Instituto Tecnológico y de Estudios Superiores de Monterrey

Campus Monterrey

School of Engineering and Sciences

Immobilized laccases on modified magnetic nanoparticles for degradation of common psychiatric drugs used during COVID-19 pandemic

A thesis presented by

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Submitted to the
School of Engineering and Sciences
in partial fulfillment of the requirements for the degree of

Master of Science

In

Nanotechnology

Monterrey Nuevo León, June 07th, 2022

Dedication

This work is dedicated to all those who gave me their unconditional confidence, support, patience, and encouragement. You were my main motivation for pushing through this work. First, I want to dedicate this work and all my hours of hard work to GOD, who is the most important person in my life and gave me the knowledge during this past two years.

Also, I want to dedicate my work to my mom and dad, Sylvia and Erik, and my siblings Rubí and Gilberto, who've been there every day of my life giving me their love and support through this scientific journey.

Finally, I want to dedicate this work to the person who came to change the way I smile, speak, write, and love, the one who showed me that there is still true love in this world, to my dear love Alejandra.

Acknowledgements

I would like to express my deepest gratitude to all those who have been side by side with me during this past two years, giving me their support. I mainly thank GOD for his support, strength, understanding, grace, and undeserved love throughout my life. I am grateful for every open door, for the opportunity he gave me to study with a full scholarship, and above all the opportunity to meet important people whom I can thank.

Consejo Nacional de Ciencia y Tecnología (CONACYT) and Tecnológico de Monterrey, México that supported me whit opportunity to develop this master's degree program by giving me support to live and a full scholarship, are thankfully acknowledged.

I want to thank to Sustainable and Applied Biotechnology group and to their leaders Dr. Roberto Parra- Saldívar and Dr. Hafiz M.N. Iqbal for helping, teaching, and providing me all necessary tools. Also, I want to express my gratitude to Dra. Elda Melchor, who has been a key factor in the development of this project.

To my parents, Sylvia and Erik, who everyday care about my well-being and give me the love of a family. You are my inspiration to work hard every day of my life, and I am so proud to be your son… I hope you feel the same about me.

I thank my sister and her family for always bringing shine to my days with their visits. I thank them for always motivating me to keep going. I also want to express my gratitude to some amazing friends who always have been proud of me and shared with me their incredible thoughts, thank you Danna, Gabo, and my little friends Valu and Panchos.

I thank Siomara Hurtado, who opened me the doors of his house and family and teaches me that love for family is the greatest motivation to work hard.

I thank to my community Puerta del Cielo and to all my leaders, which have been like a family for me, a place where I can find GOD every time I go.

Finally, I want to express all my gratitude and love to one special person, someone who is different and unique, the person who perfectly fits and even exceeds everything that I could ever imagined or asked. You came from nowhere, but you came to change my life, and to add all your incredible qualities and virtues. Believe me when I tell you there´s not enough words that explain how grateful I feel knowing that you are part of my life, thank you for being just like you are, perfect and splendid. I also want to thank you because you have been side by side with me, along the long, but also short hours, at night. Thank you for teaching me patience, gratitude and for showed me how to be happier than ever. Thank you for encouraging me to help and love others, for been my best friend, my confident and the only person who really know every part of my heart. Thank you for every word written or spoken that remains me every day how you admire me and how you are proud of everything I've done and everything I´ll do. Alejandra, the admiration represents the starting point of our love, we always recognize the other as different, special, mysterious, and worthy of attention, I admire you so much and I am so happy that you feel the same way about me. Thank you so much my dear.

Immobilized laccases on modified magnetic nanoparticles for degradation of common psychiatric drugs used during COVID-19 pandemic

by

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Abstract

The COVID-19 pandemic has brought several consequences to mental health in population, including depression, stress, anxiety, and related problems. Thus, it has been reported an increment on prescription rates of medicines to treat these disorders. Pharmaceuticals are considered as emerging pollutants (EP) of aquatic systems due to its persistence in waters since they are resistant to conventional wastewater treatments. Ecological and toxicological risks to environment, living organisms and human health derived EP have been demonstrated. Thus, different technologies have been applied to overcome this issue. Biocatalysis appears as a novel and suitable approach for the remotion of psychiatric drugs waters due to its important advantages, including biocompatibility and high power of degradation. Here, we implemented a biocatalytic system consisting of the immobilization of a purified cocktail of laccases Pycnoporus sanguineus on magnetic modified carbon nanofibers (mCNF) by physical adsorption, which was made to deal with low stability and non-reusability of the free enzymes. The structural and morphological characterization of the matrix nanomaterial and the immobilized enzyme was determined by SEM, EDS and FTIR. The enzymatic behavior of both, free and immobilized system was evaluated by the determination of the loading enzyme. The pH and storage stability were analyzed by measuring the enzymatic activity over ABTS. Finally, the immobilized system was evaluated in the degradation of 25 µg/mL of venlafaxine in ultrapure water and a real sample of wastewaters by using 10 mg of the immobilized biocatalyst. Results of the characterization confirmed the magnetic modification of the carbon nanofibers by the formation of iron oxide nanoparticles over the surface of the carbon nanofibers. Moreover, the maximum loading of laccases on the mCNFs was about 73 %, and the immobilized laccases exhibited excellent pH and storage stability. The highest enzymatic activity of the immobilized laccases was found to be at pH 5, in which the enzyme retained 75 % of its initial activity after 4 weeks at 4 °C. The immobilized laccases system has shown potential results in the degradation of venlafaxine in an aqueous medium. Finally, the nanobiocatalyst was able to remove the 69 % of the venlafaxine (VFX) after 18 h.

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1. INTRODUCTION

In December 2019, a group of patients with pneumonia of unknown origin began to be reported and epidemiologically linked to a live animal market in Wuhan, Hubei Province in China (Zhu et al. 2020, Sifuentes-Rodríguez and Palacios-Reyes 2020). Since the World Health Organization (WHO) declared the new coronavirus (2019-nCoV) as a global pandemic on March 11, 2020, a total number of 253,640,693 confirmed cases with 5,104,599 deaths have been reported across the 216 affected countries, territories, or areas (Abou Ghayda et al. 2020, WHO 2021).

As it is known, this situation has led many countries to adopt compulsory lockdowns and social distancing measures. For example, the Mexican government declared a national health emergency on March 20, 2020, and imposed restrictions on the public, private and social sectors, including voluntary isolation and closure of schools, social distancing, and restriction to non-essential activities (García-Priego et al. 2020). However, although these preventive measures are effective for the spread of COVID-19 (Tian et al., 2020), they have been reported to have an adverse effect on mental health (Galea et al., 2020). For example, it has been proven that different factors such as the number of deaths, mass unemployment, and isolation measures are the main causes of negative psychological effects on society (Galea et al., 2020), including stress, anxiety, depression (Swami et al., 2021, Lee et al. 2020) and suicidal thoughts (Thompson et al., 2021), and some other related problems, such as internet, drugs, alcohol, and tobacco addictions (Marsden et al., 2020).

As a result, coronavirus-related stress, anxiety, and depression have increased the percentage of people seeking psychiatric treatment (Flament et al., 2021), leading to increased demand for psychiatric drugs, such as antidepressants, anti-anxiety drugs, mood stabilizers, and antipsychotics (Jacob et al., 2021). Thus, the widespread use and demand of these drugs, has raised environmental concerns, since the disposal of expired or unused drugs (approximately 50%) and the release of their metabolites from urine and feces introduces large amounts of these drugs into aquatic systems (Teymoorian et al., 2021). In fact, different studies have shown that the bioaccumulation of these psychiatric substances may have negative effects on living organisms, such as endocrine disorders, and reproductive, growth and metabolic deficiencies (Argaluza et al. 2021, Thompson and Vijayan 2020, Carter et al. 2018).

