synthesis of Sorbent

In this study, poly(AN-co-DVB-80) (Figure 1.1) was formed via precipitation polymerisation. Precipitation polymerisation is a synthesis method that is used to form crosslinked monodisperse polymer microsphere (0.1-1.0 μm range). This method provides advantages to the copolymer, which involves non-incorporation of steric stabiliser or electronic surfactant. Therefore, the surface of the copolymer formed is free from any contaminant from surfactant-derived ionic charges. In addition, the morphologies of the polymer particles can be tuned by adjusting the precipitation polymerisation conditions. The formation of monodisperse particles with a narrow particles size distribution is advantageous for column packing in chromatography.

Figure 1.1: The Synthesis of Poly(AN-co-DVB-80)

In the present study, the monomers used were acrylonitrile (AN) and divinylbenzene (DVB-80). The initiator used was benzoyl peroxide (BPO), and the medium was a mixture of acetonitrile and toluene. The initiator (BPO) was utilized to initiate the polymerisation. The mixture of acetonitrile and toluene served as porogen and medium for precipitation polymerisation. Acrylonitrile (Figure 1.2) is an organic compound with the formula of \( \text{CH}_2=\text{CHCN} \), which is colorless, volatile, flammable, and water-soluble liquid at room temperature. It consists of a vinyl group linked to a nitrile and widely used in industry to produce elastomers, resins and to manufacture carbon fibres for aircraft, defense and aerospace industries.
DVB-80 (Figure 1.3) acts as a crosslinker agent, which helps in maintaining the firmness of the PAN system. For instance, the inclusion of DVB-80 units in the PAN system disrupts the nitrile-nitrile dipolar interaction along with the PAN system and consequently facilitate the access of modification reagents into polymer chains during the chemical modification process. The addition of DVB-80 is also to increase the porosity of PAN-based adsorbent and consequently to make adsorption more efficient. Poly(AN-co-DVB-80) porous particles provide micropore content which has a high specific surface area and thus has more interaction points with the analytes to be adsorbed.

The copolymer formed was chemically modified by thiourea (Figure 1.4). Thiourea is a strong hydrogen bond donor, which can form hydrogen bonds with many groups such as carboxyl, nitro and in particular phosphate groups due to its –NH₂ and sulphur group that can coordinate with pharmaceuticals to form a complex compound. Thus, the chemically modified copolymer with thiourea is expected to act as an active sorbent to adsorb pharmaceutical residues. It was demonstrated that the adsorption performance of these adsorbents was enhanced to some extent owing to their strong complexation interaction with a polar compound such as pharmaceuticals. In addition, by the presence of thiourea in a copolymer may also increase the selectivity of the copolymer as a sorbent towards the polar compound.
Figure 1.4: Chemical Modification of Poly(AN-co-DVB-80) With Thiourea

The adsorbent that has been modified with thiourea promotes ion exchange interactions with the anionic compounds (analytes). Pharmaceuticals were adsorbed at the active site of the thioamide-modified poly(AN-co-DVB-80) which were at C=S and NH groups. Therefore, thioamide-modified poly(AN-co-DVB-80) is expected to be selective for the adsorption of anionic compounds in pharmaceuticals.

Sulphonation was performed on the modified copolymer to form thioamide-\( \text{HSO}_3^- \)-modified poly(AN-co-DVB-80) (Figure 1.5). Sulphonated polymer leads to a better ion exchange resin which the polymers having positively and negatively charged functional group that can exchange their mobile ions equal charge with the surrounding medium. In addition, introducing sulphonic acid group into the polymer will transform the polymer into the ionomers. An ionomer is a polymer composed of repeat units of both electrically neutral repeating units and ionized units covalently bonded to the polymer backbone as pendant group moieties. These ionomers have excellent chemical and thermal stability and can absorb large amounts of water. They are often used as ion-selective membranes. Other than that, introducing a sulphonic group into the polymer can improve the hydrophilicity of the polymer. Incorporation of polar groups by sulphonation favors water uptake, thus inducing stronger interactions between the resin and oppositely charged ions in pharmaceuticals. The sulphonic acid group leads to the formation of proton and cation conductivity, which ideal for the membranes like proton exchange membrane fuel cells. A sulphonated polymer is highly used in membranes for fuel cells and electrodialysis, exchange resins and catalysts, surgical instruments and wound healing dressings.

