Investigation of Interaction of Duloxetine with Alginic Acid Polymers

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ABSTRACT

In this study, glutaraldehyde cross-linked alginate bead was prepared and characterized by FT-IR analysis. Its potential to adsorb an antidepressant drug duloxetine hydrochloride (DLU) was investigated. The adsorption studies were carried out in 25mg/L DLU solution in water wherein 0.015-0.035g alginate bead was utilized. The studies were conducted at 25^{o}C under atmospheric pressure with a continuous stirring at 200 rpm. The studies indicated that the polymer had a high affinity to bind to the DLU. The adsorption capacity was found as 5.33 mg of DLU /gram of alginate bead. The DLU binding capacity of the adsorbent was associated to the formation of ion-ion interaction between the quaternized amine moiety present in DLU and the carboxylates available within the alginate structure.

Furthermore, the kinetic studies performed indicated that the binding process fitted to the pseudo-second order kinetic model. The rate constant of initial adsorption was found to be 0.0125 g/mg.min. In addition, the results of adsorption equilibrium fitted the Freundlich isotherm. This further pointed out a multilayer coverage and a heterogeneous surface on the bead prepared. Overall, the results indicated that alginate bead utilized appears to be a good natural polymer for efficient removal of highly consumed DLU.

Keywords: alginate; antidepressant; duloxetine; removal; water treatment

ÖZ

Bu çalışmada, glutaraldehit çapraz bağlı aljinat boncuk, FTIR analizi ile hazırlandı ve karakterize edildi. Antidepresan ilaç duloksetin hidroklorür (DLU) adsorbe etme potansiyeli araştırıldı. Adsorpsiyon çalışmaları, su içinde 25 mg / L DLU çözeltisi içinde gerçekleştirildi, burada 0.015-0.035g aljinat boncuk kullanıldı. Çalışmalar, 25 °C'de, atmosferik basınç altında, 200 rpm'de sürekli bir karıştırma ile gerçekleştirilmiştir. Çalışmalar, polimerin DLU'ya bağlanma eğiliminin yüksek olduğunu göstermiştir. Adsorpsiyon kapasitesi 5.33 mg DLU / gram aljinat boncuk olarak bulunmuştur. Adsorbentin DLU bağlama kapasitesi, DLU içinde bulunan kuaternize amin kısmı ve aljinat yapısı içinde mevcut olan karboksilatlar arasındaki iyon-iyon etkileşiminin oluşumu ile ilişkilendirilmiştir.

Ayrıca, gerçekleştirilen kinetik çalışmalar, başlangıç adsorpsiyon oranı sabitinin 0.0125 g / mg.min olarak tahmin edildiği, yalancı ikinci dereceden kinetik modele bağlanan bağlama sürecinin olduğunu göstermiştir. Dahası, adsorpsiyon dengesinin sonuçları, çok katmanlı bir kapsama ve heterojen bir yüzeye işaret eden Freundlich izotermine oturtulmuştur. Genel olarak, sonuçlar, kullanılan aljinat kordonunun, yüksek oranda tüketilen DLU'nun etkili bir şekilde giderilmesi için iyi ve doğal bir polimer gibi görünmektedir.

Anahtar kelimeler: aljinat; antidepresan; duloksetin; giderim; su arıtma

DEDICATION

I dedicate this thesis first and foremost to myself.

I also dedicate this thesis to my family and friends for all their endless love, patience, and kindness. Without their support, I would not be able to arrive this juncture of my life.

ACKNOWLEDGMENT

I would like to thank to my supervisor Assoc. Prof. Dr. Hayrettin Ozan Gulcan. His advice, patience, and motivation from the early stage of this thesis has inspired and enriched my growth as a student.

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AC	Active carbon
APIs	Active pharmaceutical ingredients
Cmax	Maximum plasma concentration
CNS	Central nervous system
CYP	Cytochrome P450
DA	Dopamine
FDA	Food and Drug administration
GABA	gamma-aminobutyric acid
MAOIs	Monoamine oxidase inhibitors
MDD	Major depressive disorder
MOFs	Metal-organic frameworks
NE	Norepinephrine
NSAID	Nonsteroidal anti-inflammatory
OWC	Organic wastewater contaminants
PNCs	Polymer-based nanocomposites
PPCP	Pharmaceuticals and personal care products
PVC	Polyvinyl chloride
SNRIs	Selective norepinephrine reuptake inhibitor
SSRIs	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressant
WHO	World Health Organization
WWTP	Wastewater treatment plant
5-HT	Serotonin

Chapter 1

INTRODUCTION

1.1 Pollution through Drug Removal

It is a known fact that, pharmaceuticals are also an important source of contamination of groundwater and surface (Burke, 2008). As population grows day after day, diseases become more common, and the medications are easier to obtain from all over the world (Comber et al., 2018). Drugs such as painkillers, contraceptives, antidepressants and antibiotics are broadly prescribed and it turns out that they have a huge impact on the pollution of the environment (Jebiwot, 2016). Thus, an urgent attention is required even though the level is not risky inside the water (Luo et al., 2018). Being exposed to drinking unclean water for a long time may create major problem to human immunity by altering the microflora of the digestive tract. Many researches claim that this can be the reason of the decrease in wildlife and affects the ecosystem (Carrington, 2014). In one study, for instance, the presence of ibuprofen (a painkiller) causes a significant failure on the growth of a species *Lemna minor*, eventually disappears from the environment, which is a water plant also called duckweed, proves the effect on the ecosystem (Connors, Lanza, & Sirocki, 2013).

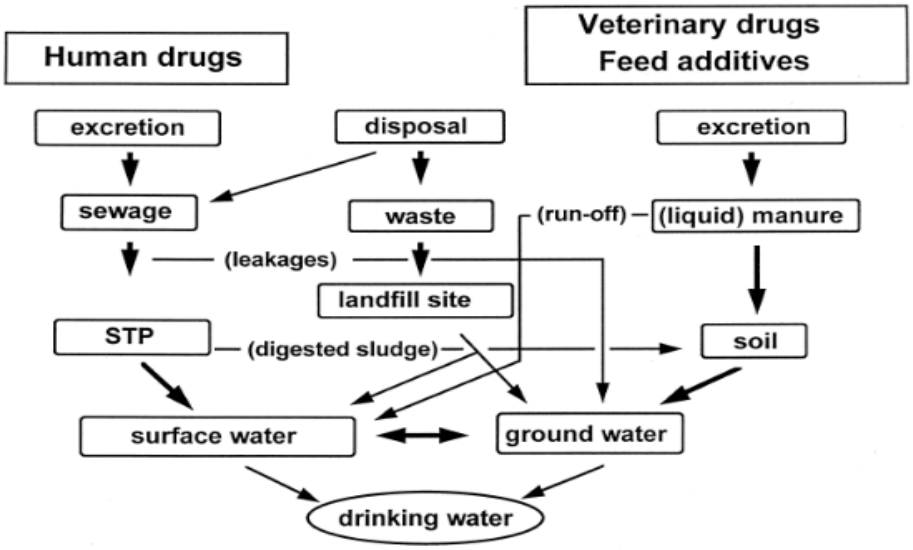


Figure 1: Pharmaceuticals in the environment (adapted from World Health Organization, 2011)

In reality there are several different examples of routes that are indicated in figure 1 to show how drugs ended up in our water supplies (World Health Organization, 2011). Human themselves all have an impact on this, as the ingested drugs are not totally absorbed through the body. In fact, merely a portion of the drug is absorbed. For instance, in a range of 77-85% of ibuprofen, which is a nonsteroidal anti-inflammatory drug (NSAID), is eliminated from the body by urinary tract (Connors et al., 2013) or digestive tract (Luo et al., 2018). Thus the excess intact compounds that are not metabolized, eliminated from the body and goes to sewage directly or indirectly, which eventually ends up to our drinking water (Burke, 2008) (Jebiwot, 2016) even though there are sewage treatment plants (STP) (Monteiro & Boxall, 2010). On the other hand, Prof Joakim Larsson claimed that it is not the excess pharmaceuticals that is flashed through the toilets make the pollution grow but it is the industries that manufacturing drug (Larsson, 2014). Last but not least, hospitals are also responsible for this pollution (Luo et al., 2018).

Actually, the researches state that it is the active pharmaceutical ingredients (APIs) that accumulate in the environment and create a huge risk also to aquatic species (Jebiwot, 2016) (Burke, 2008). Researches also claim that these APIs accumulated as a result of the wastewater treatment plant (WWTP) process (Gonzalez et al., 2014), which is not an efficient process to remove APIs as shown in the figure2.

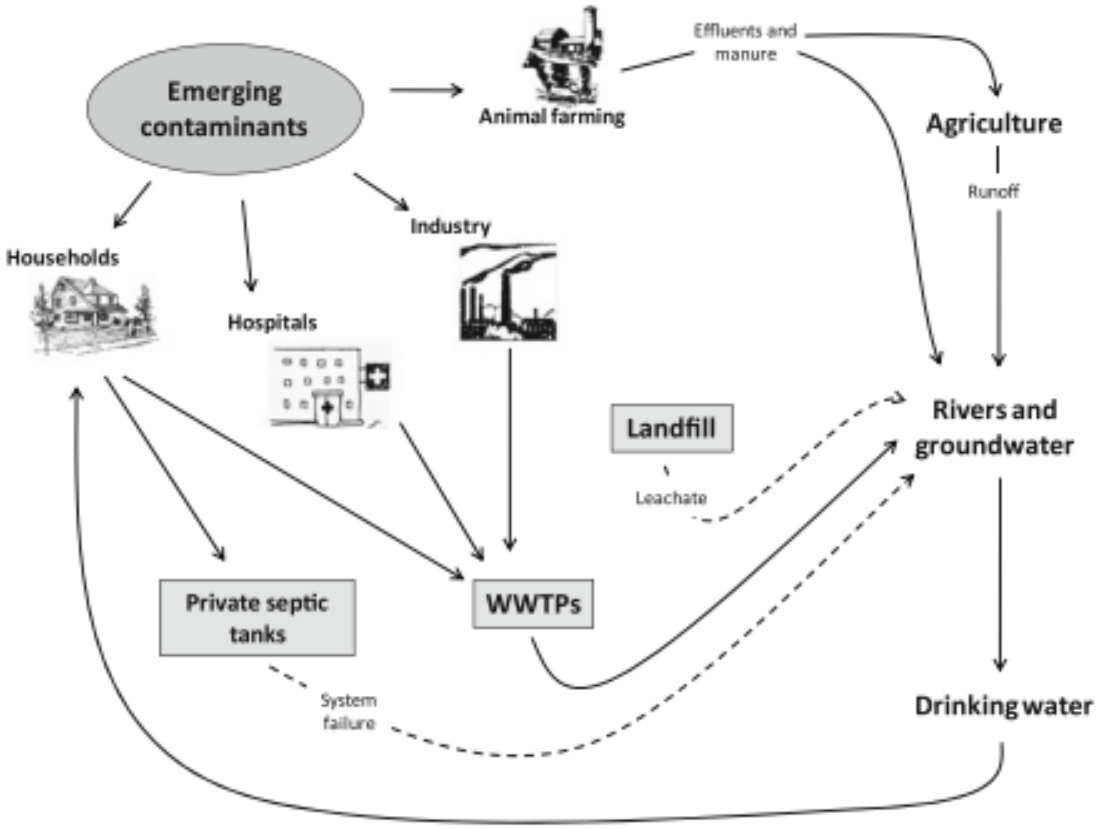


Figure 2: The removal of emerging contaminants from water and wastewater (adapted from Gonzalez et al., 2014)