Due to the inability to remove psychiatric drugs from aquatic systems by wastewaters treatment plants (Escudero et al. 2021), different degradation and removal techniques have been studied and applied, such as photodegradation (Osawa et al. 2020), Fenton (Lumbaque et al. 2018), electrochemical procedures (Bosio et al. 2021), thermal degradation and some other combinations (Pinto et al. 2018, Mitsika et al. 2021). However, even though the application of these conventional techniques appears to be effective for the degradation/removal of psychiatric drugs, with some drugs achieving total degradation (Ferreira et al., 2018) by reviewing the most common detection techniques used after transformation reaction, it was observed that is common that many by-products with adverse toxicological effects are formed (Lambropoulou et al., 2017).

In contrast, this thesis examines the use of biocatalytic systems for the biodegradation of psychiatric drugs, which, when compared to physical and chemical treatment technologies, appears to be a more environmentally friendly and greener approach to removing these drugs from aquatic systems due to important characteristics such as high stability, simple operational processes, recyclability of catalysts, and a high bioconversion rate that results in non-toxic by-products (Sheldon and Woodley 2018).

In general, biocatalysis can be achieved in three different ways: (a) whole-cell biocatalysis, (b) isolated- enzyme biocatalysis, and (c) isolated-immobilized enzyme into a potential solid host carrier for enzyme immobilization, such as nanomaterials, which are potential materials for wide range of enzymes owing to its ease of handling, operational procedures, and some other chemical and physical properties (Bilal and Iqbal 2019). Whole-cell biocatalysis and the isolated-enzyme biocatalysis have been widely used due to some important advantages, including its ease operational process, high reaction rates and relative less cost, which is mainly attributed to the lack of hard purification processes. However, these first two might present some problems such as cross-reactivity, side reactions, lower yield of bioconversion compared with the amount of raw material implemented, which is mainly caused by the difficulty to separate products from catalysts, enzyme deactivation by solvents, and most importantly, despite that in theory cells and enzymes can be recycled, the cross reactivity might reduce its recyclability and increment operational cost. Thus, by the enzyme immobilization, these problems can be effectively solved while catalytic properties remain or are improved (Bilal and Iqbal 2019, Sheldon and van Pelt 2013, Sheldon and Woodley 2018).

The synergistic integration of biocatalysis engineering with nanostructured materials has emerged as a new interface named nanobiocatalysis, which is an innovative area that focus on the incorporation of the enzymes into a nanostructured material (Ansari and Husain 2012). As well known, isolated enzymes have important properties, such as high specificity, high reaction rate under mild reaction conditions of pH and temperature, low energy reactions, water solubility, and biodegradability (de Jesús Rostro-Alanis et al., 2016). However, the implementation of enzymes has some important issues that commonly are hampered by different factors, including high isolation and purification cost, lack of stability and short lifespan, inhibition by non-natural substrates, and difficult to operate due to its hard/low recovery and recycling process (Del Arco et al., 2020, Homaei et al., 2013, Rodríguez-Delgado et al., 2015). Fortunately, the nanobiocatalysis, has been allowed to overcome the most of previously mentioned obstacles by using different immobilization methods to attach the enzymes into nanostructured materials, providing stability, high catalytic behavior, and reusability, which leads to lower reaction times and allows to implement different bioreactors designs (Homaei et al., 2013, López et al., 2014).

Finding the proper immobilization method and a good solid support for enzyme immobilization is a critical step to design nanobiocatalysts. In the beginning of nanobiocatalysis, enzymes were immobilized by simple methods such as simple adsorption and covalent attachment, then with recent research on the field of biotechnology and nanotechnology, the application of different nanostructured materials, including mesoporous materials, electrospun nanofibers, carbonaceous materials, and metallic materials, including magnetic and non-magnetic materials; has allowed taking advantage of the main characteristic of nanobiocatalysis, the high

surface/volume ratio of nanomaterials, which improves some biocatalyst properties like enzyme loading into the solid support, leading to higher enzyme activity compared to free enzyme or enzyme immobilized into conventional materials (Del Arco et al., 2020, Kim et al., 2008).

The principal reason of the use of different nanostructured materials for the immobilization of enzymes is the feasibility of work on the control over size at nanometer scale, by the modification of pore size, thickness of nanofibers or nanotubes and particle size of nanoparticles (Kim et al., 2008). As one of the previously mentioned supports materials, magnetic nanomaterials are gaining remarkable ground over other type of supports owing to its important characteristic but principally to their magnetic behavior, which allows to easily recovery by the application of a magnetic field (Del Arco et al., 2020, Bilal et al., 2020). Metallic MNPs, such a Fe_3O_4, $MnFe_2O_4$, $FeFe_2O_4$, $CoFe_2O_4$ have a great interest for biocatalytic applications as supported carrier material for enzyme immobilization (Del Arco et al., 2020, Kudr et al., 2017). As mentioned above, the increasing interest is owed to some important properties like high specific area, elevated enzyme loading ability, controllable particle size, modifiable surface, small volume, and the most important, easily, and rapid separation from solutions in comparison of conventional materials, where centrifugation and filtration are the only option to separate and reuse the enzyme. Also, this material is commonly used because its good biocompatibility, non-toxic properties, and the interesting low process cost (López et al., 2014, Nicolás et al., 2014).

2. THEORICAL FRAMEWORK

2.1. Bioaccumulation of psychiatric drugs in aquatic systems, toxicity, and environmental concern

2.1.1. Environmental concern

COVID-19 pandemic has affected the way that people used to live (lifestyle, hobbies, personal care, expenses, feeding, etc.) (van der Werf et al., 2021, Lee et al. 2020), and how society relates professionally and casually (Sommerland et al. 2021, Marra et al., 2020). In fact, during and after pandemic, important consequences in different areas have come, such as economy crisis, which is mostly affected by the mass unemployment (Kawohl et al., 2020), government public debt caused by public health invest (Amis et al. 2020), lack of manufacturing, loss of service industries and weakening of global market (Pak et al., 2020); house violence (Bradbury-Jones and Isham 2020), vulnerable education (Azorín 2020) and mental health problems (Kumar and Nayar 2021, Steardo and Verkhratsky 2020), including depression and anxiety symptoms (Rabeea et al., 2021), bipolarity (Spelber and Strakowski 2021), suicidal thoughts (Thompson et al., 2021) ,insomnia (Pappa et al., 2020) , psychotic attacks (Janoczkin et al. 2021) and convulsions (Andraus et al., 2021) .

Moreover, due to mental health problems, after deconfinement, people as never seen before, have attended to hospitals for psychiatric admissions due to anxiety, depression, or psychological problems (Flament et al., 2021). In consequence, the increment of psychiatric or psychological treated patients caused by COVID-19 stress have led to the overuse and increment in sales of psychiatric

drugs, which has been confirmed by purchases studies made in Germany (Jacob et al. 2021, Kostev and Lauterbach 2020), Italy (Ammassari et al. 2021), Canada (Stall et al. 2021), England (Howard et al. 2020), and United States (Vaduganathan et al. 2020). Thus, as in shown in Figure 1, the overuse of psychiatric drugs might cause its released and increment of concentrations from different sources, including hospitals and houses to wastewater plants. (Nason et al. 2021). Hospitals indeed, produce a lot of medical wastes, including psychiatric drugs and transformation products released through feces and urine from patients but also through direct disposal of expired medicines (Pacheco et al. 2021). In fact, different studies have shown that these emerging contaminants are usually detected in magnitude of concentrations of ng/ to mg/L (Castillo-Zacarias et al. 2020), which in case of inadequate treatment, might cause a risk for both environment and public health (Pacheco et al. 2021).

