MAGNETIC DEEP EUTECTIC SOLVENTS BASED ADSORBENT FOR THE REMOVAL OF SELECTED NON-STREOIDAL ANTI-INFLAMMOTARY DRUGS

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by

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LIST OF SYMBOLS

C_e	Equilibrium concentration of solutions
C_0	Initial concentration of solutions
cm^3/g	Pore volume
H_2O	Water
K	Kelvin
K	Intra particle diffusion rate constant
k_1	Rate constant of pseudo first order model
k_d	Equilibrium constant
k_{ext}	Diffusion rate parameter
K_f	Adsorption capacity
K_T	Temkin constant of equilibrium binding energy
m^2/g	Surface area
Nm	Nanometer
q_m	Langmuir consisted identified with the adsorption limit
q_t	Amount of solute adsorbed
R	Universal gas contant
R_L	Dimensionless separation factor
R^2	Coefficient of determination
T	Temperature
V	Volume
W	Mass of the adsorbent used
A	Underlying sorption rate
$\Delta G°$	Change of free energy

ΔH°	Change of enthalphy
ΔS°	Change of entropy

LIST OF ABBREVIATIONS

AIBN	Azobisisobutyronitrile
BenzylIM	Benzyl imidazole
BET	Brunaeur Emmelt Teller
BJH	Barret-Joyner-Halenda
BuIM	Butyl imidazole
C	Carbon
CD	Cyclodextrin
CHN	Carbon, hydrogen, nitrogen
ChCl	Choline chloride
CTAB	Cetyl trimethyl ammonium bromide
DES	Deep eutectic solvent
DR	Dubinin-Radushkevich
EDGMA	Ethylene glycol dimethyacrylate
Fe_3O_4	Iron (III) oxide
FTIR	Fourier transform infrared spectroscopy
GC-FID	Gas chromatography-flame ionization detector
GC-MS	Gas chromatography mass spectrophotometry
GO	Graphene oxide
H	Hydrogen
HPLC	High performance liquid chromatography
IM	Imidazole
ILs	Ionic liquid
LC-MS	Liquid chromatography-mass spectrophotometry
MAA	Methyl methacrylate
MeIM	Methyl imidazole
MIP	Molecular imprinted polymer
MMIP	Magnetic molecular imprinted polymer
MNP	Magnetic nanoparticles
MSPE	Magnetic solid phase extraction
N	Nitrogen
NIP	Non-imprinted polymer

NP	Nanoparticles
RAM	Restricted access material
SDS	Sodium dodecyl sulfate
SEM	Scanning electron microscope
SiO_2	Silicon dioxide
SPE	Solid phase extraction
TEM	Transmission electron microcope
TGA	Thermogravimetric analysis
UV-vis	Ultraviolet visible
VSM	Visible sample magnetometer
XRD	X-ray diffraction

MAGNETIK PELARUT EUTEKTIK TERDALAM BERASASKAN PENJERAP UNTUK PENYINGKIRAN UBAT ANTI-RADANG BUKAN STEROID TERPILIH

ABSTRAK

Dalam kajian ini bahan berasaskan magnetic kolin klorida-butil imidazol (Fe_3O_4@ChCl-BuIM) telah dihasilkan melalui kaedah pemendakan bersama untuk penyingkiran diklofenak dan naproksen dari sampel air. Bahan yang telah disintesis dicirikan dengan menggunakan instrumen analitikal seperti spektrometer transformasi inframerah Fourier (FTIR), penganalisis elemen CHN, magnetometer sampel bergetar (VSM), mikroskop pengimbasan elektron (SEM), mikroskop pengaliran elektron (TEM), meter pembelauan X-ray (XRD), penganalisis termogravimetrik (TGA), dan penganalisis permukaan Brunauer-Emmet-Teller (BET). Kajian penjerapan awal Fe_3O_4@ChCl-BuIM telah menunjukkan kapasiti penjerapan yang sangat baik untuk penyingkiran diklofenak dan naproksen daripada sampel air berbanding dengan Fe_3O_4 yang tidak diubahsuai. Kedua-dua analit yang disasarkan tertarik dengan zarah Fe_3O_4@ChCl-BuIM melalui interaksi $\pi - \pi$ dan ikatan hidrogen, dengan itu meningkatkan kapasiti penjerapan. Kajian penjerapan berkumpulan menunjukkan bahawa penjerapan kedua-dua analit ke permukaan heterogen Fe_3O_4@ ChCl-BuIM adalah melalui mekanisma kimia. Selain itu, didapati penjerapan itu boleh dilaksanakan, spontan dan eksotermik. Prestasi penjerap diaplikasikan dan disahkan untuk menyingkirkan diclofenak dan naproksen dari sampel air sisa farmasi di mana sisihan piawai relatif (RSD%) antara hari dan intra-hari untuk kedua-dua analit dicatatkan dalam julat 0.66% -1.43% dan 0.94 % -1.35%, masing-masing. Berdasarkan penemuan ini, ChCl-BuIM kemudiannya digunakan sebagai monomer