Moreover, researchers state that APIs started to express resistance to these treatment processes (Blum et al., 2017). More studies claimed that the effluents after wastewater treatments include more pharmaceuticals compared to the patients' bloods. Another study in 2007 indicated a specific antibiotic called ciprofloxacin levels were high enough in effluents to meet the residents of Sweden (Larsson, 2014). Studies in countries that are highly populated such as Germany suggested that

APIs are present in drinking water (Burke, 2008). Even in 2000s a report claimed that US streams have many organic wastewater contaminants (OWC) that provide risk on human wellbeing (Kolpin et al., 2002).

Consequently, it is important to remove the pharmaceuticals from water where it is hard to remove, as it is rely on physical properties as well as chemical properties. Furthermore, typical wastewater treatments were not planned to remove all of the APIs from the water, thus, there are other processes called Ozonation (World Health Organization, 2011) as well as activated carbon (AC) process. Ozonation is the process of oxidation by ozone, which shows respectable results even though ozone levels are low and AC process is when carbon is warmed to stimulate the active sites to attract the contaminants (Burke, 2008). Although AC is known as prevalent adsorbent they have few deficits such as the pollutant uptake takes too much time, the hydrophilic micro pollutant elimination is insufficient and too much energy is needed (500-900°C) (Alsbaiee et al., 2016). More wastewater treatments will be considered in ‘polymers used for drug removal’ section in Chapter 2.

1.2 Antidepressants

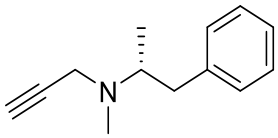
1.2.1 History of Antidepressants

Stress is the indispensable part of our lives. This, if not tolerated well, can cause serious diseases referred to as simply stress related diseases. From this point of view, drugs relieve the symptoms of stress have become significant savers, therefore antidepressant drug employment has reached to enormous numbers day by day. Antidepressant drugs show their activity via different mechanisms, and they are listed below (Lieberman, 2003).

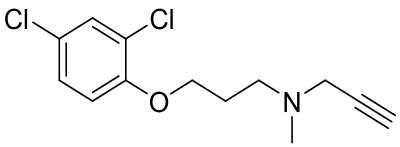
1.2.1.1 Monoamine Oxidase Inhibitors

Dopamine deficiency results in depression symptoms. Dopamine is metabolized by monoamine oxidase, thus this enzyme is a target for the treatment of depression. There are two isoforms of the enzyme, drugs show different selectivity to both of them (Lieberman, 2003).

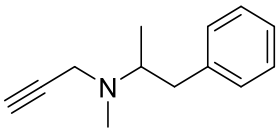
Some representatives of MAO inhibitors:



(2R)-N-methyl-1-phenyl-N-prop-2-ynylpropan-2-amine



3-(2,4-dichlorophenoxy)-N-methyl-N-prop-2-ynylpropan-1-amine



N-methyl-1-phenyl-N-prop-2-ynylpropan-2-amine

Figure 3: Structure of Selegiline, Clorgiline and Deprenyl, respectively.

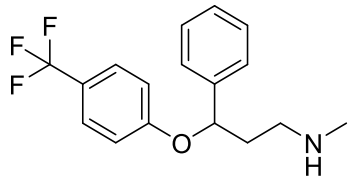
1.2.1.2 Tricyclic Antidepressants

These compounds have 3-fused benzene rings therefore, they are referred to as tricyclic antidepressants (TCAs). Their mechanism of action is complex. They can act on adrenergic, serotonergic, and dopaminergic systems to increase the functions of noradrenaline, serotonin and dopamine, respectively (Bauer, Möller & Schneider, 2006).

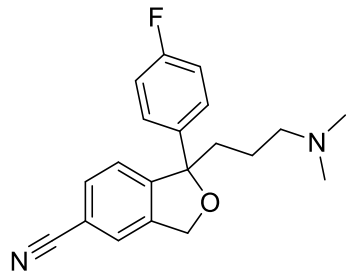
1.2.1.3 Selective Serotonin Reuptake Inhibitor

Selective serotonin reuptake inhibitors (SSRIs) block the reuptake of serotonin into the pre synaptic nerve. This increase the duration of action of serotonin in the synapse that is in turn, aiding to relieve of depression symptoms (Kauffman, 2009) (Hillhouse & Porter, 2015).

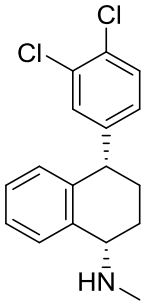
Some representative SSRIs:



N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine



1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-3H-2-benzofuran-5-carbonitrile



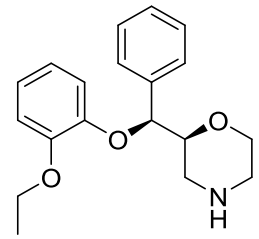
(1S,4S)-4-(3,4-dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine

Figure 4: Structure of Fluoxetine, Citalopram and Sertraline, respectively.

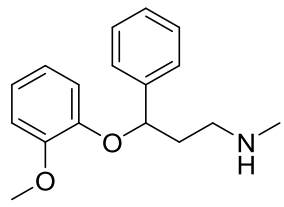
1.2.1.4 Serotonin-Norepinephrine Reuptake Inhibitor

Similar to serotonin, norepinephrine activity is also important to keep the mood under stress conditions. Therefore, in order to increase the efficiency of both serotonin and norepinephrine neurotransmitters SNRIs are utilized, which is why they are called dual action antidepressants. These compounds inhibit the reuptake of norepinephrine as well as serotonin into the pre synaptic nerve. This increases the duration of action of these neurotransmitters in the synapse (Hillhouse & Porter, 2015).

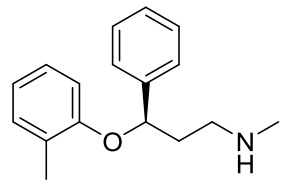
Some representative SNRIs:



(2S)-2-[(S)-(2-ethoxyphenoxy)-phenylmethyl]morpholine



3-(2-methoxyphenoxy)-N-methyl-3-phenylpropan-1-amine



(3R)-N-methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine

Figure 5: Structures of Reboxetine, Nisoxetine, and Atomoxetine, respectively.

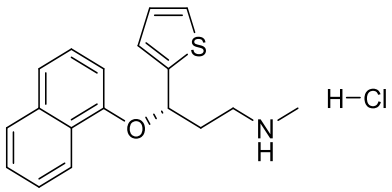
1.3 Duloxetine Hydrochloride

An antidepressant drug called duloxetine hydrochloride is used for anxiety disorders (ADs) also called as generalized anxiety disorder (GAD) (Berardis et al., 2008) and depression in human, which is known as major depressive disorder (MDD) (Ogbru, 2017). GAD is a condition, which is prolonged with parallel loss of functions as in MDD. Most importantly it is clinically confirmed that duloxetine hydrochloride is a primary care for managing GAD (Carter & McCormack, 2009). MDD affects the social functioning of the individuals as it causes not only once but repeating episodes of depression (4.1%) (Hillhouse & Porter, 2015). This antidepressant is also used to treat people with diabetes, or a condition that causes extensive pain (such as arthritis or chronic muscle pain) to comfort the nerve pain (Fitzcharles, Lussier & Shir, 2010). Moreover, in the previous years, it has been indicated that duloxetine has the potential for the treatment of pain in Parkinson's disease (Djaldetti et al., 2007). It helps to patient to recover the unstable mood and sleep. Also their hunger and energy levels were increased while their anxiety decrease. As SNRI, duloxetine hcl, serves to reestablish the amount of neurotransmitters 5-ht and NE in the brain while display almost no interest in dopaminergic, cholinergic and gamma-aminobutyric acid (GABA) receptors (Delgado, 2009).

Duloxetine is derived from fluoxetine that is belong to SSRI class as it is mentioned before. With the hydrochloride salt duloxetine is named as duloxetine hydrochloride which is the one that is used in this thesis. There are other medicines, which involves in this SNRI classification named as venlafaxine, milnacipran and desvenlafaxine with the brand names Savella, Effexor and Pristiq, respectively (Ogbru, 2018).

1.3.1 Structure

Chemically known as (S)-N-Methyl-3-(naphtalen-1-yloxy)-3-(thiophen-2-yl) propan-1-amine; hydrochloride and it is shown below in figure 6. With the $C_{18}H_{20}CINOS$ molecular formula, duloxetine hydrochloride has 333.874g/mol molecular weight.



(3S)-N-methyl-3-naphthalen-1-yloxy-3-thiophen-2-ylpropan-1-amine;hydrochloride

Figure 6: The structure of Duloxetine HCl

1.3.2 Prescription and Precautions

It has been noted that both generic name (duloxetine) and brand name (Cymbalta) drug are available (Procyshyn, 2017) for oral administration (Brunton, Chabner & Knollman, 2010). Patients should rely on doctors' advices however normally it should be taken 1 or 2 times during the day without depending on being full or hungry. It is an oblong, delayed-release capsule; available as 20, 30 and 60mg (Ogbru, 2018 & Procyshyn et al., 2017). Relating the age of the patient the dosage can be different. Doctors may advice to start from the lower doses and increase in particular periods to decrease the intensity of the side effects. Like every other antidepressants it has been noted that if the patient stops to take the drug all of a sudden when he/she feels healthy again, then he/she will encounter with much more badly side effects (Procyshyn et al., 2017).