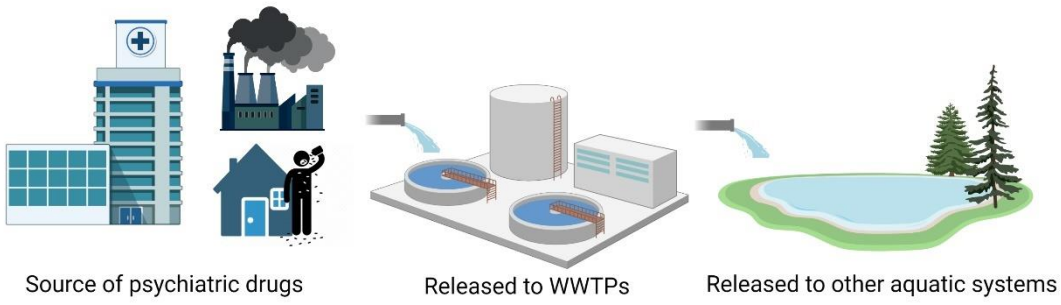

Figure 1. Principal psychiatric drugs sources of contamination of aquatic systems

2.1.2. Bioaccumulation of psychiatric drugs in aquatic systems

Pharmaceuticals are commonly one of the most detected emerging contaminants compounds in wastewater plants (Aydın et al. 2021). With the increasing demand and use of pharmaceuticals during COVID-19, wastewater samples influents and effluents have detected an increment in concentration of different pharmaceuticals, including COVID- 19 treating drugs, opioids, antibiotics, and psychiatric drugs (Nason et al. 2021). These last, appears to be the most recalcitrant group of drugs in wastewater treatment plants (WWTPs) (Aydın et al. 2021). In fact, different studies have shown how psychiatric drugs presents nearly the same concentration in influents than in effluent of the WWTPs. For example, a study made in a WWTPs in Medellin and Bogota, Colombia revealed how the concentrations of some non-psychiatric drugs like acetaminophen, ciprofloxacin, and norfloxacin, went from concentrations of 9.19 µg/L, 2.29 µg/L, and 1.37 µg/L in influent to concentrations of 0.16 µg/L, 0.81 µg/L, and 0.47 µg/L in effluent, respectively. On the other hand, psychiatric drugs, such as carbamazepine and venlafaxine presented concentrations of 0.153 µg/L, and 0.056 µg/L, in influent, and concentrations of 0.140 µg/L, and 0.035 in effluent, respectively, which means that non-psychiatric drugs had a removal percentage around 65-98 % while psychiatric drugs removal percentage was around 8.5-35 % (Botero-Coy et al. 2018).

Since the effluents from WWTPs are the higher source of psychiatric drugs release to aquatic systems due to inadequate removal for these compounds during traditional wastewater treatments (Dalecka et al. 2021), it is known that due to the bioaccumulation of pharmaceuticals, including psychiatric drugs, traces of drugs might move from aquatic systems and reach agriculture, drinking water, and natural

habitats (Figure 2) (Pacheco et al. 2021, Saadat et al. 2020). Moreover, Figure 2 also shown how bioaccumulation of psychiatric drugs might be detected in different aquatic systems (Aydın et al. 2021), which are mentioned next:

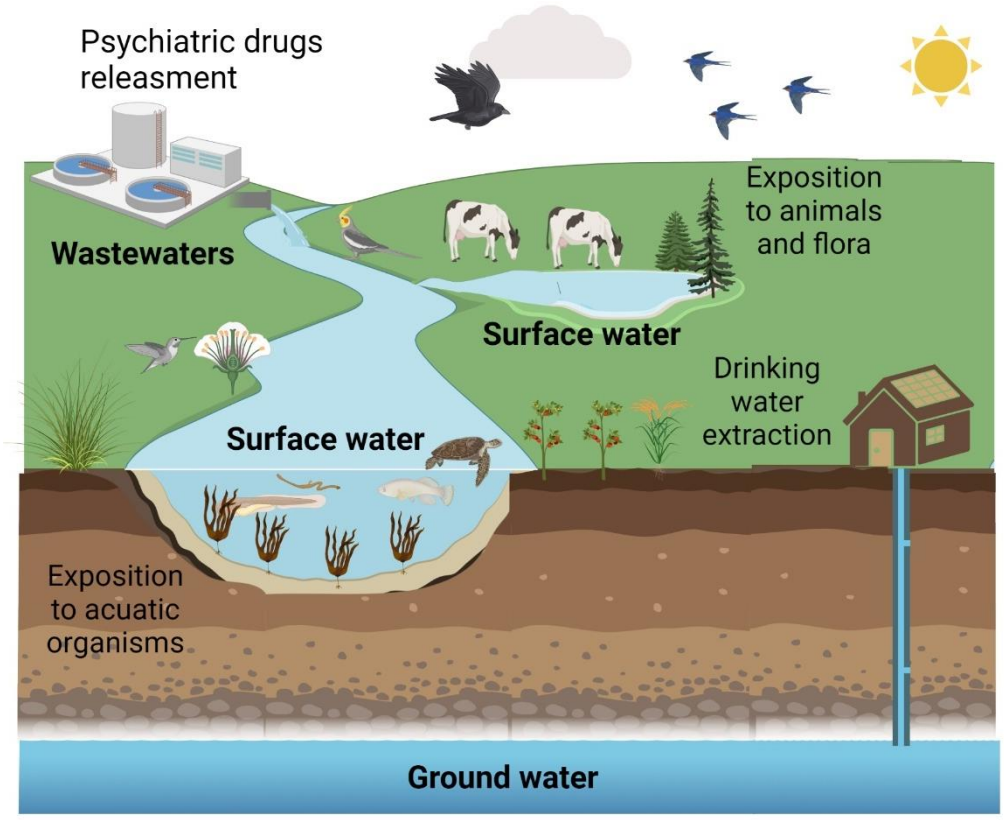

Figure 2. Presence of psychiatric drugs in different aquatics systems and its contact with humans, flora, and fauna.

- Wastewaters: wastewaters are a complex mixture of solids, dissolved matter, microorganisms, heavy metals, and emerging contaminants, including psychiatric drugs (Warwick et al. 2013). Wastewater discharges are the inflexion point for the released of psychiatric drugs into other aquatic systems included in the cycle of water (Bijlsma et al. 2021). Indeed, a lot of studies have studied the presence of antidepressants in influents and effluents of WWTPs. For example, an analysis

made with liquid chromatography couple with mass spectrometry (LC-MS) in four WWTPs in Belgium confirmed the presence in influents of about 18 of psychiatric drugs (e.g. sertraline, moclobemide and melitracen) in concentrations around of 25 ng/L (Boogaerts et al. 2019). Another study made in a municipal WWTPs in Canada conclude that primary and trickling filter/solids contact are not able to efficiently remove psychiatric drugs, such as venlafaxine (VFX) and its metabolite O-desmethylvenlafaxine (ODVFX), citalopram (CIT), and carbamazepine (CBZ), which were detected in concentrations up to 4.3 µg/L (Lajeunesse et al. 2012). Moreover, studies made in hospitals wastewaters have identified as one of the most common emerging contaminants presented in these wastewaters, psychiatric drugs, including CBZ, VFX, CIT, sertraline, diazepam, etc. (Nason et al. 2021, Teymoorian et al. 2021). Thus, monitoring and detection of psychiatric drugs before and after processing by wastewater plants become a major concern to reduce subsequent emissions to other aquatic systems.