bersama untuk sintesis magnetik polimer pencetak molekul kolin klorida butil imidazol (Fe_3O_4@MIP-ChCl-BuIM) untuk penjerapan naproksen. Tujuan untuk menambahkan ChCl-BuIM sebagai monomer bersama adalah untuk menyokong peranan monomer utama, asid metil akrilat (MAA) semasa pra-pempolimeran untuk meningkatkan kebolehcapaian dan pemilihan ke arah naproksen, dengan itu meningkatkan interaksi naproxen dengan penjerap. Berdasarkan kajian penjerapan, Fe_3O_4@MIP-ChCl-BuIM menunjukkan kapasiti penjerapan yang lebih baik berbanding dengan Fe_3O_4@MIP kerana kehadiran ChCl-BuIM menghasilkan pembentukan kompleks stabil melalui interaksi $\pi - \pi$ dan ikatan hidrogen antara penjerap dan naproksen. Kajian kinetik dan isotherm membuktikan permukaan heterogen penjerap dan penjerapan pelbagai lapisan. Kajian termodinamik menunjukkan bahawa proses penjerapan adalah eksotermik dan spontan. Untuk selanjutnya mengesahkan kaedah yang dioptimumkan, sistem yang dioptimumkan telah digunakan pada sampel air sebenar untuk mengkaji linear dan reproduksi. RSD% untuk antara hari dan intra-hari dicatatkan dalam lingkungan 0.97−2.19% dan 1.80−2.30%, masing-masing dengan peratusan penyingkiran sekitar 94.8%−96.2%. Kajian pengiktirafan pesaing Fe_3O_4@MIP-ChCl-BuIM dilakukan dan Fe_3O_4@MIP-ChCl-BuIM menunjukkan pemilihan yang tinggi terhadap naproksen. Maklumat dari kajian ini akan memberikan gambaran utama tentang sifat DES yang boleh diperluas untuk mencetak NSAIDs lain untuk penjerapan yang sangat selektif.

MAGNETIC DEEP EUTECTIC SOLVENT BASED ADSORBENTS FOR THE REMOVAL OF SELECTED NON-STEROIDAL ANTI-INFLAMMOTARY DRUGS

ABSTRACT

In this study, material based on magnetic choline chloride-butyl imidazole (Fe_3O_4@ChCl-BuIM) was synthesise via simple co-precipitation method for removal of diclofenac and naproxen from water sample. The synthesised material was characterized by using analytical instrument such as Fourier transform infrared spectroscopy (FTIR), CHN elemental analyser, vibrating sample magnetometer (VSM), scanning electron microscope (SEM), transmission electron microscope (TEM), X-ray diffractometer (XRD), thermogravimetric analyser (TGA), and Brunauer-Emmet-Teller (BET) surface analyser. Preliminary adsorption study of Fe_3O_4@ChCl-BuIM has showed excellent adsorption capacity for removal of diclofenac and naproxen from water samples compared to unmodified Fe_3O_4. Both targeted analytes were attracted to the Fe_3O_4@ChCl-BuIM particles by $\pi - \pi$ interaction and hydrogen bonding, thus improved the adsorption capacity. Batch adsorption study indicate that the adsorption of both analyte onto the heterogeneous surface of Fe_3O_4@ChCl-BuIM were through chemisorption mechanism. Besides, it was found that the adsorption was feasible, spontaneous and exothermic. The performance of adsorbent was applied and validated to remove diclofenac and naproxen from pharmaceutical waste water samples where the relative standard deviation (RSD%) inter-day and intra-day for both analytes were recorded in the range of 0.66%−1.43% and 0.94%−1.35%, respectively. Based on this findings , ChCl-BuIM was then employed as co-monomer in preparation of magnetic molecular

imprinted polymer (Fe_3O_4@MIP-ChCl-BuIM) as highly selective adsorbent towards naproxen. The purpose of adding ChCl-BuIM as co-monomer was to enhance the performance of principal monomer, methylacrylate acid (MAA) by improving the accessibility and selectivity towards naproxen. . Based on the adsorption study, Fe_3O_4@MIP-ChCl-BuIM has showed better adsorption capacity compared to Fe_3O_4@MIP since the presence of ChCl-BuIM resulted in formation of stable complexes through $\pi - \pi$ interaction and hydrogen bonding between adsorbents and adsorbate. The kinetic and isotherm study proved the heterogeneous surface of the adsorbents and multilayer adsorption. Thermodynamic study showed that the adsorption process is exothermic and spontaneous. The adsorbent was applied and validated for the removal of naproxen from pharmaceutical waste water samples. The RSD% for inter-day and intra-day was recorded in the range of 0.97%−2.19% and 1.80% −2.30%, respectively, with removal percentage around 94.8% − 96.2%. Competitive recognition studies of the Fe_3O_4@MIP-ChCl-BuIM were performed and it displayed highly selective toward naproxen. Information from this study will provide the key insights on the nature of DES as co-monomer functionalized with principal monomer in MIP which could be extended to imprint other NSAIDs for highly selective adsorbent .

CHAPTER 1

INTRODUCTION

1.1 General background of research

During the last decades, environmental quality has continuously deteriorated due to the accumulation of various undesirable pollutants. The production of a number of man-made trace pollutants such as pharmaceuticals, cosmetic products, dyes, pesticides and many more, has contributed to harmful effects on human and environments. Nowadays, pollutants such as non-steroidal anti-inflammatory (NSAIDs) are considered emerging pharmaceutical contaminants due to their major effects on human health and environmental. NSAIDs are a class of drugs that are widely prescribed for anti-inflammatory and analgesic (pain-killing) effects (Rodriguez-Alvarez et al., 2013). These drugs are usually used for the treatment of mild to moderate pain, fever and for tissue damage resulting from osteoarthritis and rheumatoid arthritis.