1.3.3 Side Effects

The doctors and patients who are using it are warned by the Food and Drug administration (FDA) as the drug itself is in black box warning list. It has serious side effects like having suicidal thoughts and actions (Kuehn, 2007). On the other hand, it has been stated, that there are patients that have not encounter any of the side effects and it is usually easy to tolerate. Here below usually seen side effects were given in the form of bullet points.

- Nausea
- Headache
- Dry mouth
- Constipation
- Dizziness
- Loss of appetite
- Tiredness
- Drowsiness
- Increased sweating
- Diarrhoea

The drug duloxetine sometimes raise the levels of 5-HT too much, which may cause a severe situation known as serotonin syndrome (toxicity). There are other serious side effects as well such as damaging liver, changing in blood pressure, problems on vision and with urination and sexual dysfunction (Procyshyn et al., 2017).

1.3.4 Clinical Pharmacokinetics of Duloxetine HCl

The maximum plasma concentration (C_{max}) of duloxetine after 6 hours later is 47ng/mL if the dose is 40 mg twice a day. If the dose is 80 mg C_{max} it is 110ng/mL (Knadler et al., 2011). C_{max} is also called peak plasma concentration, peak height concentration or maximum drug concentration and it is the maximum level of concentration that a drug achieve in plasma which relies upon dose administered, rate of absorption and rate of elimination. The maximum level shows that the rate of absorption is equal to rate of elimination of drug (Brunton, Chabner & Knollman, 2010). The half-life and the distribution volume of duloxetine are stated as 10-12 hours and 1640 L, respectively. The pharmacokinetics of duloxetine is changeable according to age, sex, ethnicity, smoking, cytochrome P450 (CYP) enzymes and hepatic and renal function. It is confirmed that the concentration of duloxetine decline by 30% when the patient is smoking. In addition, when the genotype CYP 1A2 is inhibited the release of duloxetine inclined critically. Also, the release of duloxetine is increased with the CYP2D6 metabolized drugs (Knadler et al., 2011).

1.4 Objective of the Thesis

There is emerging need and interest to find solutions regarding the pollution caused by pharmaceuticals. Based on the fact that pharmaceuticals have a diverse nature of structures, it is not possible to come up with a single solution covering each pollution caused by a different drug. From this point of view, the chemical structure of each, total industrial production of each drug, total worldwide utilization of each drug, prescription non-prescription status of each drug, those regimen of each drug, and hospital utilization become important parameters in order to estimate the significance and the range of possible pollution caused by a single drug molecule (Rivera-Utrilla et al., 2013).

Antidepressants, like antibacterial agents and overall contraceptives, are important group of pharmaceuticals with a worldwide utilization. Regarding the worldwide utilization of antidepressants and their over the counter status in the majority of the world the pollution caused by these agents is reaching to critical levels day by day. The effect is not only to human kind but also to any living system within the environment. Trash of unused drugs, toilet waste following drug administration to human kind, and industrial waste are among them the major sources (Jones, Voulvoulis & Lester, 2007).

Duloxetine is one of the new agents in the antidepressant group of drugs. It has a worldwide utilization. It is offered with 30-60 mg dose regiment, therefore, each duloxetine drug product (package) contains around 1g of the compound. Beside major depressive disorder it has indications in some neuropathy and stress related urinary incontinence (Norton et al., 2002). From this point of view, duloxetine

pollution to the environment is reaching to alarming levels (Minguez et al., 2016). Within this study, we try to identify the interaction of duloxetine molecule, with alginate polymers. We initially considered that the main functional group in duloxetine (i.e., secondary amine) is very suitable to interact with carboxylic acid residues abundantly available in alginate polymer. From this point of view, we have prepared alginate polymer beads and investigated the duloxetine binding to this polymer. The application of our study is not only important for aiding in duloxetine pollution treatment but also for other amine containing drug molecules.

Chapter 2

LITERATURE REVIEW

2.1 General Information about Polymers

2.1.1 Definition of Polymers

Many repeating small molecules that are called monomers cluster together to form a large molecule, called polymers. In other words, polymers are defined as long repeating chains that are comprised of simple monomers, usually connected by covalent bonds. Originally, the term polymer comes from a Greek word that is polymeros (poly means many and meros means parts). A macromolecule alternatively, is another term that is used instead of polymer by some scientists. For example ethylene is a monomer and by polymerization it becomes polyethylene (Cowie & Arrighi, 2007) (Namazi, 2017).

2.1.2 Classification of Polymers

Table1: Classification of polymers (adapted from Young & Lovell, 2011)

Based on origin of source	**Based on structure**	**Based on molecular forces**	**Based on mode of polymerization**
1-Natural polymers	1-Linear polymer	1-Elastomers	1-Addition polymers
2-Semi-synthetic	2-Branched chain polymer	2-Fibres	2-Condensation polymers
3-Synthetic polymer	3- Cyclic polymer	3-Thermoplastics a-crystallites b-amorphous	
	4- Network polymer	4-Thermosetting polymers	

Based on origin

Polymers can be described in three classes: natural, synthetic polymers or semi-synthetic polymers. The ones that are found in nature and also can be extracted from the nature are called natural polymers. Agar, starch, gum etc are the examples for plant origin, while chitin, alginate psyllium etc. are animal origin natural polymers. The plastics that made from artificial components by human are defined as synthetic polymers. Polyethylene, polyester, silicone, polystyrene, polyvinyl chloride (PVC) etc. are all the examples for synthetic kind of polymers. Modification of physical properties of natural polymers by chemical treatment in order to be commercialized is described as semi synthetic polymers and an example can be vulcanized rubber (Young & Lovell, 2011).

Based on structure

Although polymers are indicated as long chains and it is seemed to be they are linear polymers, there are different skeletal structures of polymers, which are shown in the figure 12.

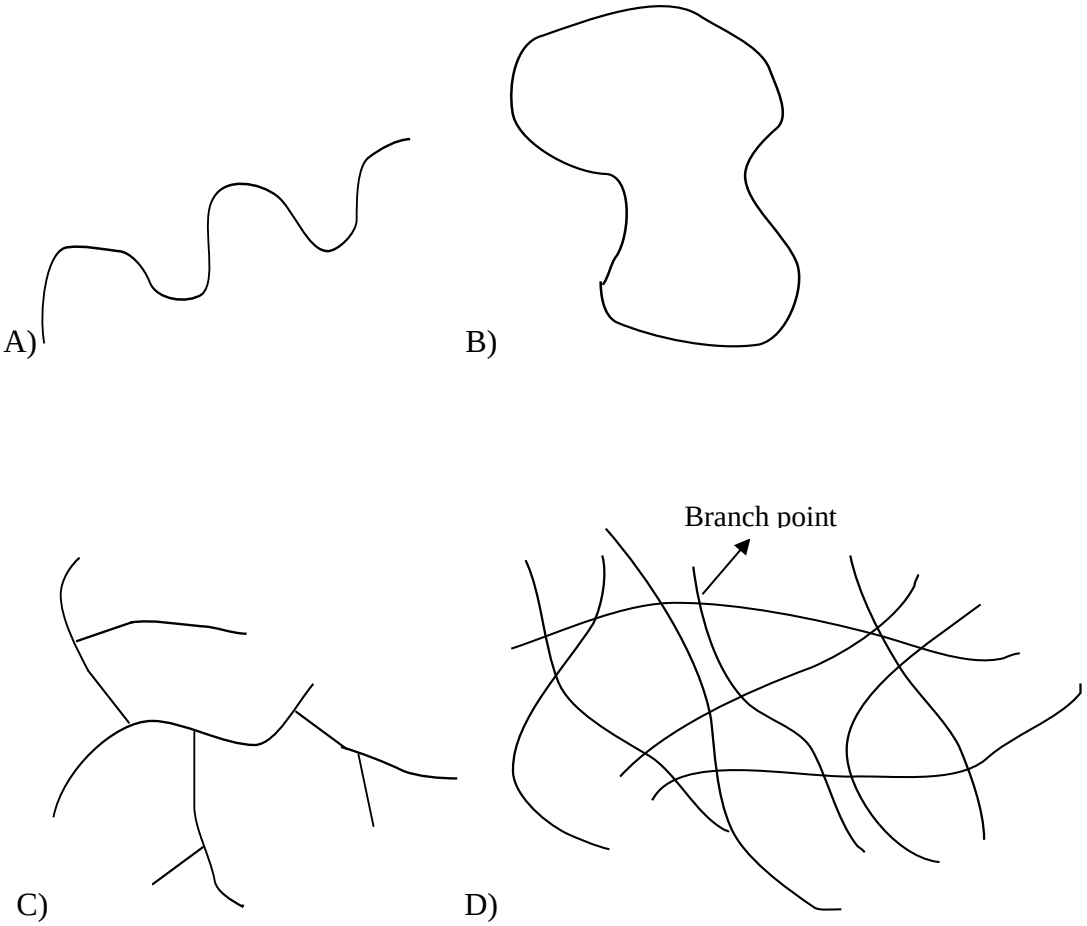


Figure7: Structures of polymers; A) Linear polymer B) Cyclic polymer C) Branched polymer D) Network polymer (adapted from Young & Lovell, 2011)

Cyclic polymers are not linear and have no chain ends opposite to linear polymers. There are also branched polymers that have side chains with different lengths, which are connected to main chain. The size and number of their branches describe these kinds of polymers. Moreover, there are 3D polymers, which are known as network polymers. In these polymers by a sequence of junction points (branch points) one chain can be bonded to more than one chain more than once, which means they are crosslinked. Thus, crosslink density defines the network polymers, which is the same with the number of junction points. By the process called polymerization branched and network polymers are existed. By polymerization, any alteration in the structure of these polymers brings out to significant changes in terms of properties. For instance, synthetic polymer polyethylene has higher melting point when it is in linear

structure compared to branch form. Additionally, although network polymers are swell reasonably in suitable solvents but they do not melt or dissolve when heating up. A product can be flexible or rigid according to crosslink density, shows the importance of degree of crosslinking. For example, natural rubber with low levels of sulphur-crosslinking density will be a flexible material whilst, when the sulphur levels are high it will be rigid material (Young & Lovell, 2011).

Based on polymerization

By different types of polymerization process different polymer types can occur. First type of polymerization is called addition polymers, which is produced by connecting the same type monomers for instance,-[A-A-A-A-A-A]-. The addition polymerization will be completed in three stages; initiation, propagation and termination. Process also involves radical polymerization without losing any molecule.

However, on the other hand, condensation polymers produced by different monomer units (it can be two or three) by using molecules like H_2O and it can be shown like –[C-A-C-A-C-A] which is called copolymers. If amide bonds, ester bonds and carbonate bonds are produced by the condensation polymerization they are called polyamides, polyesters, and polycarbonates, respectively (Hiemenz & Lodge, 2007).