- Groundwaters: since groundwaters represents almost 75 % of fresh drinking water and it is widely implemented in agriculture, industry, and animal breeding, monitoring and detection of emerging contaminants in groundwater is important to make a proper quality assurance of the waters (Pinasseau et al. 2020). Different studies and techniques have been applied for the monitoring of psychiatric drugs in groundwaters. For example, an ultra-high liquid chromatography analysis made of groundwater samples one industrial community in Olomouc, Czech Republic, identified the presence of some antidepressants, antipsychotics, and by-products at high concentrations (up to 1 mg/L) and it was concluded that further investigation in remediation was needed (Křesinová et al 2016). Moreover, another study made

across United States in almost 1100 sites, revealed that one psychiatric drug (carbamazepine) appears as one of the 4 most detected pharmaceuticals detected all the samples (Bexfield et al. 2019). Moreover, psychiatric drugs like carbamazepine, fluoxetine, and sertraline have been identified in concentrations up to 20 ng/L in different areas like cemeteries (Paíga and Delerue-Matos 2016), urban communities (Wolf et al. 2012) and even rural communities (Chiffre et al. 2016). Contamination of groundwaters might be a high environmental concern due to it is the principal drinking water supply of many communities around the world, it is implemented in agriculture and animal husbandry, which means that can be directly in contact with humans through edible food primally.

- Surface water: surface waters, including sea, lakes, and rivers and streams represent another important aquatic system that has been detected to be compromised by the bioaccumulation of pharmaceuticals (psychiatric drugs included). Due to psychiatric drugs are more difficult to remove during WWTPs bioaccumulation in surface waters of these drugs has an increasing environmental concern (Dalecka et al 2021). The presence of psychiatric drugs in surface waters has been extensively studied in different countries across Asia, Europe, and America (Jameel et al. 2020). For wxample Bangladesh (Hossain et al. 2018) and Sri Lanka (Guruge et al. 2019) in India studies that confirmed the presence of psychiatric drugs like carbamazepine at concentrations in the other of ng/L.

2.1.3. Toxicity of psychiatric drugs

Along the history, contamination of aquatic systems has provoked several consequences for microorganisms, food supplies, animals, and human being. From

bacterial and viral diseases (Pinon and Vialette et al. 2018) to radiation (Kryshev et al. 1998) or heavy metal (Fu and Xi et al. 2020) contaminate on. In case humans, the contamination of surface waters by psychiatric drugs becomes an important environmental concern since humans can be in direct contact with contaminated waters through swimming and recreational activities (Teymoorian et al. 2021), edible food contaminated for irrigation waters (Mordechay et al. 2021), catched fishes (Huerta et al. 2020) or even drinking water (Peng et al. 2019). For example, a study made in fishes collected in United States urban rivers commonly used for fishing, revealed that the psychiatric drugs carbamazepine and venlafaxine were the pharmaceuticals detected at higher concentrations (order of ng/L). A risk that human could present in case of be in constant contact with different psychiatric drugs, such as carbamazepine, phenothiazines and clozapine, is related to hematological toxicity that is presented by the combination of two or more drugs with neutropenia/agranulocytosis risk (Flanagan and Dunk 2008).

Several studies have shown that even low levels of psychiatric drugs might affect the reproduction, growth and survivance of aquatic microorganisms and animals (Thompson and Vijayan 2020). For example, samples of waters from a hospital WWTPs in Greece showed that the exposure to different psychiatric drugs, including bupropion, citalopram, fluvoxamine, sertraline and venlafaxine with algae, fishes and invertebrates resulted in high values of toxicity units according to risk quotient approach (RQ) (Papageorgiou et al. 2019). In addition, other studies also studied the toxicological effects of psychiatric drugs in aquatic systems, fluoxetine has been shown to alters fish behavior (Wiles et al. 2020), venlafaxine interfere with larval minnows' growth (Thompson and Vijayan 2020), amitriptyline, fluoxetine and

mianserin also affects the growth of zebrafish larvae (Wu et al. 2017), and carbamazepine and fluoxetine that affected the locomotion, DNA, and reproducibility of freshwater planarians (Ofoegbu et al., 2019). Moreover, the bioaccumulation of psychiatric drugs in organisms out of the aquatic systems is reported. For example, a study conducted by (Carter et al., 2018) reported that carbamazepine has inhibitory effects over the metabolism of plants.

Thus, the presence of psychiatric drugs in aquatic systems, including wastewaters, groundwaters and surface waters like rivers, streams, and lakes in different urban and rural communities across the world has been extensively studied. In general, results have concluded that psychiatric drugs are one of the most detected emerging contaminants in aquatic systems samples, in which drugs like carbamazepine and sertraline appears almost in all monitoring studies. This in consequence represents a highly environment concern due to its feasibility that reach aquatic organisms, plants, animals and even humans.

2.2. Conventional process for the removal of psychiatric drugs from waters

Wastewater treatment plants have the objective of removing pollutants from wastewater before reusing it or discharging it back to the environment. Typical wastewater treatment plants use diverse processes that are commonly divided into two treatment stages and some of them can include a tertiary treatment (Gerba & Pepper, 2019; Mandal et al., 2020; Singh et al., 2021; Sonune & Ghate, 2004). Primary treatment involves physical processes for the removal of solids from wastewater (Mandal et al., 2020). Secondary treatment includes biological

processes for the degradation of organic matter (Mandal et al., 2020; Sonune & Ghate, 2004). The tertiary treatment is stage where advanced treatments are conducted for removing the contaminants that could have not been removed during the first two stages (Dhodapkar & Gandhi, 2019; Gerba & Pepper, 2019). However, wastewater treatment plants usually have low removal efficiency of diverse persistent contaminants, including pharmaceuticals such as psychiatric drugs (Jelic et al., 2011; Wu et al., 2020; Zhang et al., 2008).

There are reports where the removal efficiency of diverse psychiatric drugs of wastewater treatment plants was evaluated. A research carried out by (Jelic et al., 2011) studied three different WWTPs during two years for evaluating the removal efficiency of 43 pharmaceuticals compounds, including psychiatric drugs such as carbamazepine, diazepam, and lorazepam. Samples of the influent, effluent, and the sludge were taken to determine the occurrence of the pharmaceuticals and the efficiency of the WWTPs. According to the results, 32 pharmaceuticals were detected at the influent, and after the treatment 29 were detected at the effluent, and 21 were accumulated in the sludge, which means the processes are moderately effective for removing psychiatric drugs.

As most of the current technologies of WWTPs do not have 100% of efficiency removing some specific contaminants such as psychiatric drugs, efforts have been made to develop or adapt technologies at lab-scale with potential as high-efficiency removal technologies. Different methodologies for the remotion of psychiatric drugs have been reported, in general it can be classified as psychical or chemical techniques (Table 1), including adsorption (Rasheed et al. 2020), membrane filtration (Rizzo et al. 2019), photodegradation (Osawa et al. 2021), Fenton process

(Lumbaque et al. 2018), electrochemical degradation (Bosio et al. 2021), and some others.

2.2.1. Physical treatments

Physical treatments reported for removing psychiatric drugs from water include adsorption, membrane filtration, and thermal degradation (Graumans et al., 2021; Rasheed et al., 2020; Rizzo et al., 2019). Adsorption is promising approach for removing contaminants, as there is a wide range of adsorbents, it is a straightforward process with lower operation costs compared to technologies such as reverse osmosis (Crini & Lichtfouse, 2019). There are reports of several adsorbents, such as activated carbon, biochar, and metal oxide nanoparticles, that were successfully employed for removing diverse psychiatric drugs (Rizzo et al., 2019; Rocha et al., 2020). For example, a study carried out by (Aydın et al., 2021) employed magnetite (Fe_3O_4) red mud nanoparticles (RM-NPs) for the adsorption of carbamazepine, paroxetine, lorazepam, fluoxetine, and diazepam. The results showed a removal efficiency between 80% for lorazepam and 97% for diazepam from the initial concentration of 0.1 mg/L within 30 min. Moreover, biochars and activated carbon have been applied for the adsorption of carbamazepine from wastewaters, in which it was possible to remove concentrations ranging from 0.5 to 20 ppb (Naghdi et al. 2019, Pereira et al. 2021).