The widespread use of NSAIDs has led to their continuous release into the environment through different paths, including excretion and improper disposal of unused drugs (Vergeynst et al., 2015). Previous study has reported that the existence of NSAIDs in the environment are associated with hospital waste water, industrial effluent waste, disposal of expired drugs and also excretion by humans and animals (Madikizela et al., 2017). Waste water treatment only removes half of the pharmaceuticals and the removal of NSAIDs is usually incomplete as most treatment for this drug removal requires special purifying treatment (Deziel., 2014). Therefore,

incomplete NSAIDs removal has caused these compounds to accumulate in the environment and traced in groundwater and surface water (Petrovic et al., 2009). Some NSAIDs were also detected in drinking water (Carmona et al., 2014).

Although the concentrations of NSAIDs detected in the environment are relatively low, however, due to their toxicity, continuous release and chronic exposure to these substances may affect the hematopoietic, intestinal and renal systems that may be harmful to human health (Khetan and Collin, 2007). If a person is already taking NSAIDs and is exposed to it at the same time, the person may suffer from health problems, particularly if they are exposed in the long term. Thus, because of its impact on human health and aquatic life, NSAIDs has been classified as organic pollutants and the existence of NSAIDs in the environment has become a major concern (Caro et al., 2005). Therefore, early treatment of NSAIDs during clinical or pharmaceutical disposal is extremely important to prevent the release of certain quantities of these drugs into the environment.

The most competent and financially practical technique for removing organic pollutants would be adsorption. In adsorption, the selection of adsorbents is a vital criteria for ensuring excellent removal of target analyte from the sample solution. Recently, the use of magnetic nanoparticles (Fe_3O_4) as an adsorbent has gained a lot of interest due to its unique properties such as low toxicity, high surface area and superparamagnetic properties (Gupta and Gupta, 2005). Since it possessed superior magnetic properties, the target analyte can be easily separated from the sample solution using external magnetic field during adsorption process. This allowed simple and rapid adsorption process. However, the application of Fe_3O_4 particles for adsorption study is quite challenging as this materials tends to agglomerate in aqueous sample solution. Besides, it can also easily oxidized in air, thus will affect its stability

towards target analyte and cause loss of magnetism. Therefore, this problem can be solved by surface modification of Fe_3O_4 particles. In previous study, the surface of Fe_3O_4 has been modified by using surfactants (Dalali et al., 2011), synthetic polymer (Meseguer-Lloret et al., 2017), silica (Ranjbakhsh et al., 2012) and ionic liquids (Wu et al., 2016). Among these, ionic liquids (ILs) is the most popular functionalization agent due to its low toxicity, non-volatile, highly polar, good stability and high thermal stability properties. Besides, ILs has been recognised as green solvent and the best alternative compared to other conventional solvent (Renee et al., 2009).

However, some ILs suffer from some drawbacks such as challenging preparation method and high cost. Therefore, a new type of solvent known as deep eutectic solvent (DES) was introduced in 2003 (Abbot et al., 2003). DES have attracted considerable attention since they have comparative physical and chemical properties, but they are much cheaper, safer and less challenging to obtain than ILs. Most DES are biodegradable, have inexpensive raw materials and easy to prepare (G. Li et al., 2016). Besides, DES preparation used simple method that require the mixture of two components known as hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) heating at certain temperature until a homogenous liquid of DES was formed (Abbott et al., 2003). In contrast, ILs preparation method are quite complex where it require high cost precursor and challenging synthesis route (Shamsuri and Abdullah, 2010).

DES is usually composed of an organic salt or quaternary ammonium salt as HBA component with HBA compound such as amides, alcohols, amines and carboxylic acid. Diverse properties can be obtained from DES depending on their component, therefore, it is possible to achieve intended applications. To the best of our knowledge, DES based on the mixture of choline chloride (ChCl) and imidazole

(IM) has never been synthesised. ChCl is known as low cost compound with biodegradable properties whereas imidazole is a polar compound with aromatic structure that will form strong electrostatic attraction towards aromatic NSAIDs compound. With this into account, modifying magnetic (Fe_3O_4) with this new form of DES will ensure great removal performance of NSAIDs from water samples with low cost and simple developed method. Therefore, in **part I** Fe_3O_4 was modified by synthesised ChCl-BuIM to produce magnetic choline chloride-butyl imidazole (Fe_3O_4@ChCl-BuIM) for removal of selected NSAIDs, diclofenac and naproxen from water samples.

In recent years, molecular imprinted polymer (MIP) has been widely used to enhance adsorbent selectivity towards target analytes. MIP is a synthetic polymer material with artificially generated recognition sites that can specifically rebind a target molecule to other closely related compounds (X. Li and Row, 2017). MIP is usually synthesized by the complex form between template and monomer that was then joined by a cross linker (He at al., 2007). MIP's unique binding sites are created by the template's self-assembly with other functional group and monomer, followed by co-polymerization. Therefore, selecting the appropriate monomer is an important criteria to assure the production of highly selective MIP. Nowadays, the existence of co-monomer in the synthesis of MIP has gained a lot of interest due to the drawback of conventional MIP synthesis method such as limited site accessibility to target analytes, low rebinding capacity, slow mass transfer rate and incomplete removal of templates (Liu et al., 2016).