Based on molecular forces

Elastomers are called for the polymers that have elastic property such as rubber. When these polymers are stretched they are capable to turn back to their normal shape as the van der Waal forces are weak and cannot keep them in that shape.

On the other hand, fibers can be used in textiles, as they are thread like polymers. They have high tensile strength, as strong hydrogen bonds are their intermolecular forces. Silk, wool and cotton can be the examples for this class.

Interestingly, thermoplastics monomers are connected together with van der Waals forces as well. These polymers are tough if they are arranged in an order. If the monomers are arranged together in an order, the region is called crystallites and if they are aligned irregularly it is called amorphous. These thermoplastic polymers arranged in both ways which means they have both regions that are crystalline and amorphous. It is important to note that, heating thermoplastic polymers become soften where at room temperature they are solid. Examples can be: Polystyrene and Teflon.

Comparing to other polymers, which are identified by molecular forcers, thermosetting polymers are the ones that are strongest among the others because their monomers are connected with strong covalent bonds. They are network polymers with high levels of cross linkage, which makes them more rigid and more brittle. If a force is applied on, it cannot be reused (Young & Lovell, 2011).

2.2 Polymers in our Life

In fact, polymers are present ever since life has started to begin and they have a critical role in animal and also in plant life, as they are DNA, RNA, and proteins. Moreover, polymers have being used in decoration and as a shelter decades ago since they are occurring naturally. Still in our daily life we are using synthetic polymers such as plastic bags (Young & Lovell, 2011). Furthermore, as it is mentioned before Teflon is thermoplastic polymer nowadays is used in our kitchen as a cookware coating. We have cloths that are made from i.e. Synthetic fibers (Namazi, 2017). It has been claimed that the polymer manufacturing is already higher than aluminum manufacturing (Karak, 2009).

2.3 Polymers used for Drug Removal

On earth, there is plenty of water. However, in order to use the water resources for drinking, purification is crucial before it has been discharged. There are lots of studied methods and ways for treating wastewater with polymers and here below is listed some, according to years.

The process called coagulation was involved in wastewater treatments ever since before 1900s. It is the process where small particles join to form large flocs (aggregates) for adsorbing organic materials that are dissolved and settling for the elimination. In order to improve the coagulation process and place more efficient coagulants, complex polymeric coagulants were established for water and wastewater treatment. Mixing polymeric aluminum and/or iron (Al/Fe) modifies the clay based montmorillonites (K10 and KSF) verified that the new two K10 and KSF montmorillonite coagulants have better characteristics to increase the impurities to settle and to eliminate the impurities and organic pollutants from raw sewage

(coagulation). Flocculation, which is the similar form of coagulation, settles out the contaminants by specifically adding polymers that can be non-ionised, ionized, anionic, cationic, or an amphoteric with different composition of polar groups (flocculants). The ionized flocculants are known as soluble polyelectrolytes (Radoiu et al., 2003).

In 2010 polymers as a membrane purification systems were suggested. The system has two membranes, which membrane one is for pre-treating the particles and membrane two is for disconnecting the salt by reverse osmosis. The process involves addition of chlorine, control of pH levels, and particle flocculation before the first membrane. After the pre-treatment dechlorination and second control of pH levels were available. Membranes can be covered with hydrophilic moieties so that water will intensely bind to the membrane surface. In those days the scientists claimed that this process would bring the innovation to polymer chemistry (Geise et al., 2010).

In another study, pharmaceuticals and personal care products (PPCP) contaminants, which as it is said before it is the world's new environmental problem. Therefore, in order to remove the PPCP lots of materials were built. However, polymers are the interest of this thesis. In 2013 coordination or network polymers also called as metal-organic frameworks (MOFs) are made from metal ions that are linked together by organic ligands and has numerous characteristics such as porous structure, high relative surface area, magnetism and luminescence. Up until these days MOFs were being used in drug delivery as well as used as absorbent for eliminating pharmaceutical contaminants, dye, metal ions and organic solvents. Therefore, it is important to note that diclofenac sodium and chlorpromazine hydrochloride

compounds that are the most common pollutants of PPCP, is successfully removed by porous copper based MOF (Luo et al., 2018).

Fascinatingly, in 2014 natural polymers were used in a study, which are cellulose, chitosan, and sodium alginate. They are compared with the synthetic polymers, which are made from copolymers of urea and epichlorohydrin. These polymers were selected as they have high numbers of amine groups, which can be connected with the functional groups of antibiotics present in the water by hydrogen bonds. It has been noted that the likelihood of synthetic polymers compared to natural polymers to form hydrogen bonds is greater; because of the two nitrogen atoms, which allows better chance to form hydrogen bonding instead of amino group. Having this as an advantage the investigators confirmed that the synthetic polymers are better at removal of pharmaceuticals by adsorption by eliminating 75% of the drug in 6 hours. Furthermore in the study, they examine chitosan and alginate in the form of blending, which helps to stimulate the removal of the drug more easily. In theory, for alginate it is easy to uptake the drug as its carboxylate groups form hydrogen bonds, interacting with the drug. However, it was confirmed that alginate alone or with chitosan or even with the synthetic polymers has no effect in the improving the removal of drug while chitosan with synthetic polymers displayed the best results. Further investigation of recycling of beads has been studied by examining the release of the drug to water from the beads that are loaded with drugs. It has been confirmed that 9% of drug was returned back to distilled water (Ahmed et al., 2014).

In 2016, a group from Cornel University suggested that when β-cyclodextrin is crosslinked with rigid aromatic groups producing higher surface area and mesoporous polymer the micro pollutants eliminated. Thus they suggested that this

finding could be useful in flow-through water treatment as the polymer of β-cyclodextrin shows fast attachment with the range of organic contaminants with adsorption. Moreover, this polymer can be renewed more than once by the technique of slight washing without losing any performance (Alsbaiee et al., 2016). Also, it is important to mention that with adsorption method, fluoxetine hydrochloride; an antidepressant drug can be removed by β-cyclodextrin carboxymethylcellulose polymer from wastewater as they are interacting (Bonenfant et al., 2012).

In 2017, researchers stated that nano particles could purify the water from contaminants as they have high surface area however; its agglomeration limits the use. Therefore, nanomaterials converted to nanocomposites, which can be used for decontamination of water. Nanocomposites are described as 21st century constituents. They have lots of phases and one of them is in the nano range (10-100 nm). They can be divided in two different classes, which are non-polymer based and polymer based nanocomposites. In early years, the polymer-based nanocomposites (PNCs) are the most studied area as they have wide range of useful characteristics. For example, they have the ability to form film, flexibility in dimensions and functionally active (Pandey, Shukla & Singh, 2017).

2.4 Alginate Polymer

2.4.1 Alginate Chemistry

Alginates are non-toxic and biodegradable polymers that are extracted from brown algae cell walls such as *Macrocystis Pyrifera*. These naturally occurred alginates are anionic linear copolymer polysaccharide consisting two monomers that are 1,4-linked β-D mannuronic acid (M) and 1,4- α-M guluronic acid. A differ in composition of these two residues will eventually change the characteristic property of the alginate. For instance, increasing the G block residues in an alginate makes an alginate unbreakable whilst, increasing the M blocks produce elastic alginates. Thus, the ones that are for commercial use have an alteration of the arrangement of M and G residues and their molecular weight changes between 33000 and 400000 g/mol. Last but not least, the solubility of alginates differs according to the residues as well. For example, if the structure of alginate is heterogeneous then it is more soluble compared to the homogeneous alginates at low pH (Szekalska, 2016).

2.4.2 Alginic Acid Derived Polymers

The term Alginic acid derivatives are being used for Alginic acid and its salts, which are sodium alginate, calcium alginate, ammonium alginate and propylene glycol alginate. Information will be given for sodium alginate only as it is the interest of the thesis and also it is the most, examined one among other alginates. Sodium alginate (NaAlg) extraction has numerous stages but it is not complex. An algal material is treated with mineral acid. After this stage alginic acid is switched to sodium salt that is water soluble with the company of sodium carbonate. Finally, it is transformed into its salt sodium alginate with further purification (Szekalska, 2016).

2.4.3 Biological Applications of Sodium Alginate in Pharmaceutical Products

Sodium alginate is available both for oral and topical use. In pharmaceutical products, for oral administration, Gaviscon Double Action tablets® has 250 mg sodium alginate as a main ingredient in order to relieve heartburn and protect esophagus, forming barrier (Thomas et al., 2014). For dermal application, a pharmaceutical product with the brand name Guardix-SG® used as a barrier after operations such as thyroid surgery to prevent any further complication (Park et al., 2013).

All of the derivatives have important role in pharmaceutical industry. Among the others, sodium alginate has been used as a diluent in capsule formulation, viscosity increasing agent and a tablet binder. Moreover, as alginates have unique properties such as ability to make viscous solutions and ability of sol/gel transition they are capable of variety of applications. They are all used in food industry as a texturizer, stabilizer and thickener. For instance, sodium alginate is used in pastas and creams (Szekalska, 2016).

By different type of modifications in their structure different biomedical applications are available. For instance, by chemical modification, oxidation, NaAlg becomes oxidixed-NaAlg which is used in the improvement of corneal wound healing therapy (Wright et al 2013).

Chapter 3

EXPERIMENTAL

3.1 Materials

Sodium Alginate salt was purchased from Sigma Chemical Co. (1% w/v aqueous solution at 25 °C), Glutaraldehyde (GA) (25% w/w) from Merck Germany, Hydrochloric acid solution (37 %) and methanol were supplied by Sigma Aldrich, Germany. Ultrapure deionized water was used to prepare solutions and all chemicals used for this thesis work were used without any further purification. Duloxetine hydrochloride was kindly provided by the Ilko Ilac Sanayi (Ilko Drug Company), Konya, Turkey.

3.2 Methods

Preparation of the Crosslinked Alginate beads

A 4% sodium alginate solution was prepared by adding 4g of sodium alginate powder in 100 mL distilled water followed by gentle heating and magnetic stirring to enhance dissolution. After cooling, the alginate solution was added drop-wise into a crosslinker solution containing a mixture of methanol, 1% glutaraldehyde and 1% 1 N HCl, using a 25-ml hypodermic syringe (1 mm diameter) under constant stirring. The beads formed immediately on contact with the crosslinker solution and were left in the crosslinking solution for 60 minutes to further enhance crosslinking. Unreacted glutaraldehyde that adhered to the surface of the beads were washed off repeatedly with distilled water before drying the beads in an oven at 30 °C.