Another example of psychical treatment is membrane filtration (e.g., forward osmosis). The main advantages of this technology include that no chemicals are needed, low solid waste generation and high efficiency (Crini and Lichtfouse et al. 2019, Meshksar et al. 2021). This methodologically approach have showed better

results for the degradation of psychiatric drugs compared to simple adsorption techniques (Naddeo et al. 2020). For example, Liu et al. evaluated the removal of carbamazepine and sulpiride, by coupling a forward osmosis membrane (FO) with electrochemical oxidation (EO) and obtain degradation efficiencies greater than 94 % (Liu et al. 2018).

Membrane filtration is another common contaminant removal technology for removing contaminants from water. The main advantages of this technology include that no chemicals are needed, low solid waste generation and high efficiency (Crini & Lichtfouse, 2019). The material of the membrane, ceramic or polymeric, and the pore size are the main characteristics that influence the application and efficiency of membrane filtration (Meshksar et al., 2020).

In contrast, even though thermal treatment of water has been reported in the literature for the removal of contaminants from water, and desalination (Akay et al., 2021; Graumans et al., 2021; Hao et al., 2022; Pang et al., 2020), it is required to conduct more studies regarding the application of thermal treatments in the degradation of psychiatric drugs from water, as the publications related to thermal degradation of psychiatric drugs are focused on the thermal approach but not in aqueous media (Ferreira et al., 2018; Pinto et al., 2018).

Physical treatments such as membrane filtration or adsorption are very employed in psychiatric drugs removal as they offer some advantages, for example most of them do not require harmful chemicals, nor produce toxic reaction by-products. However, they also have some drawbacks, as it is required and additional step for degrading or confining the contaminant removed from water. I this way, further research is needed to develop cheaper materials with higher selectivity to

enable the application of these technologies at real conditions in a WWTPs. Also, it is required to conduct more studies where combined processes are employed, for example UV degradation/filtration, as a possible alternative for degrading the concentrated contaminants.

2.2.2. Chemical treatments

Chemical treatments are widely employed in water decontamination of a wide range of chemicals from water, as compared to other technologies the contaminants are degraded into non-toxic compounds and in most cases, it is not required further steps (Ahmed et al., 2017). For the degradation of psychiatric drugs, among the most employed technologies are photodegradation (Trawiński & Skibiński, 2017), electrochemical (García-Espinoza et al., 2018), and advanced oxidation (Saeid et al., 2020), like Fenton process (Oller & Malato, 2021) or ozonation (Nika et al., 2021).

Photodegradation is a technology that uses UV radiation or visible light as source of energy for breaking down the molecules of contaminants present in water and transforming them into other less harmful compounds in most cases (Blánquez et al., 2020). This technology has been applied for the degradation of psychiatric drugs such as carbamazepine (blan-Nogueras et al., 2017), alprazolam (Shi et al., 2019), benzodiazepines (Calisto et al., 2011), among others. A research conducted by (Osawa et al. 2019), evaluated the photodegradation of venlafaxine, trazodone, amitriptyline using UV-Vis radiation and nanowires of cobalt-titanate as photocatalyst (Co-TNW). The results showed that the use of the photocatalyst enhanced the removal efficiency of amitriptyline compared to the photolysis without the catalyst. For trazodone, a removal of 90% was achieved after 15 min. For the

venlafaxine a removal efficiency of 99% was achieved after 90 min in both cases, with catalyst and without using it. Moreover, the photodegradation under simulated solar light radiation of carbamazepine using a $BiOCl/Fe_3O_4$ composite as catalyst was evaluated in a study by (Chen et al., 2017). I was reported that the efficiency of the degradation of carbamazepine was 90.3% after 60 min. Also, the effect of anions in water during the degradation was evaluated, showing that nitrate slightly increased the photodegradation, while the inhibiting effect was in the order of $CO_3^{2-} > SO_4^{2-} > Cl^-$.

Advanced oxidation processes (AOP) are a group of chemical treatments where the contaminants in water are oxidized through the reaction with hydroxyl radicals into safer or easier to handle compounds (Dave & Das, 2021). Some of the most reported AOPs include ozonation, Fenton processes, and electrochemical oxidation. In the ozonation, ozone (O3) is using as oxidant due to its highly oxidizing capability. Researchers reported the use of ozonation assisted by UV radiation for the degradation of carbamazepine in wastewater (Somathilake et al., 2017). The authors evaluated the dosage of O3, the wavelength and intensity of radiation. The results showed that using a dose of 14.4 mg/h a degradation below the detection limits was achieved after 0.5 min. The intensities of UV radiation with better results were 0.62 mW/cm2 for UVA and 0.82 mW/cm2 for UVC. Moreover, A research conducted by (Aghaeinejad-Meybodi et al., 2021), studied the ozonation and catalytic ozonation of fluoxetine comparing the efficiency in the presence of boehmite and γ-alumina as catalysts. Results demonstrated that pH had a major influence on the efficiency of the process, as the removal was less than 50% at pH of 7 but increased as with higher pH.

Fenton processes or Fenton reaction, consists in the oxidation by strong oxidizing agents, such as hydroxyl, produced by the catalytic decomposition of hydrogen peroxide by Fe^{2+} and/or Fe^{3+} (Vasquez-Medrano et al., 2018). There are variations of the traditional Fenton process, like photo-fenton, that additionally combines the use of UV and/or visible light, increasing the ratio of degradation of contaminants (Ameta et al., 2018). Electro-Fenton is another variation that is reported for the degradation of psychiatric drugs and other contaminants, which consists in the Fenton's reaction taking place in an electrochemical cell (Gümüş & Akbal, 2016).

A study carried out by (Dwivedi et al., 2016) evaluated a fenton process coupled with ozonation for the degradation of carbamazepine and oxcarbazepine in simulated wastewater. The authors used Response Surface Methodology to find the optimal conditions for the degradation of the psychiatric drugs, and reported that at pH 2, a Fenton dosage of 1.61 g/dm^3, 0.427 of Fe2+/H2O2 ratio the degradation was 92.49% after 25 min. Additional study conducted by (Mitsika et al., 2021) evaluated photo-Fenton degradation of alprazolam and diazepam and optimized the process. The authors reported that the Response Surface Methodology allowed the optimization of the parameters, and the degradation efficiency of alprazolam and diazepam was 100% after 180 min.

Electro-Fenton processes were evaluated in the degradation of carbamazepine from water without using any extra oxidant in a study conducted by (Li, J. et al. 2021). The system did not use H_2O_2 and the reaction took place in the presence of sodium molybdate. After 60 min the removal efficiency was near to 100%, compared to traditional electro-Fenton which only achieved 34%. Also,

electrochemical oxidation has been evaluated in the degradation and detection of psychiatric drugs in water. This process consists in the either by direct oxidation of the drugs by the electron transfer from the contaminant to the anode, or indirect oxidation through the generation of oxidizing species like hydroxyl radicals (da Silva et al., 2021).

A study evaluated the electrochemical oxidation of alprazolam, clonazepam, diazepam, lorazepam, and carbamazepine from water using as electrodes platinium-coated titanium and boron-doped diamond (Bosio et al., 2021). The authors evaluated different current densities, pH, and electrolyte concentrations. The results showed that all the drugs were degraded after 5 min at a current density of 75 A/m^2 for both electrodes. The effect of matrix was evaluated using municipal wastewater, and the degradation efficiency was 40% for platinium coated titanium and 33-52% for boron-doped diamond.