The application of DES as a co-monomer in the preparation of MIP has attracted considerable attention among researchers. Several studies have agreed that

introducing DES in the preparation of MIP can improve the selectivity and affinity of the polymers (G. Li et al., 2018). In addition, DES can provide better efficiency for MIP compared to traditional functional monomers such as acrylic acid and acrylamide (Liu et al., 2016). DES is also known as polar solvent with good compatibility in aqueous media. Therefore, coupling new DES with MIP could be a novel technique as it combines the advantages of DESs' aqueous affinity capability and MIPs' molecular recognition capability. To the best of our knowledge, DES based on ChCl-BuIM has never been used as co-monomer in the preparation of MIP. Therefore, in **part II**, the synthesised ChCl-BuIM was adopted as the co-monomer during synthesis of MIP to produce adsorbents, magnetic molecular imprinted polymer (Fe_3O_4@MIP-ChCl-BuIM) for efficient and selective removal of naproxen from water samples.

1.2 Objectives of the research

i. To synthesis and characterize magnetic deep eutectic solvent-based choline chloride-butyl imidazole (Fe_3O_4@ChCl-BuIM).
ii. To study adsorption behaviour of magnetic deep eutectic solvent-based choline chloride-butyl imidazole (Fe_3O_4@ChCl-BuIM) towards diclofenac and naproxen
iii. To synthesis and characterize magnetic molecular imprinted polymer choline chloride-butyl imidazole (Fe_3O_4@MIP-ChCl-BuIM).
iv. To study adsorption behaviour of magnetic molecular imprinted polymer choline chloride-butyl imidazole (Fe_3O_4@ChCl-BuIM) towards naproxen

1.3 Scope of the study

This study involved the synthesis and characterization of Fe_3O_4@ChCl-BuIM as an adsorbent to apply in removing of naproxen and diclofenac from water sample. The ChCl-BuIM was then employed to be co-monomer in magnetic molecular imprinted polymer (Fe_3O_4@MIP-ChClBuIM) to improve the affinity of the imprinted polymer adsorbents towards naproxen. All the materials were characterised by using Fourier transform infrared spectroscopy (FTIR), CHN elemental analyser, vibrating sample magnetometer (VSM), scanning electron microscope (SEM), transmission electron microscope (TEM), X-ray diffractometer (XRD), thermogravimetric analyser (TGA), and Brunauer-Emmet-Teller (BET) surface analyser. Preliminary batch adsorption study was carried out to evaluate the performance Fe_3O_4@ChCl-BuIM and Fe_3O_4@MIP-ChCl-BuIM for the removal of NSAIDs and were applied for real sample analysis.

1.4 Outline of the thesis

This whole thesis consist of five chapters**. Chapter 1** is a brief introduction on the non-steroidal anti-inflammatory drugs, magnetic nanoparticles, molecular imprinted polymer and deep eutectic solvent. This chapter also contained the research objectives and scope of the research. **Chapter 2** is the literature review on properties of targeted analyte, magnetic nanoparticles, molecular imprinted polymer and deep eutectic solvent. Meanwhile, **Chapter 3** is the methodology which consist of synthesis and characterisation techniques, batch adsorption study of diclofenac and naproxen and also method validation. This chapter consists of two major parts where **Part I** is

the study on magnetic nanoparticles modified choline chloride-butyl imidazole (**(**Fe_3O_4@ChCl-BuIM) employed as an adsorbents for removal of diclofenac and naproxen from aqueous sample. Meanwhile, **Part II** is the study on choline chloride-butyl imidazole (ChCl-BuIM) as co-monomer in magnetic molecularly imprinted polymer (Fe_3O_4@MIP-ChCl-BuIM) for removal of naproxen from water samples. **Chapter 4** represents all the results of the experiments and discussion. This chapter also consists of two major parts which discusses the characterisation, interaction mechanism, optimization, method validation and real water sample analysis. Lastly, **Chapter 5** focuses on the conclusion of this research and future suggestion for this study.

CHAPTER 2

LITERATURE REVIEW

2.1 Non-steroidal anti-inflammatory drugs

2.1.1 Introduction

Over the last decades, the high demand for production and consumption of pharmaceuticals has caused it to become one of the most significant classes of environmental contaminants. Many studies reported that pharmaceuticals contaminants are detected in groundwater, freshwater, drinking water and surface water (Bound and Volvoulis, 2005). One of the widely used pharmaceuticals worldwide is non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are generally used to relieve fever, pain, and inflammation caused by conditions such as arthritis and rheumatoid arthritis. Some studies have also reported NSAIDs application in chemotherapy and chemoprevention for cancer. NSAIDs are known to decrease the proliferation, angiogenesis, motility, and invasiveness of cancer cells (Hilovska et al., 2015).

2.1.2 Properties and classification of NSAIDs

Based on their molecular structure, most NSAIDs are polar compound which are mainly derivatives of the carboxylic acid. Therefore, most NSAIDs have acidic properties in the range of pK_a from 4−6. The main properties of studied NSAIDs are tabulated in **Table 2.1.** The mechanism action of NSAIDs is through the inhibition of cyclooxygenase enzyme (COX) where this enzyme plays an essential role in inhibiting

prostaglandin synthesis. Prostaglandins are known as lipid autacoids obtained from arachidonic acid that play a significant part to generate an inflammatory response (Ricciotti and FitzGerald, 2011). As a result, the patient may experience a reduction in pain, fever, and inflammation upon NSAIDs intake due to prostaglandin inhibition. COX enzyme usually exist in two isoforms known as COX-1 and COX-2. COX-1 is produced continuously in most tissues, while COX-2 is caused by inflammation. Each NSAIDs differ in their potency, length of action, how they are removed from the body, how heavily they inhibit COX-1 versus COX-2 and their tendency to cause ulcers and encourage bleeding.