3.3 Drying Rate of the Beads

Nearly equal weight of crosslinked beads were collected and dried at 30℃ in a Vacucell vacuum drying oven. In different time intervals, their weight is measured on a Shimadzu Model analytical balance and used for plotting the graph shown in figure 8.

3.4 Swelling of the Beads

The equilibrium swelling degree of the crosslinked alginate beads was determined using the gravimetric method. To achieve this, known mass of the beads were immersed in buffer solution (pH 7.4) at 37 ˚C. To ensure complete equilibration, the beads were left in the buffer solution and allowed to swell for 48 hours. Thereafter, the excess liquid adhering to the surface of the wet beads was removed by blotting with a filter paper before weighing the swollen beads using an electronic balance. The already swollen beads were then re-dried in an oven at 30 ˚C until a constant mass was obtained.

The equilibrium swelling percentage of the beads (%) was calculated using equation (1) below:

$$Equilibrum\ swelling\ degree\ \% = \frac{M_s - M_d}{M_d} * 100 \qquad (1)$$

Where; M_s and M_d represent the mass of both the swollen and dry alginate beads respectively.

3.4 Bead Size Measurement

Ten random samples of the completely dried alginate beads were selected and their sizes were determined using a micrometre screw gauge (Sargent, USA) with an accuracy of ± 0.01 mm.

3.5 DLU Adsorption Experiments

The adsorption of aqueous DLU solution (initial concentration of 25 mg/L) was undertaken by adding 0.25g of crosslinked alginate beads into 50 mL of drug solution. The effect of time (5 – 1200 minutes) and dosage (0.015 - 0.35 g) was also investigated to determine optimum time and dosage required for maximum adsorption of DLU. All adsorption experiments were performed in the laboratory using 150 mL stopped flasks at 25± 1 °C and atmospheric pressure with vigorous agitation (250 rpm) using a mechanical shaker. At pre-determined time intervals, the supernatants were filtered employing a 0.45 μm membrane. The amount of DLU in the liquid phase was determined using Ultraviolet Spectroscopy (λ_{max}: 288 nm). All experiments were made in triplicates and the average value(s) obtained from each experiment was reported.

DLU uptake capacities (mg/g) with respect to time and removal percentage (%) were then calculated using equations (2) and (3):

$$q_t = \frac{C_i - C_t}{mass} * Vol \qquad (2)$$

$$Removal\ \% = \frac{C_i - C_t}{C_i} * 100 \qquad (3)$$

Where C_i and C_t in mg/L represent the initial DLU concentration and DLU concentration at pre-determined time *t*, volume of DLU is in Litres and mass of crosslinked alginate beads is in grams.

3.6 Experiments on the Adsorption Kinetics of DLU

The pseudo first-order and second-order kinetic models have been used to fully understand and identify the mechanism(s) behind the adsorption process. In this study, both models were applied to the experimental data obtained to determine the

model that best describes the adsorption process of DLU onto the crosslinked alginate beads.

Both kinetic models can be expressed using Equation (4 and 5):

$$In(q_e - q_t) = q_e - K_1 t \qquad (4)$$

$$\frac{t}{q_t} = \frac{1}{qe^2 K_2} + \frac{1}{q_e t} \qquad (5)$$

Where; q_t is the amount of DLU adsorbed onto the alginate beads at time *t*, q_e is the amount of DLU adsorbed at equilibrium, k_1 and k_2 are the pseudo first order and second order rate constants for adsorption. Calculated values of q_e, k_1, k_2 for both models were evaluated from their linear plot (In (q_e-q_t) vs t for first order and t/q_t vs t for second order kinetic model) and compared to the experimentally obtained values. The model that shows the best fit based on R^2 values (regression coefficient) close to 1 is assumed to be the accepted model for the adsorption process.

3.7 Determination of Adsorption Isotherm Constants

Adsorption isotherms provide the relationship between the amount of pollutant absorbed on the solid phase (adsorbent surface) and the solute concentration remaining in solution when the two phases are at equilibrium (Zhu et al., 2012). Two adsorption equilibrium isotherms relating to DLU adsorption onto the crosslinked alginate beads were tested in this study namely, Langmuir and Freundlich isotherm.

The Langmuir isotherm suggests monolayer coverage and homogeneous surface of adsorbent with the assumption that each site on the adsorbent surface can only absorb one molecule of pollutant. The adsorption sites are also assumed to have sites of

uniform energies for adsorption (Baccar et al., 2010). Linearized form of the as-said isotherm is given in equation (6).

$$\frac{C_e}{q_e} = \frac{C_e}{q_m} + \frac{1}{q_m K_L} \qquad (6)$$

An important characteristic of the Langmuir isotherm is the dimensionless separation factor R_L (eq. 7), which indicates if the adsorption process is favourable or not. R_L values of 0 and greater than 1 represents irreversible and unfavourable adsorption, respectively while values between 0 and 1, signify a favourable adsorption process.

$$R_L = \frac{1}{(1+C_o K_L)} \qquad (7)$$

The Freundlich isotherm on the other hand suggests a heterogeneous (multilayer) surface of adsorbent with different binding energies i.e. a non-uniform sorption energy distribution on adsorbent surface (Hazzaa & Hussein, 2015). The adsorption of DLU onto the crosslinked alginate beads was also fitted using the Freundlich isotherm. The simple form of the empirical Freundlich's model is given in eq. 8.

$$q_e = K_F C_e^{\frac{1}{n_f}} \qquad (8)$$

Where q_e was previously described (Equation (4)), the parameters define:

C_o: The initial concentration of DLU

C_e: The concentration of DLU at equilibrium in liquid phase

K_F and $1/n_f$: The Freundlich distribution and linearity coefficients, respectively.

The Freundlich constants K_F which gives valuable information about the bond energy between adsorbent and adsorbate while 1/n which is related to adsorption intensity

can be readily obtained from the plot of the linearized form (eq. (9)) of the Freundlich isotherm equation:

$$logq_e = logK_F + \frac{1}{n_f} logC_e \qquad (9)$$

3.8 Characterization by UV-Vis Spectroscopy

DLU stock solution of 1000 mg/L was prepared by dissolving the required amount of drug in distilled water. The concentration of DLU in solution was then analysed using a T90+ UV/vIS Spectrophotometer with a 1 cm quartz cuvette. DLU concentrations in the supernatants were calculated from a standard calibration curve (Figure 12) obtained after serial dilutions of the aqueous DLU stock solution at 288 nm (Λ_{max}: maximum adsorption peak of DLU).

3.9 Characterization by FT-IR Spectroscopy

FT-IR spectral measurements were obtained to identify if there was any chemical interaction between the drug, sodium alginate and crosslinking agent. Infrared spectra of DLU drug, sodium alginate powder, dried crosslinked alginate beads and DLU adsorbed alginate beads were obtained using a Perkin Elmer Universal ATR TWO FT-IR spectrophotometer. FT-IR spectra of all samples in figure 11 were recorded in the range of 4000 – 550 cm^{-1} with a resolution of 2 cm^{-1}.

Chapter 4

RESULTS AND DISCUSSION

4.1 Characterization of the Crosslinked Alginate Beads and DLU Adsorbed Alginate Beads

4.1.1 Drying Rate of the Beads

Approximately equal weight of beads were chosen and placed into an oven at 30°C. In different time intervals, the beads were taken from the oven and the weight was measured. Results shown in figure 8 indicate that the beads dried completely after 70 hours.

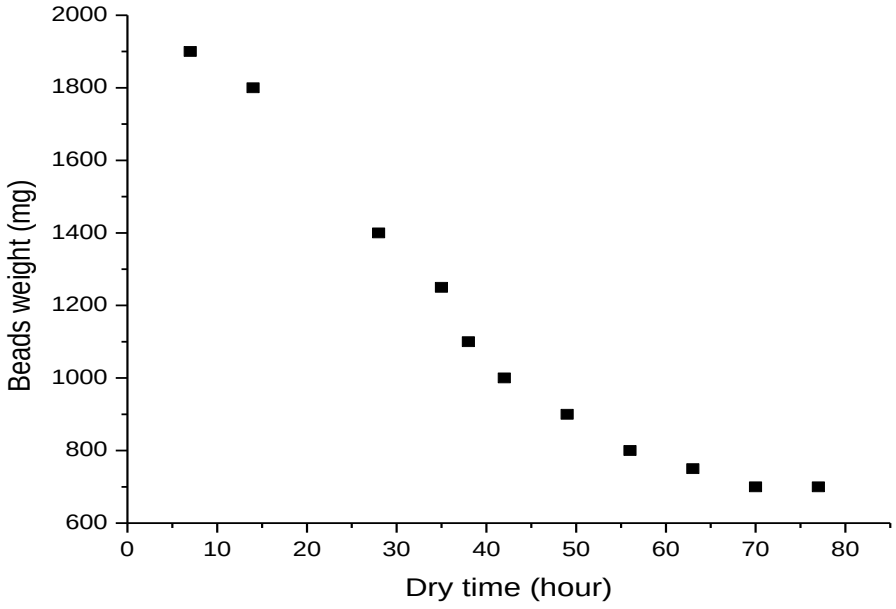


Figure 8: Drying time of beads

4.1.2 Swelling of the Beads

The swelling behaviour of the glutaraldehyde crosslinked sodium alginate beads in buffer solution (pH 7.4) at 37 °C was investigated. The basic reason for the employment of pH 7.4 is mainly related to keep carboxylic acids of alginate in carboxylate form regarding the pKa of carboxylic acid. This pH definitely guaranties the status of carboxylic acid in carboxylate form, while making the amine group of duloxetine protonated that is in turn, triggering a possible ion-ion type interaction. On the other hand, gluteraldehyde crosslinking possibly yielding out hemichetal is also stabilized at this pH, since lower pH can facilitate chetal degredation back to aldehyde, given damage to crosslinking. After attaining equilibrium, the maximum swelling % of the beads in the buffer solution was found to be 1400 %. The relatively high swelling obtained in this study is due to the fact that sodium alginate is a hydrophilic polymer with a high water uptake capacity as seen in previous studies (Shi et al., 2006; Tahtat et al., 2017). At pH 7.4, the carboxylic acid (COO^-) present in the polymer backbone are fully ionized and interact with the H^+ ions in water which acts as a bridge resulting in increased swelling of the beads (Shi et al., 2006). From figure 9 it is clear to see that the maximum adsorption occur in the first one hour.