2.3. Biocatalytic systems to remove Psychiatric drugs from wastewaters

Biocatalysis is the result of the advances in molecular biology and biotechnology achieved during the past two decades (Sheldon and Woodley 2018), which appeared as result of the necessity to develop greener, sustainable, and profitable processes in different industries, including pharmaceutical industry (Bell et al. 2021), food industry (Bilal and Iqbal 2020), fine chemicals production industry (Thompson, M. P. et al., 2018), and more recently, in bioenergy production processes (Kim et al., 2018). The increasing interest in biocatalysis is since it provides significant benefits over conventional catalysis (e.g., inorganic catalysts),

such as higher catalytic properties, high specificity, high reaction rate under mild reaction conditions of pH and temperature, low energy consumption, and biodegradability (de Jesús Rostro-Alanis et al., 2016), which are primarily given by two fundamental principles: (1) biocatalysts are not consumed or permanently modified during catalysis reactions, and (2) chemical equilibrium is not altered by the presence of biocatalysts (Lopez-Cantu et al., 2021).

Moreover, biocatalysis processes have been widely applied for the biodegradation/biotransformation of a wide range of emerging contaminants, such as personal care products, industrial chemicals, steroids hormones, pesticides, and pharmaceuticals, in which are included psychiatric drugs (Asif et al., 2018). In general, the bioconversion of psychiatric drugs by biocatalytic systems have been achieved in three different ways (Figure 3): (a) whole-cell biocatalysis, (b) isolated-enzyme biocatalysis, and (c) isolated-immobilized enzyme into a nanomaterial (Bilal and Iqbal 2019, Sheldon and Woodley 2018, Martínez SAH et al. 2021).

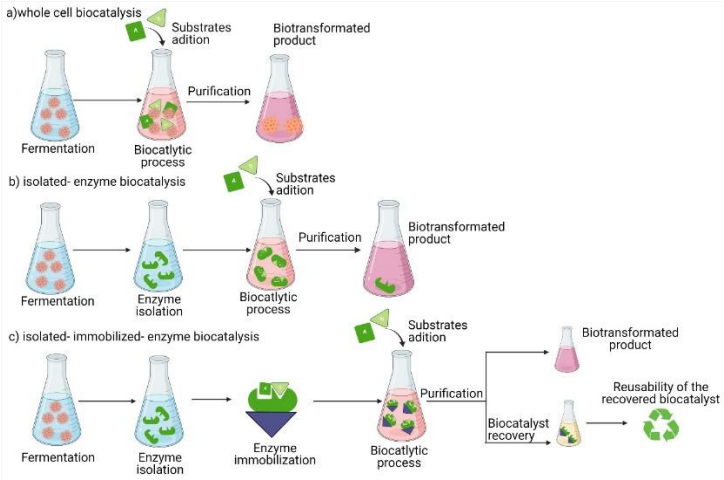

Figure 3. Schematic illustration of various routes to design and deploy biocatalytic processes

2.3.1. Whole-cell biocatalysis of psychiatric drugs

The whole-cell biocatalytic process, which is represented in Figure 1a, represents those cases in which the growth of the biocatalyst and the subsequent catalytic reaction occurs all in a whole-cell format (Sheldon and Woodley 2018). This format of biotransformation has been used in different biotransformation processes due to several advantages, such as high surface-area-to-volume ratio, high catalytic activity, and low energy requirements (Pinto et al., 2020, Liu et al., 2019). However, the whole-cell biocatalysis approach presents some disadvantages related to the low diffusion rate of the substrate into the cell to the reaction centers, where takes place the enzymatic reaction (Kladko et al., 2021), which leads to low stability, cross reactivity, impossibility to recycle the biocatalyst and time-consuming purification steps (Sheldon and Woodley 2018, Haghighatian et al., 2020).

Different psychiatric drugs have been successfully biotransformed by whole-cell biocatalysis (Table 2). For example, Kózka et al. removed some common antidepressants, such as sertraline, clomipramine, mianserin and paroxetine using a white-rot fungus *Pleurotus ostreatus* (Kózka et al., 2020). Results show that it was possible to biodegrade 96 % of some antidepressants in 96 h. Another study conducted by (Llorca et al., 2019) was able to completely remove venlafaxine its metabolite desmethylvenlafaxine using commercial *Trametes versicolor* and *G. lucidum* within 360 h.

Even though whole-cell biocatalysis is the simplest way to apply biocatalysis for the biotransformation of psychiatric drugs, it seems to have as greater disadvantage the total time that takes to degrade and purified the products. In literature, the shortest time reported for the biotransformation of psychiatric drugs

was reported by (Tislet et al., 2019), who degraded 100 % of the antidepressant fluoxetine within 48 h using zebrafish embryos as biocatalysts. In addition, the biotransformation of some other mood stabilizers and anxiolytics, such as amitriptyline, carbamazepine and oxazepam, has been successfully achieved in a time rage between 144-360 h by the application of different microorganisms, including *Chlorella sorokiniana* (Gojkovik et al., 2019), *Aspergillus luchuensis* (Dalecka et al., 2021) and *Stropharia rugosoannulata* (Castellet-Rovira et al., 2018).

2.3.2. Isolated-enzyme biocatalysis of psychiatric drugs

The isolated-enzyme biocatalysis process is represented in Figure 3b. It consists in the application of purified enzymes extracted from cells with the principal objective to overcome the diffusional limitations that occurs in the whole-cell biocatalysis (Sheldon and Woodley 2018). The isolated-enzyme biocatalysis is based in the principle that enzymes are natural biocatalysts that can be implemented to catalyze chemical reactions without affecting the chemical equilibrium of the rection media (Rostro-Alanis et al., 2016). Therefore, this biocatalytic approach provides selectivity for the efficient biotransformation of a wide range of water pollutants, such as dyes (Routoula and Patwardhan 2020), plastics (Magalhães et al., 2021), and pharmaceuticals (Asif et al., 2018), including psychiatric drugs.

Even though there are different enzyme that have been applied for the biotransformation of psychiatric drugs, such as horseradish peroxidase, lignin peroxidase and soybean peroxidase (Pylypchuk et al., 2020, Morsi et al., 2021), laccases are the most common enzymes implemented for the degradation of psychiatric drugs due to its important characteristics. Laccases are multi-copper

extracellular enzymes obtained from fungi, plants, insects, and a few bacteria (Masjoudi et al., 2021). The widespread application of laccase enzymes is due to the ability to catalyze the oxidation of a variety of organic substrates without the presence of oxidizing agents (Lopez-Cantu et al., 2021).

Commercial laccases and laccases from different microorganisms, such as *Trametes versicolor* (Asif et al., 2018), *aspergillus oryzae* (Tufail et al., 2021), *paraconiothyrium* (Ostadhadi-Dehkordi et al., 2012) have been applied for the biotransformation of psychiatric drugs (Table 3). For example, the anxiolytic and mood stabilizer, carbamazepine was biotransformed by commercial laccases using ABTS as mediator to reach 95 % of degradation within 24 h (Naghdi et al. 2018). Moreover, compared to whole-cell biocatalysis, the isolated-enzyme assisted biocatalysis have shown that biotransformation can be achieved in shorter times, since a wide range of psychiatric drugs have been successfully degraded using laccases in a time range between 1 h to 72 h, which is shorter than the range in whole-cell biocatalysis (Alharbi et al., 2019, Gonzalez et al., 2019, Tufail et al., 2021).

However, this biocatalytic approach presents some disadvantages, including that lower biotransformation rates are achieved due to their lack of long-term operational stabilities (Xie and Zang 2018). For example, a study conducted by (Gonzalez et al., 2019) implemented a mixture of different enzymes, including laccases, revealed that the anxiolytic venlafaxine was degraded only around 50 % within 72 h, which is the longest time reported in enzyme catalyzed biodegradation. Moreover, the cost of using free enzyme is such that reuse is necessary, however, isolated enzymes are hardly recyclable and separable (Masjoudi et al., 2021).