As indicated in **Table 2.2**, NSAIDs are classified into several groups based on their selectivity towards COX-1 and COX-2 (Nawaz, 2012). For example, some NSAIDs such as celecoxib, parecoxib, and valdecoxib tend to block COX-2 more compare to COX-1. These drugs are known as selective COX-2 inhibitors whereas classical NSAIDs or known as non-selective COX inhibitors such as aspirin, ibuprofen, ketoprofen, naproxen, indomethacin, nabumetone, and oxaprozin will block both COX-1 and COX-2 enzymes. The common side effects of NSAIDs, such as constipation, diarrhoea, and vomiting, are common. Hence, only a low dose of NSAIDs should be taken and should be prescribed only by the doctor. NSAID use can also be associated with a range of severe side effects, including gastrointestinal complications, cardiovascular events, renal failure and hypersensitivity responses (Madrakian et al., 2013). NSAIDs are still widely used as a medication for any form of pain although there was proof of the connection of prolonged use of NSAIDs with an adverse reaction in certain high-risk groups (Haag et al., 2011). High dose or long term use of NSAIDs could also lead to the development of ulcers in the gut, known as peptic ulcers. This is because NSAIDs decrease prostaglandin action, which then reduces inflammation.

However, prostaglandins also play an essential role in protecting the lining of the stomach by producing mucus. In this sense, the stomach is open to acids that caused ulcers or bleeding. The therapeutic impacts of NSAIDs are mainly the consequence of COX-2 inhibition, whereas the toxic effects such as kidney, gastrointestinal and renal failure due to COX-1 inhibition.

Table 2.1 Physiochemical properties of studied NSAIDs compound

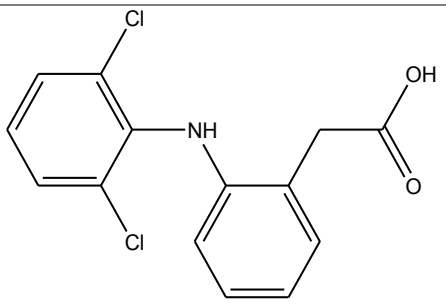
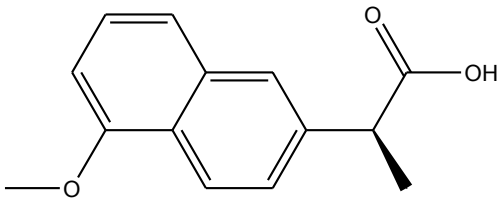
Analytes	**Chemical structure**	**Molecular formula**	**Molecular weight (g/mol)**	**p*Ka***
Diclofenac		$C_{14}H_{11}Cl_2NO_2$	296.148	4.15
Naproxen		$C_{14}H_{14}O_3$	230.259	4.15

Table 2.2 Classification of NSAIDs

Selectivity	**Group**	**Drugs**
Non-selective COX inhibitors	Salicylates	Aspirin
	Propionic acid derivatives	Ibuprofen, naproxen, ketoprofen
	Antranilic acid	Mefenamic acid, meclofenamic acid
	Heteroaryl acetic acid	Diclofenac
	Oxicam derivatives	Piroxicam, tenoxicam
	Indole derivatives	Indomethacin
	Pyrrolo-pyrrole derivatives	Ketorolac
	Pyrazolone derivatives	Phenylbutazone, oxobutazone
Preferential COX-2 inhibitors	Alkanones	Nabumetone
Selective COX-2 inhibitors	Diarylheterocycles	Celexociv, valdecoxib, parecoxib, etoricoxib, lumarixocib
Weak COX inhibitors	Para-aminophenol derivatives	Acetaminophen

2.1.2 The occurrence and removal of NSAIDs from water samples.

Due to excessive use and large discharge into the environment, particularly in water bodies, NSAIDs are regarded to be emerging pollutants (Abujaber et al., 2018). In Spain, the average concentrations of diclofenac, naproxen, and ibuprofen detected in tap water were 18, 11 and 29 ng/L, respectively (Carmona et al., 2014). Meanwhile, in Iran, the average concentration of diclofenac, naproxen, and ibuprofen detected were 24, 39 and 47 ng/L, respectively. Besides, the concentration of NSAIDs detected in Africa was around 221 μg/L. While in most countries in Europe, the concentration detected is in a lower amount. The differences in NSAIDs levels in the environment across different countries could be explained by differences in the sanitation systems (Mlunguza et al., 2019). In most countries, wastewater treatment systems such as waste water treatment plant (WWTPs) and developed wetlands were not initially designed to prevent the penetration of NSAIDs into the environment. Therefore, NSAIDs can enter the environment in different ways, such as through industrial waste, during the disposal of expired or unused drugs and through animal and human excretions (Kummerer, 2016). Even though the levels of these drugs in the environment are low, continuous exposure of these drugs can damage human renal, intestinal, and hematopoietic systems (Khetan and Collin, 2007). Among these NSAIDs, considering the level of toxicity of freshwater effluents, it is possible to find diclofenac, ibuprofen, and naproxen as the most prominent NSAIDs (Ahmed, 2017). Therefore, numerous studies has been conducted for the removal and extraction of these NSAIDs compound as summarized in **Table 2.3**