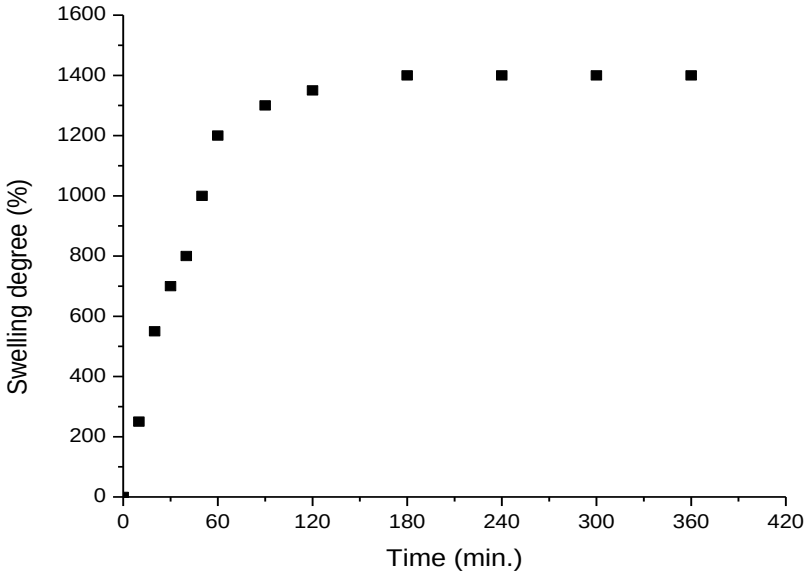


Figure 9: Swelling of the NaAlg beads

4.1.3 Bead Size Measurement

Figure 10 below shows the image of the crosslinked alginate beads immediately after washing with distilled water before drying and after loading DLU with the aid of a microscope (Model Olympus cx31). The crosslinked alginate beads formed were found to be almost spherical in shape with an average diameter of ±0.5 mm.

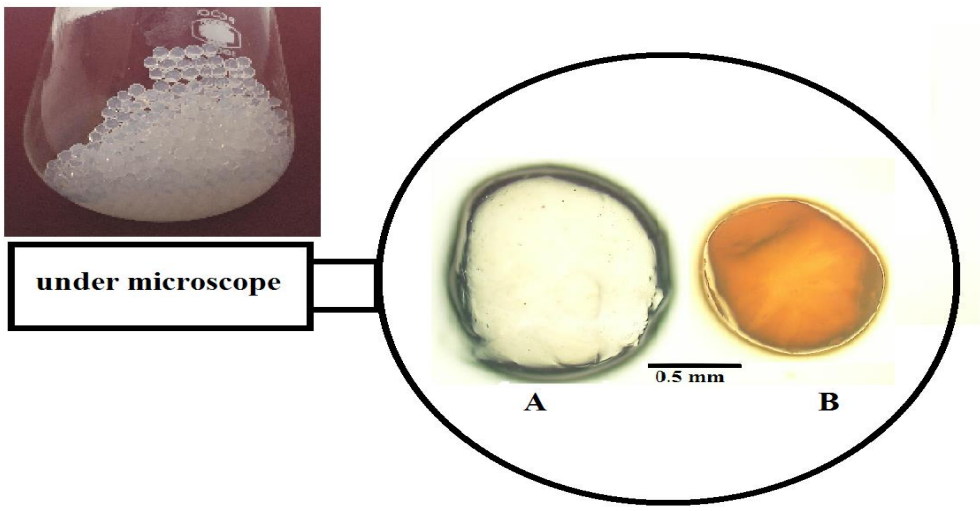


Figure 10: Microscopic pictures of (A) NaAlg and (B) DLU-loaded NaAlg bead.

4.1.4 FT-IR Spectra of Samples

An FT-IR spectrum of DLU drug, sodium alginate powder, crosslinked alginate bead and alginate-DLU drug is depicted in Figure 11. As seen from the FT-IR spectra of DLU, broad peaks between 3000 and 2800 cm^{-1} represent the N-H and C-H vibrations, respectively. Peaks obtained at 1600 and 1450 cm^{-1} represent the skeletal vibrations of both the thiophene and naphthalene rings present on the backbone of DLU while the phenoxy and alkyl C-O vibrations were seen at 1200cm^{-1} and 1050 cm^{-1}. Several peaks observed around 700 cm^{-1} was due to the aromatic C-H bending of the thiophene and naphthalene rings. Similar observations have been reported in literature (Mani et al., 2014).

In the case of sodium alginate powder, three major peaks were observed around 1600, 1400 and 1000 cm^{-1} which represent the asymmetric, symmetric carboxylate salt groups (COO^-) and C-O-C stretching vibrations respectively (Papageorgiou et al., 2010).

A new peak found at 1740 cm^{-1} in the crosslinked alginate bead was due to the C=O of the aliphatic aldehyde. The result obtained from the FT-IR measurements confirms the crosslinking of the alginate with glutaraldehyde (GA). Furthermore, no new peaks were found after adsorption of the drug by the crosslinked alginate beads i.e. alginate-DLU. This indicates the absence of any chemical interaction between the adsorbent and DLU implying that the removal is most probably a physical process.

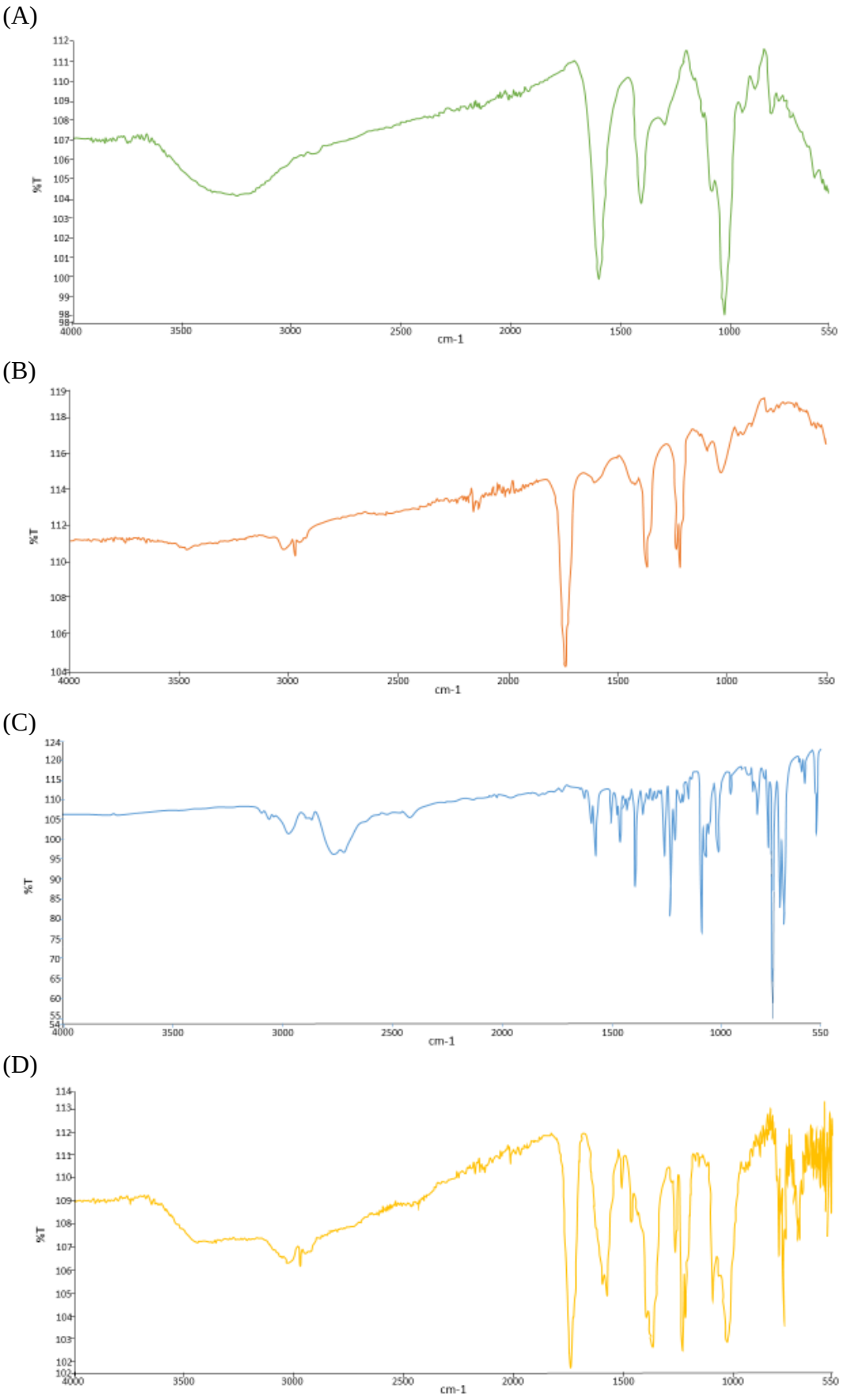


Figure 11**:** FTIR spectra of (A) sodium alginate powder, (B) dried crosslinked Alginate Beads, (C) DLU and (D) DLU adsorbed Alginate Beads.

4.1.5 UV-Vis Spectra

The adsorption of DLU with respect to time was investigated using UV-vis spectroscopy and the obtained results (UV-vis spectrum) is shown in Figure 12. At time t = 0 (i.e. before adding the adsorbent), the spectrum of DLU solution (25 mg/L) was recorded. As clearly seen from the Figure 13, the spectrum obtained initially showed a broad band with an intensity of 1.465 a.u. at 288 nm, which is ascribed to DLU itself. No other bands were observed. However, after adding the crosslinked alginate beads to the DLU solution, the spectrum showed similar absorption peak but with less intensity (0.734 a.u). The peak at 288 nm kept reducing as time went on until about 360 minutes where the absorption peak of DLU almost disappeared completely (0.062 a.u.). This confirms the removal of DLU from the aqueous solution via adsorption.