The sulphonation can take place before polymerisation (pre-sulphonation) or via post-sulphonation which gives direct influence on the degree of the sulphonation and properties of the sulfonated copolymer. Most of the post-sulphonation processes are conducted in a homogenous way which allows the use of less reactive reagent, like complexes of \( \text{SO}_3^- \) with amines or phosphates.
Polymers can be sulphonated with a large range of reagent with different selectivity and reactivity.

![Sulphonation of Thioamide-Modified Poly(AN-Co-DVB-80) With Sulphuric Acid](image)

**Figure 1.5: Sulphonation of Thioamide-Modified Poly(AN-Co-DVB-80) With Sulphuric Acid**

### 1.2 Targeted Compound in This Study

Figure 1.6, 1.7, and 1.8 show the molecular structure of the targeted compounds that are mafenamic acid (MA), salicylic acid (SA) and diclofenac (DCF), respectively. MA is an anthranilic acid derivative and belongs to a nonsteroidal anti-inflammatory drug (NSAID). It is used for the treatment of analgesia. Other than that, it also used as an antirheumatic and antipyretic drug, for the treatment of dental pain, headache, and dysmenorrhea (Naveed and Qamar, 2014). MA has side effects that cause headaches, nervousness, vomiting, diarrhea, hematemesis, and haematuria. SA is a medication that widely used as a removal of the outer layer of the skin such as ringworm, warts, acne, and dandruff. SA causes stomach ache, diarrhea, and headache if excessively consumed. DCF is a NSAID that is used to reduce inflammation, joint stiffness caused by arthritis and as an analgesic reducing pain in a certain condition. DCF causes side effects like chest pain, weakness, coughing up blood, and vomit if excessively consumed. In addition, DCF is also known as a compound that affects organ histology and gene expression in fish at concentrations as low as 1 µg·L⁻¹.

MA, SA and DCF are some of the pharmaceutical residues that may affect the aquatic environment and water supplement. In Malaysia, MA, SA and DCF were detected in the Langat River with a concentration of Sewage Treatment Plant (STP) effluent 146 ng/L, 36 ng/L and 217 ng/L, respectively (Al-Odaini et al., 2010).
Figure 1.6: Molecular Structure of MA

1.7: Molecular Structure of SA

1.8: Molecular Structure of DCF
1.3 Dispersive Solid Phase Extraction (dSPE) Techniques

In this study, dispersive solid-phase extraction (dSPE) technique was used for the extraction process. dSPE is a sorbent-based technique that is widely applied in sample preparation for both samples clean up or analyte preconcentration. It shows considerable benefits over conventional solid phase extraction (SPE), especially in terms of the simplicity of the procedure. This technique is based on the dispersion of a solid sorbent in liquid samples in the extraction isolation and clean-up of different analytes from complex matrices. DSPE is used in pretreatment technique for the analysis of several compounds, for example, extraction, isolation, clean-up, and preconcentration of residues of veterinary drugs, animal tissue, foodstuff, etc. DSPE has a wide range of applications in several fields because it is considered as a selective, robust, and versatile technique.

1.4 Research Problems and Research Approaches

The presence of pharmaceutical manufacturers in Malaysia may lead to the discharge of pharmaceutical waste into water sources. On the other hand, the pharmaceutical waste is also introduced into the water sources by excretion from individuals or patients that have consumed pharmaceutical compounds for medicinal purposes. Pharmaceuticals contain an active ingredient that might cause toxicity and pollutes the water. Pharmaceuticals exist in the long term with low concentration and may harmful to aquatic life and human. Most of the factories in Malaysia are inefficient in the removal of these pollutants since the primary and secondary treatments usually applied were not designed for this purpose. However, since legislation on the discharge of pharmaceuticals is expected to come out soon, it is necessary to find efficient treatments (Coimbra et al., 2018). Thus, many works were dedicated by researcher to enhance the uptake of low concentration of pharmaceuticals in water by designing various adsorbents such as activated carbon, carbon nanotubes (CNTs) and zeolites (Basheer, 2018).