Table 2.3: Previous study on removal and extraction of NSAIDs

NSAIDs	Materials	Samples	Instrument	References
Naproxen, diclofenac, ibuprofen, and indomethacin	Magnetic nanoparticles-surfactant	Urine and wastewater samples	HPLC	(Sharifabadi et al., 2014)
Ibuprofen, naproxen, and diclofenac	Magnetic multi-walled carbon nanotube	Tap, river and dam water samples	LC-UV fluorescence	(Abujaber et al., 2018)
Naproxen, ibuprofen, and diclofenac	Molecularly imprinted polymer	River water	HPLC-DAD	(Madikizela et al., 2017)
Diclofenac	Magnetic nanoparticles-surfactant	Human plasma and urine	UV-Visible	(Ershad et al., 2015)
Naproxen	Molecularly imprinted polymer-carbon nanotube	Human urine	Luminescene spectrometer	(Madrakian et al., 2013)
Naproxen	Molecularly imprinted polymer	Wastewater samples	HPLC	(Sun et al., 2008)

Table 2.3: (Continued)

Naproxen, diclofenac meloxicam,flurbiprofen, tiaprofenic and mefenamic acid	-	Human serum	HPLC-UV	(Nawaz, 2012)
Ibuprofen, naproxen, and diclofenac	Polyethylene glycol-multi-walled carbon nanotube	Tap water, well water, river water, and wastewater	GC-FID	(Sarafraz-yazdi et al., 2012)
Naproxen and ketoprofen	Carbon black	River water	UV-Visible	(Cuerda-correa et al., 2010)
Ibuprofen	Molecularly imprinted polymer	Urine samples	HPLC	(Lagha et al., 2011)

2.2 Deep eutectic solvent

2.2.1 Introduction

Ionic liquid (ILs) is recognised as a green solvent as an alternative to conventional volatile organic solvents. In the latest years, it has been studied in various fields including analytical chemistry (Renee et al., 2009) catalysis (Welton, 2004), and biosensors (Y. Liu, et al., 2005) owing to it low toxicity, chemically inert, non-volatile and highly polar properties. However, ILs suffering from some disadvantages which are difficult and challenging synthesis processes and expensive raw materials. Therefore, to obtain materials with ILs properties but a much cheaper and simple synthetic method, deep eutectic solvent (DES) was introduced. DES is a known green solvent that was first discovered in 2003 as a new class of ILs. DES physicochemical characteristics are similar to conventional ILs, such as low vapour pressure, non-volatile, high polarity and low toxicity but the synthesis technique is more straightforward and cheaper owing to the low price of the required raw materials (Li & Row 2017).

2.2.2 Synthesis of deep eutectic solvent

After DES was discovered, numerous DES have been prepared by researchers. Most DES are synthesised in a simple step by mixing and melting two components known as hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) at certain molar ratio and temperatures. In the year 2003, the first DES was obtained by using method of heating the HBA and HBD component at 80℃ and stirred until a homogeneous liquid formed (Abott et al., 2003). This method was commonly applied for the preparation of DES. Besides, DES was also prepared by freeze drying method

where the mixture of HBA and HBD were freeze dry to produce a clear viscous liquid of DES (Gutierrez et al., 2009). The resulting combination of these components are known as eutectic mixture. An eutectic system is a combination of two or more components that exhibits a single chemical composition that solidifies at lower temperatures than individual component. DES compound's low melting point is due to the interaction of hydrogen bonding between HBD and HBA components (Dai et al., 2013). **Figure 2.1** is the structure of HBA and HBD components that can be used to form DES (Li & Row, 2017). The most common synthesised DES were based on quartenary ammonium salt, choline chloride (ChCl) as HBA with other HBD, such as urea, glycerol, and ethylene glycol. Some study has reported the used of organic salts such as zinc chloride and iron (III) chloride as HBD component (Zaharaddeen et al., 2015). Besides, DES was also apparently synthesised on the basis of sugar molecules such as glucose, sucrose and xylose and carboxylic acid such as citric acid, lactic acid, and benzoic acid.

There are unlimited opportunities to prepare various DES due to high flexibility in choosing their individual compounds and composition. Physiochemical properties such as freezing point, density, viscosity and conductivity can be designed based on DES structure. Therefore, different properties can be obtained from DES depending on their component, therefore it is possible to achieve intended applications. To date, some research has been reported on the applications of DES in organic synthesis, catalysis, materials preparation and electrochemistry (Khezeli et al., 2015). DES has been widely implemented in several fields of chemistry in the latest years, including the preparing of inorganic materials, organic synthesis, analytical chemistry and biochemistry (Garcia et al., 2016). **Table 2.4** is the summary of DES components and their application.