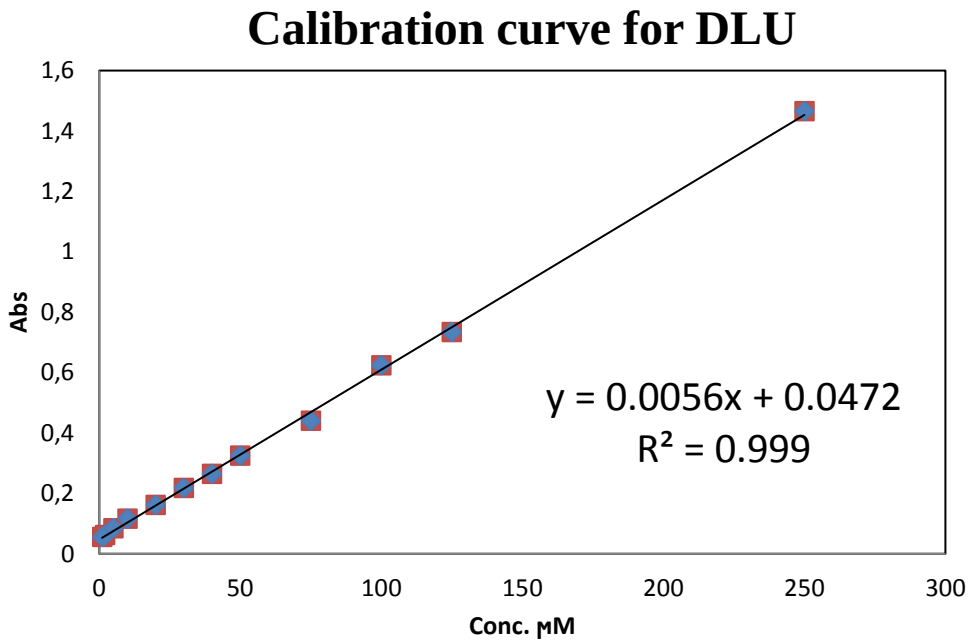


Figure 12: calibration curve of DLU

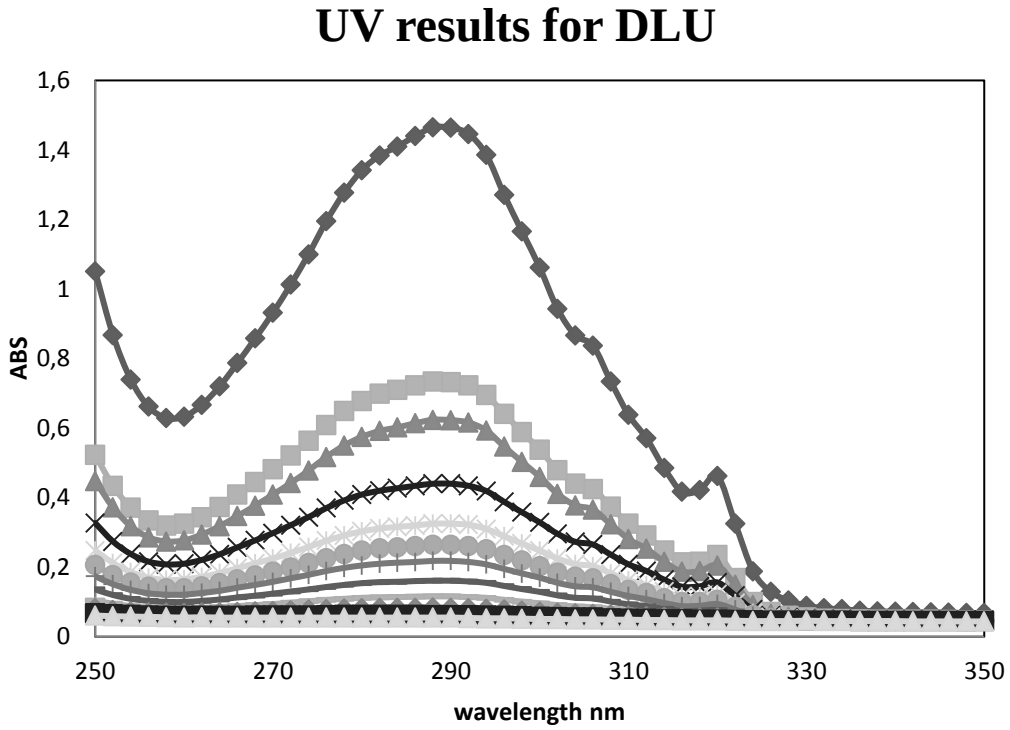


Figure 13: UV-vis spectra of DLU before and during adsorption

4.2 Determination of Factors Affecting DLU Adsorption and Adsorption Kinetics of DLU on Crosslinked Alginate Beads

4.2.1 Effect of Alginate Beads Dosage on DLU Removal

The adsorption of aqueous DLU solution (initial concentration of 25 mg/L; volume: 50 mL) was first undertaken using varying masses (0.015 - 0.35 g) of alginate crosslinked polymer to determine the optimum dosage required (Figure 14). As seen from the figure, there was a rapid increase in the removal of DLU from 35% to 90% as the mass of crosslinked alginate beads increased from 0.015g to 0.10 g. This is due to the increase in the number of available adsorption sites as the mass of beads increased. A further increase in mass to 0.25 g resulted in 100 % removal while an additional increase in the mass of crosslinked alginate beads to 0.30 g led to a slight decrease in DLU removal %. Therefore, 0.25 g crosslinked alginate beads were

selected as the optimum amount of adsorbent required for all other experiments (kinetic and isotherm studies).

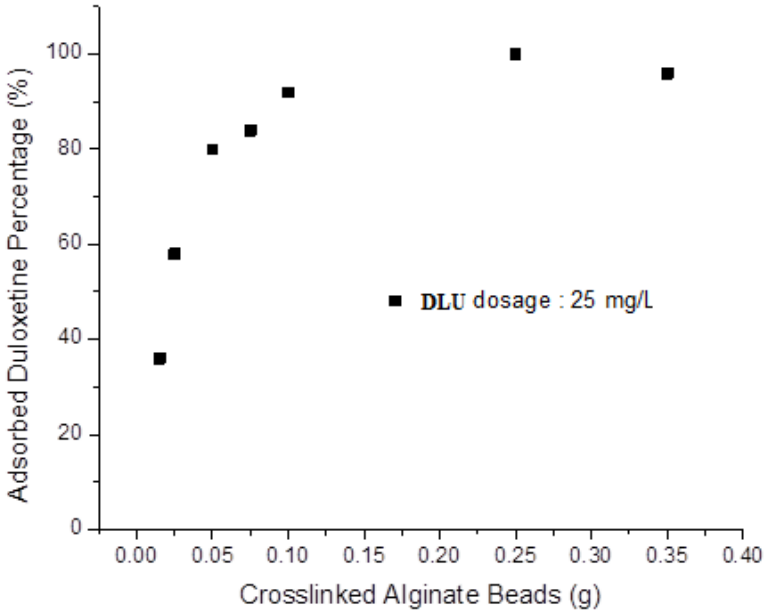


Figure 14: Effect of dosage on removal of DLU

4.2.2 Effect of Time on Removal of DLU

The effect of time (5 - 1200 minutes) on the removal of DLU by the crosslinked alginate beads was investigated and the result obtained is depicted in Figure 15. The results indicated that the adsorption of DLU onto the crosslinked alginate beads was very rapid during the initial 60minutes (about 90% removal obtained) and reaches its saturation point (i.e. equilibrium adsorption capacity of ≈ 100%) after about 200 minutes since a further increase in time did not have any impact on the removal of DLU. These results suggest a fast removal of DLU by the crosslinked polymer where most of DLU molecules present are adsorbed in the first 60 min.

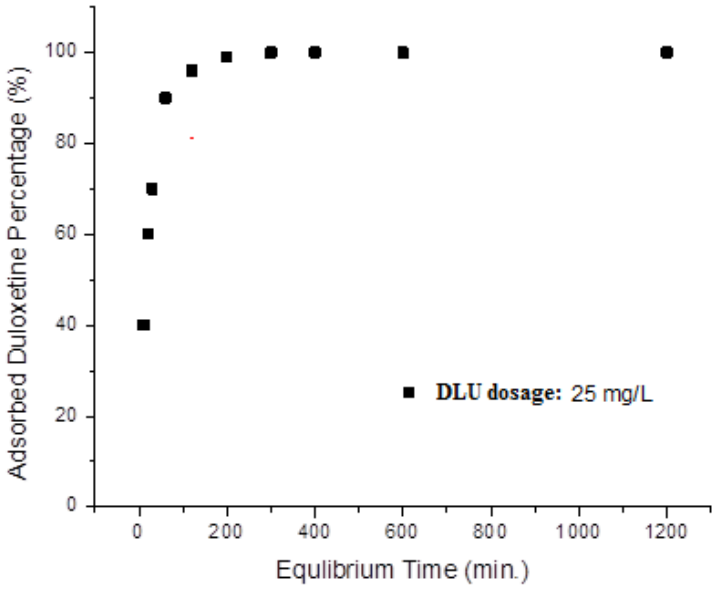


Figure 15: Effect of time on removal of DLU

4.2.3 Kinetics of DLU Adsorption onto Crosslinked Alginate Beads

The modelling of the adsorption process of DLU by the adsorbent in this study was investigated using two common models, namely; the Lagergren pseudo first order and pseudo-second order model. Linear plot of both models is depicted in Figure 16 below while the parameters obtained are summarized in Table 2. As seen from the table, the pseudo second order model has a higher regression coefficient (0.9993) closer to 1 as compared to the first order model (0.9548). Also the calculated q_e value of the second order model (5.33 mg DLU/ mg of crosslinked alginate beads) is closer to the experimentally obtained value of 5.03 mg/g. This suggests that the mechanism of the adsorption process is well described by the pseudo second order model.