However, the major disadvantages of these adsorbents are due to their low adsorption capacities, relatively weak interactions with ions, and difficulties of separation and regeneration from water. Ion-exchange resins were able to remove ions substantially; however, they had low selectivity and showed a high degree of swelling and poor mechanical stability (Samiey et al., 2014).
To overcome these limitations, porous and highly functionalised poly(AN-co-DVB-80), microspheres particles were prepared in the present work. The DVB-80 monomer acted as a crosslinking agent that helped to maintain the firmness and develop a three-dimensional molecule (and hence develop porosity) in the PAN copolymer system. The efficacy of the adsorption capacity was expected to improve with the development of the porosity of the PAN-based polymeric adsorbent. The porous resin had active functional groups upon its chemical treatment with thiourea (on the nitrile units) to develop a basic anion exchanger of poly(AN-co-DVB-80) matrix. Thioamide was selected to instill three amine groups on each of the cyano group with longer pendant chains. The anion exchangers which carried cationic groups (≡N⁺, =NH⁺ and –NH₂⁺) were expected to attach to the reversely charged counterions by electrostatic interactions. In addition, sulphuric acid was introduced onto the thioamide-modified poly(AN-co-DVB-80) by sulphonation to increase the ion exchange resin and induce stronger interactions with the polar compounds (Patiño et al., 2016).

In the present work, a multi-residue method based on dSPE followed by HPLC analysis was used to determine the detection of the pharmaceutical residues during the extraction.

1.5 Objectives of The Study

1. To synthesis porous poly(AN-co-DVB-80) copolymer via precipitation polymerisation.
2. To chemically modify the poly(AN-co-DVB-80) copolymer with thiourea to form thioamide-modified poly(AN-co-DVB-80) and sulphonated with sulphuric acid to form thioamide-HSO₃⁻-modified poly(AN-co-DVB-80).
3. To evaluate the performance of chemically-modified poly(AN-co-DVB-80) to capture pharmaceuticals via dispersive solid-phase extraction (dSPE) technique.
1.6 Project Motivation and Research Novelty

In the present work, the novel thioamide-modified poly(AN-co-DVB-80) and thioamide-HSO$_3$-modified poly(AN-co-DVB-80) were produced and used for the extraction of pharmaceuticals to evaluate the performance of the adsorbents. Thus, the polymeric material that is produced in this work is expected to have a potential for application in environmental clean-up, specifically to extract polar pharmaceuticals.

Preparation of porous and highly functionalised poly(AN-co-DVB-80) by using thiourea and sulphuric acid has not been reported elsewhere. The presence of the primary amines in thioamide groups is expected to form various active cationic groups ($\equiv$N$^+$, =NH$^+$ and $-$NH$_2^+$) for the capture of anionic polar compounds. The presence of sulphur in the thioamide group and OSO$_2$ from sulphonation is expected to form various anionic groups (-SH, R-S-H$_2$, O-SO$_2^{2-}$) for the capture cationic polar compounds. In addition, S groups from the thioamide group can be used to form hydrogen bond and in water and can coordinate with pharmaceutical to form complex form. the sulphonation will enhance the ion exchange of the polymer and promoted better interaction with the pharmaceutical residues.

The combination of porous characteristic and highly functionalised copolymer is expected to produce adsorbent with high capacity and selectivity to extract pharmaceuticals due to the pharmaceuticals’ potential to bind through either the S or the amine N atoms in thioamide modified poly(AN-co-DVB-80) and -SO$_3$ in thioamide-HSO$_3$-modified poly(AN-co-DVB-80).
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