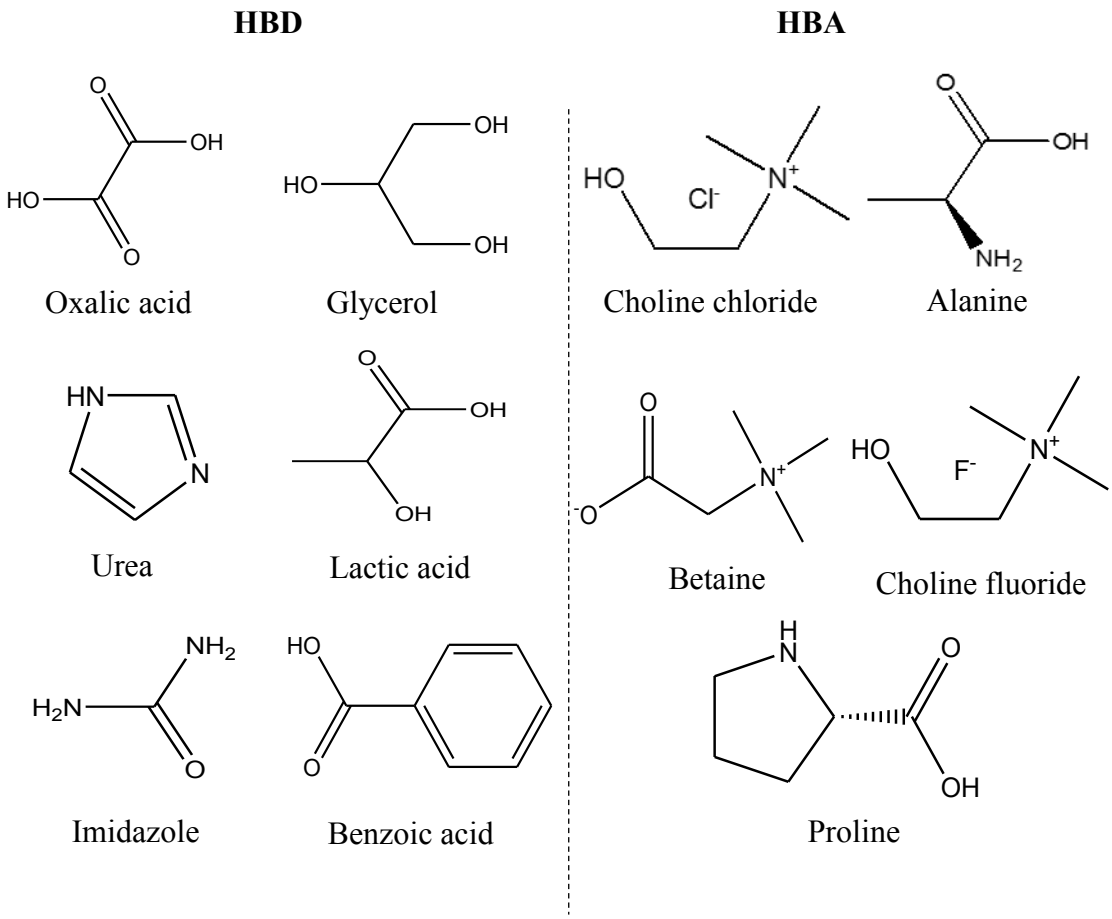


Figure 2.1: Common structure of HBD and HBA of DES

Table 2.4: Summary of synthesised DES components and their application.

HBA	HBD	Molar ratio (HBA:HBD)	Application	References
Choline chloride	Xylitol	2:1	Extraction of phenolic compounds from virgin olive oil	(García et al., 2016)
Choline chloride	1,4-butanediol	1:5		
Choline chloride	sucrose	1:1		
Choline chloride	Phenol	1:4	Ultrasound-assisted emulsification liquid phase microextraction of malachite green in farmed and ornamental aquarium fish water samples	(Aydin et al., 2017)
Choline choride	Ethylene glycol	1:2	Extraction of erulic, caffeic and cinnamic acid from olive, sesame,almond and cinnamon oil.	(Khezeli et al., 2016)
Choline chloride	Glyceol	1:2		
Choline chloride	Glycerol	1:2	Extraction media for quantitative determination of ochratoxin a in wheat and derived products	(Piemontese et al., 2017)
Choline chloride	Urea	1:2		

2.2.3 Deep eutectic solvent based polymer

Due to its unique properties, there have been increasing interest in synthesis of DES based with other materials such as silica, graphene and polymer. DES based on molecular imprinted polymer (MIP) has gained a lot of attention in the latest years since DES can modify the synthesis procedure of MIP to improve the selectivity and affinity of MIP towards targeted analyte. The mechanism of DES-based MIP materials towards targeted analyte usually involve multiple interactions such as hydrogen bonding, electrostatic, ion exchange and hydrophobic, therefore will provide more stable complex during pre-polymerization process. **Table 2.5** is the list of DES based MIP that have been synthesised from previous study. Most researchers has reported that this DES based material able to promote a functional monomer to form the specific binding sites thus give it more rigidity without swelling or shrinking. Besides, the surface of this materials are porous and rough, thus suitable for releasing target molecules from the surface. Research into DES-based MIP is expected to show significant progress in the future due to its unique properties and advantageous

Table 2.5: Summary on the synthesised DES based polymer

Type of DES (HBA : HBD)	DES-based MIP	Template	References
Betaine : ethylene glycol	DES-MIP	Levofloxacin and tetracycline	(X. Li and Row, 2017)
Choline chloride: MAA, Betaine: MAA	Fe_3O_4-CTS@DES-MIPs[a]	Catechins	(Ma et al., 2018)
Choline chloride: ethylene glycol Choline chloride: glycerol Choline chloride: butanediol	Hybrid DES-MIP	Rutin, scoparone, and quercetin	(G. Li, Ahn et al., 2016)
Choline chloride : glycerol	DES-MIP	Honeyscukle	(G. Li, Wang et al., 2016)
Choline chloride : ethylene glycol Choline chloride: glycerol Choline chloride: butanediol Choline chloride: urea	DES-MMIP[b]	Tanshinone I, tanshinone IIA and cryptotanshinone	(G. Li et al., 2018)