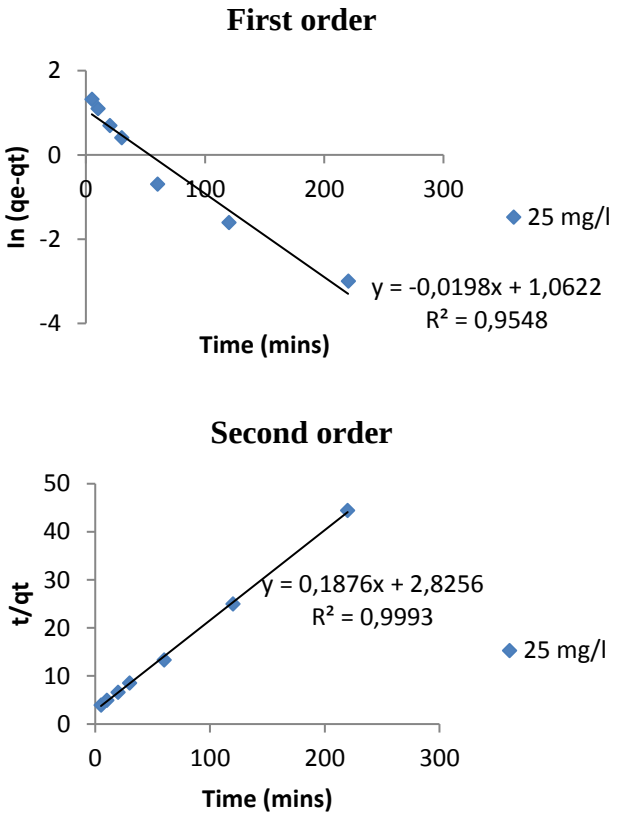


Figure 16: Pseudo 1st order and 2nd order kinetics of DLU adsorption onto crosslinked alginate beads (initial concentration = 25 mg/L)

Table 2: Pseudo first order and second order constants

DLU initial concentration C_0: 25 mg/L	Pseudo 1st Order	Pseudo 2nd Order
R^2	0.9548	0.9993
K	0.0198	0.0125
$q_{e,cal}$ (mg/g)	1.06	5.33

4.3 The Adsorption Isotherm of DLU through the Interaction with Beads Prepared

The adsorption isotherm of DLU onto the beads was evaluated using both the Langmuir and Freundlich's isotherms. The plot of log q_e versus log C_e (Freundlich); Figure 17 and $1/q_e$ against $1/C_e$; Figure 18 (Langmuir) for both isotherms was done to determine which adsorption isotherm best fits the adsorption process. The linear plot of the Langmuir isotherm (y = 0.0674X + 0.0385) had a regression coefficient (R^2 = 0.9272) while that of Freundlich (y = 0.3952X + 0.9837) had a higher regression of coefficient 0.9927. The comparison of the regression coefficient (i.e. R^2 values) of both isotherms indicate that the adsorption at equilibrium is more fitted to the Freundlich isotherm which further suggests the multilayer adsorption of the DLU molecules on the surface of the crosslinked alginate beads (Bonenfant et al., 2012). Table 3 below presents the parameters obtained from both isotherms established at 298K.

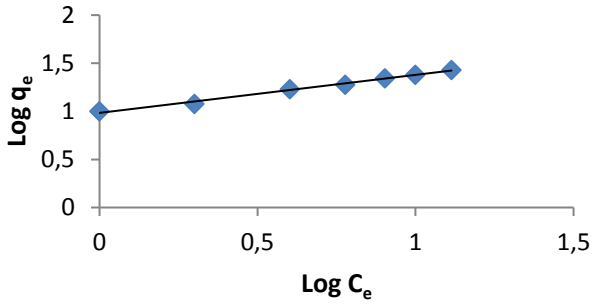


Figure 17: Freundlich adsorption isotherm

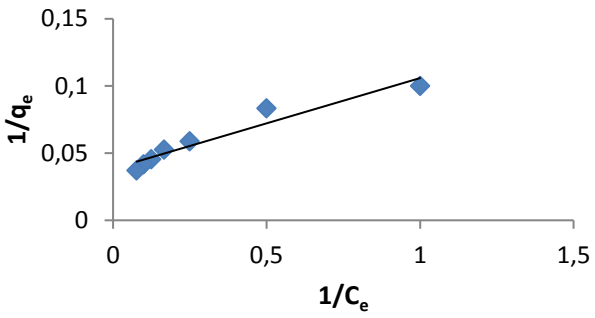


Figure 18: Langmuir adsorption isotherm

Table 3: Adsorption isotherm parameters

Isotherms	Parameters
Langmuir	R^2 = 0.9272 K_L = 0.571 L/mg R_L = 0.065
Freundlich	R^2 = 0.9927 K_F = 9.63 mg/g $(L/mg)^{1/n}$ 1/n = 0.3952 n = 2.53

As seen from the table, the Freundlich distribution (K_F) and linearity (1/n) coefficients calculated are 9.63 mg/g $(L/mg)^{1/n}$ and 0.3952, respectively. The separation factor R_L, and adsorption intensity n, obtained from both isotherms can be useful in identifying the favourability of the adsorption process. In the case of R_L, values between 0 and 1 i.e. $0 < R_L < 1$ indicates a favourable adsorption while n values between $1 < n < 10$ shows similar property (Priyantha et al., 2015). The values of R_L (0.065) and n (2.53) obtained in our study for both isotherms indicate that the adsorption process is favourable.

4.4 Proposed mechanism of adsorption process

The DLU binding capacity to the adsorbent (crosslinked alginate beads) was associated to the formation of ion-ion interaction between the quaternized amine moiety present in DLU and the carboxylates (COO^-) available within the alginate structure (Figure 19). This mechanism was also confirmed by the FT-IR spectrum of the adsorbent after loading the DLU since no new peaks were found in the FT-IR spectra to confirm the presence of a new chemical compound formed.

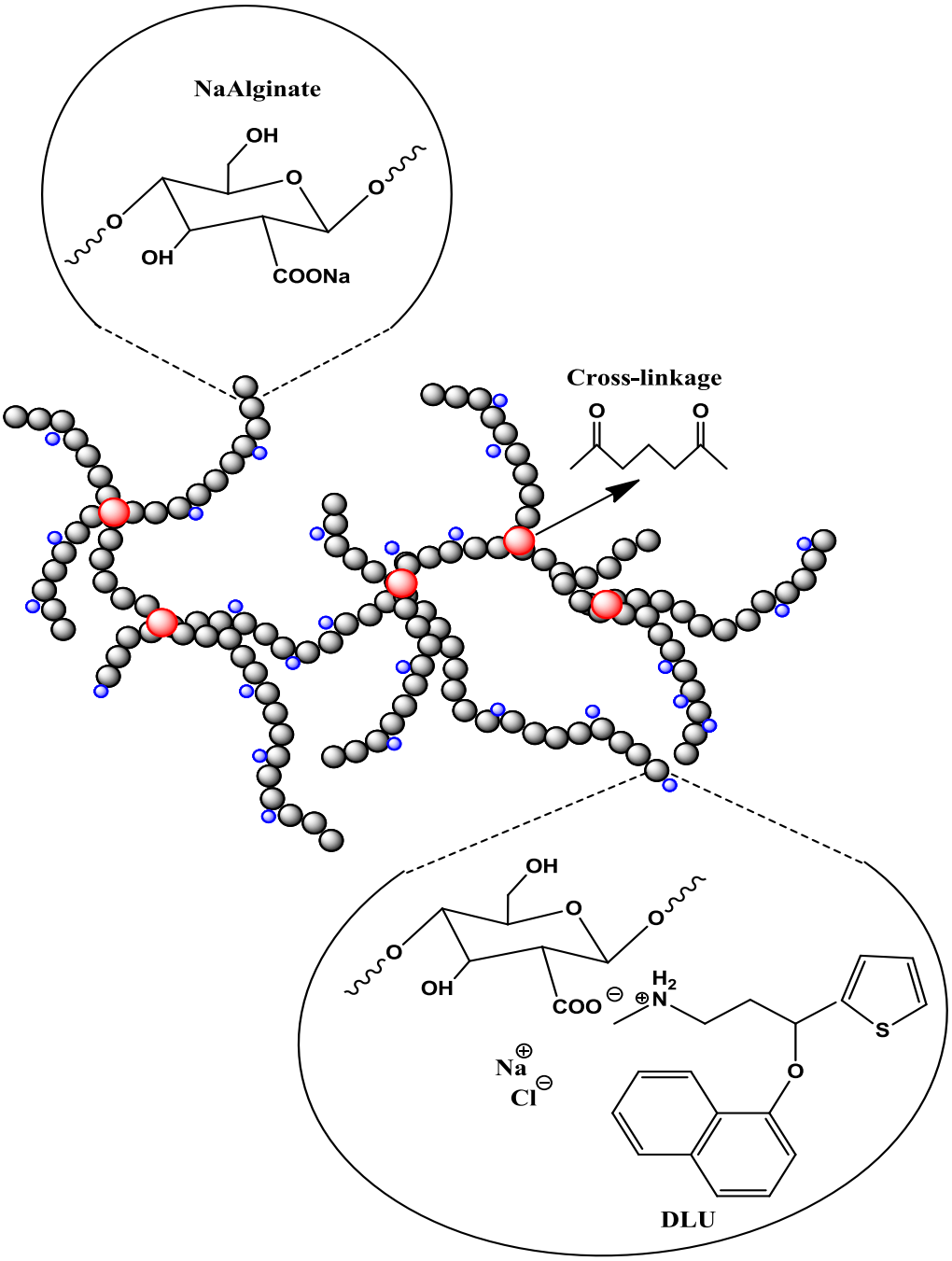


Figure19: Binding mechanism of alginate and duloxetine

Chapter 5

CONCLUSION

Antidepressant drug employment has growing up since the last 4 decades depending on the over-the prescription status of these drugs as well as the stress conditions that people face. From this point of view, these drugs are generally utilized arbitrarily, similar to their waste. Research studies indicate the accumulation of drug substances in the environment, and not surprisingly antidepressant drugs appear to be at the top of this list. The lack of waste conditions of these drugs worldwide suggests that antidepressant drugs would be a big threat for the environment in the near future. Therefore, there is an urgent need for the development of new technologies and strategies to find solutions for the treatment of nature to clean these antidepressant drug wastes.

Duloxetine is relatively a new and effective antidepressant drug molecule. However, its worldwide employment becomes bigger day-by-day making this drug also as a treat for the environment. Beside, this drug also has under indications such as its employment for the treatment of urinary retention problems in kids and elders.

Within this study, our basic approach was to design and make a novel alginate bead polymer capable of interacting with duloxetine molecule. The only available functional group for strong interactions within the structure of duloxetine is the amine group. Therefore, we have initially hypothesized that alginate structure would

be ideal with its carboxylate residues chemically available to make ionic or hydrogen bonds with the amine in duloxetine.

Following the preparation of the alginate cross-linked bead we analysed the capacity of the adsorption of duloxetine through a set of experiments. First of all, we found that the alginate crosslinked beads we prepared have a high affinity for DLU (i.e., 5.33 mg of DLU/g Bead with an initial concentration of 25 mg/L). The DLU binding capacity of the adsorbent was associated to the formation of ion-ion interaction between the quaternized amine moiety present in DLU and the carboxylates (COO^-) present within the alginate structure. In order to describe the adsorption process, the results indicated the pseudo-second-order kinetic model fitting to the Freundlich adsorption isotherm as the best explanation. This indicated that adsorption process appears to be happening through a multilayer coverage of DLU onto the polymer that has heterogeneous surface.

Finally, the polymer we prepared is a suitable for the removal of duloxetine. Regarding the effectivity, cheap price and ease of preparation characteristics of the cross-linked alginate beads we prepared, treatment of duloxetine waste and its determination with this technology might provide quite a lot advantages. Furthermore, the methodology and the polymer prepared might be also effective for the waste treatment of other alternative antidepressant drugs within the same category of duloxetine. However, more research studies are required to assay this future of the beads prepared.

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