2.3.3. Isolated-immobilized enzyme biocatalysis of psychiatric drugs

In Figure 3c, it is schematically represented the implementation of isolated-immobilized enzymes in a biocatalytic process. The immobilization of enzymes consists in convert the enzyme from its homogenous form to a heterogenous catalysts by the addition of solid supports in which the enzyme is tagged using different immobilization methos, such as adsorption, covalent binding, cross-linking, entrapment, and encapsulation (Morsi et al., 2021).By the immobilization of enzymes into solids supports it is possible to overcome the major disadvantages of using free enzymes in biocatalytic processes due to it increment the long-term stability of the enzymes, providing resistant to degradation or denaturation (Bilal and Iqbal 2019). Moreover, the addition of solid supports in the biocatalyst design facilitates the separation of the biocatalyst from the product stream and, thereby, it allows recycling (Sheldon and Woodley 2018).

The design of nanobiocatalysts for the biodegradation have been reported for the degradation of psychiatric drugs (Table 4). Following the tendency of the isolated-enzyme biocatalysis, laccases are the most common enzymes used in immobilized form to biodegrade these compounds. Different nanomaterials are reported for the immobilization of laccases to remove psychiatric drugs from waters, including polymers (Simón-Herrera et al. 2019), metals and metal oxides (Guardado et al., 2021), and carbon-based materials (Masjoudi et al., 2021). For example, polyamide aerogels were implemented to covalently immobilize laccases from *Trametes versicolor* and catalyze the biotransformation of carbamazepine (Simón-Herrera et al. 2019). The biodegradation assays conducted to conclude that this nanobiocatalyst was able to remove 76 % of the psychiatric drug within 24 h. Also,

this nanobiocatalyst presented excellent reusability properties since it retained 22 % of its initial activity after seven cycles of use. Moreover, a study made by (Naghdi et al., 2017), demonstrated that adsorption is other immobilization technique that can be implemented to remove anxiolytics from secondary effluent of wastewaters. In this study, a nanobiocatalyst was design by adsorbing laccases into nanobiochar structure, which allowed to remove 86 % of carbamazepine within 24 h during 3 continuous cycles.

In addition, some other enzymes have been applied for the biotransformation of psychiatric drugs. For example, (Pylypchuk et al., 2020) completely degrade carbamazepine using peroxidases immobilized in a core-shell composite of magnetite and silica (Fe_3O_4@SiO_2). The encapsulated enzymes showed promising recycle properties since 50 % of the initial activity was retained after 20 cycles of use.

Recycling will depend primarily on the type of material and immobilization method (Bilal et al., 2018). In this term, not every nanobiocatalyst will be capable to be reused many times as other ones, for example, a soybean peroxidase immobilized covalently into zinc oxide retained 95 % of initial activity after 4 cycles (Morsi et al., 2021), whereas a laccase nanobiocatalyst designed with the covalently immobilization into silica nanoparticles retain almost 28 % of its initial activity but after 7 cycles.

Table 1. Degradation of psychiatric drugs by non-biocatalytic systems.

Method	Materials	Psychiatric drug	Degradation parameters	Time (h)	Remotion/ degradation (%)	Ref
Photodegradation	ZnO, TiO_2	Amitriptyline[1,2,4]	1 mg/mL of ZnO and TiO_2, 25°C, 0.03mM of AMI, pH 6.7	1	55.3- 94.3	Finčur et al. 2021
Photodegradation	TNW, Co-TNW, Fe-TNW, Ru-TNW	Trazodone[1]	20 mg of catalyst, 5 mg/ L of TRA, 25 °C, pH 5.8-6.2	8	57-98	Osawa et al. 2020
Photodegradation	PLC	Clozapine[3]	300 mg/L of CZP, 50 ppm PLC, 30 °C,	2	94.2	Kumar et al. 2021
Photodegradation	Co-TNW	Amitriptyline[1,2,4], trazadone[1], venlafaxine[1]	10 mg/L of psychiatric drug, 10 mg of Co-TNW, pH 7, 25 °C	2	85-99	Osawa et al. 2019
Photo-Fenton	Iron (III) salt	Alprazolam[2], diazepam[2]	500 mL of psychiatric drug 10 mg/L, pH 2.9	2	~100	Mitsika et al. 2021
Fenton	Iron (II) salt	Diazepam[2]	500 µg/L of diazepam, 12.5-37.5 mg/L of Fe (II), 533 mg/L of H_2O_2, pH 5	1	~70-90	Lumbaque et al. 2018
Electro-Fenton	Iron plate anode, graphite rod cathode	Carbamazepine[2,4]	300 mL CBZ 5 mg/L, EF-Na_2MoO_4 electrolyte, pH 6.3, 0.145-0.580 mA/cm^2 , 25 °C	1	80-85	Li, J. et al. 2021

Electron beam irradation	Not apply	Fluoxetine[1]	50-100 mg/L of FLX, 0.5-5.0 kGy (irradation dose), 20-22 °C	-	90 -98	Shao et al. 2018
Electrochemical	Ti/Pt and BDD electrodes	Alprazolam[2], clonazepam[2], diazepam[2], lorazepam[2], carbamazepine[4]	25-75 A/m^2, 1 L reactor, 25 °C, 100 µg/L of psychiatric drug, pH 3-10,	60 min	40-99	Bosio et al. 2021
Ozonation	O_3	Citalopram[1]	2 mg/L of citalopram, 1.5 mg/L of ozone, pH 7, 25 °C	1 h	92	Nika et al. 2021
FO-EO	IrO_2-Ta_2O_5-SnO_2	Carbamazepine[2,4], Sulpiride[3]	10mg/L of psychiatric drug, 20 °C, 480 min, 1 mA/cm^2, pH 5	480 min	86-89	Liu et al. 2018
Thermal degradation	Not apply	Citalopram[1], escitalopram oxalate[1]	1000°C at increment of 10 °C/min, 15 mg of sample	20-45 min	27-74	Pinto et al. 2018
Thermal degradation	Not apply	Paroxetine[1], Sertraline[1]	1000 °C at increment of 5 °min, 7 mg of sample	28-58 min	~100	Ferreira et al. 2018
Advanced oxidation process	$CuFe_2O_4/MoS_2$, $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)	Fluoxetine[1]	80 mL of 20 mg/L of fluoxetine, 300 rpm, 1 M methanol, 1 M tert-butanol, 1.5 molar ratio of catalyst, 20 min	20 min	97.7	Bai et al. 2020

Adsorption	Fe_3O_4	Carbamazepine[2,4] Paroxetine[1] Lorazepam[2] Fluoxetine[1] Diazepam[2]	0.1 g of psychiatric drug, 1 g of adsorbent, pH 6.5	30 min	80-97	Aydin et al. 2021
Adsorption	Biochar	Carbamazepine[2,4]	0.2 g of CBZ, 4-20 mg of adsorbent, pH 3-6	180 min	95	Naghdi et al. 2019

[1]Antidepressant, [2]Anxiolytic, [3]Antipsychotic, [4]Mood stabilizer, Amitriptyline (AMI), Carbamazepine (CBZ), Trazodone (TRA), Fluoxetine (FLX).

Table 2. Biocatalysis of psychiatric drugs by whole cell biocatalysis.