[a]Fe_3O_4-CTS@DES-MIPs – molecular-imprinted polymers-based magnetic chitosan with facile deep eutectic solvent-functional monomers.
[b]DES-MMIP – deep eutectic solvent-magnetic molecular imprinted polymer

2.3 Magnetic iron particles

Magnetic iron particles (Fe_3O_4) is a nano adsorbent that is blessed with outstanding sorption capacity, separation property, small size (less than 100 nm) and low toxicity (Orimolade et al., 2018). In recent years, Fe_3O_4 has been acknowledged as unique adsorbents with large surface areas, small diffusion resistance and highly active surface site (Sharifabadi et al., 2014). Besides, Fe_3O_4 can be easily recycled and or reused. In the last few decades, numerous methods have been developed to synthesize Fe_3O_4 which are co-precipitation (Wu et al., 2008), sol-gel (Chen and He, 2001) and sonochemical reaction (Mukh-qassem and Gendanken, 2005). Among these reported methods, co-precipitation is the most promising method due to its simplicity and high yield of products**.** In the co-precipitation method, Fe_3O_4 was synthesized from ferric and ferrous ions by adding a base such as ammonia solution under an inert atmosphere at elevated temperatures (Beiraghi et al., 2013). The reaction can be described as follows in **Equation (2.1)**:

$$Fe^{2+} + 2Fe^{3+} + 8OH^- \longrightarrow Fe_3O_4 + 4H_2O \qquad \textbf{Equation (2.1)}$$

Due to its numerous advantages, the implementation of Fe_3O_4 as a sorbent has gained a lot of interest in recent years. Since it possessed super paramagnetic properties, the adsorbate can be easily separated from the sample solution by using external magnetic field. This allowed rapid and simple adsorption process. However, 4unmodified Fe_3O_4 has several disadvantages, such as they are easily oxidized and agglomerate in aqueous solution. Therefore, modification of the Fe_3O_4 surface is necessary to overcome its limitation. The previous study has proved that modified Fe_3O_4 has better adsorption capacity and removal ability compare to unmodified

Fe_3O_4. Besides, modifying the surface of Fe_3O_4 will improve the stability of Fe_3O_4 towards target analytes. In the previous study, Fe_3O_4 has been modified by using surfactants, ionic liquid and carbon based materials such as graphene and carbon nanotube. **Table 2.6** summarize the previous research on the applications of modified Fe_3O_4.

Table 2.6: Previous study on modifications of Fe_3O_4

Fe_3O_4 coating materials	**Application**	**References**
Graphene/Fe_3O_4@ polythiophene	MSPE of polycyclic aromatic hydrocarbons from seawater samples	Mehdinia et al., 2015
Fe_3O_4@GO-DES[b]	SPE of ovalbumin, bovine serum albumin, bovine haemoglobin and lysozyme	Huang et al., 2015
SDS-Fe_3O_4 NP[b]	Removal of safranin O dye from aqueous samples	Shariati et al., 2011
MNCZ[c]	Removal of gemfibrozil, ibuprofen, diclofenac, and naproxen from aqueous sample	Attia et al., 2013
MNP-CTAB[a]	MHSPE of mefenamic acids from urine samples and human plasma samples	Beiraghi et al., 2013
IL@Fe_3O_4	Removal of red-120 and 4-(2-pyridylazo from aqueous samples	Absalan et al., 2011
Fe_3O_4/graphene oxide	MSPE of polycyclic aromatic hydrocarbons from tap, river and seawater samples	Han et al., 2012

[a]MNP-CTAB –Magnetic nanoparticles-cetyl trimethyl ammonium bromide

[b] Fe_3O_4@GO-DES –Magnetic graphene oxide deep eutectic solvent

[c]MNCZ–Magnetic nanoparticles coated zeolite

2.4 Molecular imprinted polymer

2.4.1 Synthesis of molecularly imprinted polymer

Molecularly imprinted polymer (MIP) are synthetic materials with artificially produced recognition sites to capture specific target molecules. As compared to other adsorbents, MIP possessed unique characteristics which are high selectivity towards target analyte. Usually, MIP was synthesized in the presence of a template by copolymerizing the monomer and cross-linker (Yan et al., 2013). The removal of the template will leave the binding site in shape, size and functionality that is complementary to the target analyte (He et al., 2007). MIP can be synthesized with three different imprinting approaches which are covalent, non-covalent and semi covalent. In covalent imprinting technique, the template monomer complex was co-polymerize with a cross-linking monomer (Wulf et al., 1973). These derivatives are acquired by forming covalent bonds between suitable monomer and template to produce an ' exact fit ' recognition site where the same chemical bonds in the initial monomer-template complex reform during any subsequent binding of the imprinted polymer cast.

The non-covalent approach is the formation of a pre-polymerisation complex between template and monomer. The interaction between the template and monomer is through hydrogen bonding, dipole-dipole, and ionic interactions. After synthesis, the template is removed simply by washing it with a solvent or a mixture of solvents. The non-covalent method is the most commonly used because it is experimentally straightforward and the complexation step during synthesis is accomplished by mixing the template with a suitable functional monomer in an appropriate porogen or solvent (Joshi et al., 1998). The semi covalent is a hybrid of the covalent and non-covalent