Biologic agent	Source	Psychiatric drug	Type of sample solution	Time (h)	Remove conditions	Remotion/ Degradation (%)	Reference
Pleurotus ostreatus	White-rot fungus from Manassas Virginia	Sertraline[1],Clomipramine[1],mianserin[1], paroxetine[1]	Psychiatric drugs mixture in ultrapure water	4-96	26°C, 110 rev/min, 2.5 µg/mL and 100 mg/mL of sample	20-96	Kózka et al. 2020
Trametes versicolor and G. lucidum	Commercial	Venlafaxine[1], O-desmethylvenlafaxine[1]	Ultrapure water	360	2 mg/L of VFX and ODVFX, steril media, pH 4.5, 25 °C	70-100	Llorca et al. 2019
Stropharia rugosoannulata, Ganoderma lucidum,	Donated by University of Helsinki	Venlafaxine[1], carbamazepine[2,4]	Stock solution with psychiatric drugs	144	25 °C, 135 rev/min,100 mL of medium, 4.5 g/L of cultive pellets, 40-184.7 µg/mL of sample, dark conditions	70-75 %	Castellet-Rovira et al. 2018
Trametes versicolor, Aspergillus luchuensis	Trametes versicolor native from Brunswick, Germany and A. luchuensis native from Stockholm, Sweden	Carbamazepine[2,4]	Wastewaters	168	50 g of biomass, 25 °C, 120 rev/min	<30	Dalecka et al. 2021

Chlorella sorokiniana , Chlorella vulgaris, Chlorella saccharophila, Coelastrella sp., Coelastrum astroideum, Desmodesmus sp., Scenedesmus sp., Scenedesmus obliquus	Northern Sweden green algea	Amitriptyline[1], carbamazepine[2,4], oxazepam[2]	Psychiatric drugs mixture in ultrapure water	288	25 °C, 120 rev/min, 100 mg/L of biomass, pH 7.2, 1 µg/mL of psychiatric drug	24-92	Gojkovik et al. 2019
Zebrafish embryos	Danio rerio	Fluoxetine[1]	Ultrapure water	48	26 °C, pH 7.2 ,5 mg/L of FLX, 160 embroys	100	Tislet et al. 2019

[1]Antidepressant, [2]Anxiolytic, [3]Antipsychotic, [4]Mood stabilizer, Venlafaxine (VFX), O-desmethyl venlafaxine (ODVFX), fluoxetine (FLX).

Table 3. Biocatalysis of psychiatric drugs by isolated enzymes

Enzyme	Source	Psychiatric drug	Type of sample solution	Time (h)	Remove conditions	Remotion/ Degradation(%)	Reference
Laccases	(ATCC (American Type Culture Collection) 20869)	Carbamazepine2,4	Ultrapure water	24	35 °C, pH 6, 60 U/L of enzyme concentration and 18 µM of ABTS	95	Naghdi et al. 2018
Laccases	*Aspergillus oryzae*	Amitriptyline1, carbamazepine2,4,	Synthetic wastewater containing a mixture of organic trace materials	24	20 µg/L of sample, 100 µg/min of enzyme, 30 °C	60-99	Asif et al. 2018
Laccases	*Trametes versicolor*	Carmazepine2,4	Ultrapure water	48	1.25-5.00 mg/L of CBZ, enzyme activity of 430-460 U/L, 25 °C, pH 6.9	82	Alharbi et al. 2019
Laccases	Commercial laccases from *Aspergillus oryzae*	Carbamazepine2,4	Ultrapure water	1	1 mg/L of CBZ,95-100 µM/min of laccase, 30 °C	70	Tufail et al. 2021
Laccases	Soil ascomycete, *Paraconiothyrium* variabile	nitrazepam, alprazolam, diazepam, oxazepam, clobazam, chlordiazepoxide, lorazepam	Ultrapure water	48	10 µg/mL of sample, enzyme activity 20 U/mL, 2 mM of HBT mediator, 35 °C	4.7-88.1	Ostadhadi-Dehkordi et al. 2012
Mixture of enzymes	Anaerobic sludge	Venlafaxine2	Ultrapure water	72	0.1 ng/µL of sample, 100 µL of enzymes, anaerobic atmosphere, 30 °C	~50	Gonzalez et al. 2019

[1]Antidepressant, [2]Anxiolytic, [3]Antipsychotic, [4]Mood stabilizer, Carbamazepine (CBZ), ,2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), 1-hydroxybenzotriazole (HBT).

Table 4. Biocatalysis of psychiatric drugs by isolated-immobilized enzyme biocatalysts.

Enzyme	Source	Support	Immobilization method	Immobilization yield (%)	Psychiatric drug	Type of sample solution	Remove conditions	Time (h)	Stability/reusability	Remotion/ Degradation(%)	Reference
Laccases	*Trametes versicolor*	Polyimide aerogels	Covalent	17.2	Carbamazepine[2,4]	Ultrapure water and secondaty effluent	20 ng/mL of CBZ, 200 rpm, 25 °C,	24	7 cycles, 22%	74-76	Simón-Herrera et al. 2019
Laccases	*Trametes hirsuta*	PVDF/MWCNTs	Adsorption	38.31	Carbamazepine[2,4]	Ultrapure water	5 ppm of CBZ, 223 U/mL of catalysts, pH 5, 25 °C	4	5 cycles, 20 %	95	Masjoudi et al. 2021
Laccases	*P. ostreatus*	TiO_2	Covalent	63.7	Carbamazepine[2,4]	Ultrapure water	10 µM of CBZ, 0.1 U/mL of enzyme, pH 5.5, 25 °C	48	Not reported	~10	Ji et al. 2017
Laccases	*Trametes versicolor*	Nanobio char	Adsorption	41	Carbamazepine[2,4]	Ultrapure water and secondaty effluent	20 ng/mL of CBZ, 20 mg of catalyst, 200 rpm, 25 °C	24	3 cycles, 70 %	83-86	Naghdi et al. 2017
Laccases	*Trametes versicolor*	Polyacrylonitrile–biochar	Covalent	Not reported	Carbamazepine[2,4]	Ultrapurewater	2 ppb of CBZ, 25 °C, pH 4-7	8	10 cycles, 17 %	48.6	Taheran et al. 2017

Laccases	*Trametes versicolor*	SiO_2	Covalent	35	Carbamazepine[2,4]	Ultrapurewater	10 mb/mL of CBZ, 520 μM 25 °C, pH 7	4	7 cycles, ~28%	~50	Guardado et al. 2021
Horseradish peroxidase and lignin peroxidase	Commercial enzymes	Fe_3O_4/SiO_2	Encapsulation	Not reported	Carbamazepine[2,4]	Ultrapure water	17.6 μg/mL of CBZ, 0.06 mg/mL of enzyme, pH 3-5,	72	20 cycles, 43- 50 %	60-100	Pylypchuk et al. 2020
Soybean Peroxidase	Commercial enzymes	ZnO, TiO_2	Covalent	Not reported	Venlafaxine[2]	Mixture of pollutants	2 ppm of sample, 0.3 mM of H2O2, pH 4, 2 mg of biocatalyst, 25 ° C	0.5	4 cycles, 95 %	7.3-11. 0	Morsi et al. 2021

[1]Antidepressant, [2]Anxiolytic, [3]Antipsychotic, [4]Mood stabilizer, Carbamazepine (CBZ), Polyvinylidene Fluoride (PVDF), Multiwalled carbon nanotubes (MWCNTs).

2.4. Conventional vs biocatalytic systems

As it has been discussed in this review, conventional degradation techniques, including physical and chemical treatments; and biocatalytic processes might have both advantages and disadvantages. For example, it has been demonstrated that conventional methods such as photodegradation might remove completely psychiatric drugs from wastewater (Osawa et al., 2019). In general, both physical and chemical treatments have been widely implemented for the degradation process due to the high rates of remotion that are usually obtained. However, even though these degradation approaches are efficient for the degradation of psychiatric drugs, high energy consumption is needed (Haghighatian et al., 2020). Moreover, due to typically chemicals and special materials are needed to implement these technologies, it has been reported that a large number of undesired products can be produced (Liu et al., 2019). For example, it was reported that after the photodegradation of venlafaxine from water, almost 70 by-products were formed (Lambropoulou et al., 2017). In comparison to biotransformation process, (Gonzalez-Gil et al., 2019) also reported the removal of venlafaxine from waters, however, there wasn't by-product detection.

Moreover, biotransformation is characterized by its non-toxic and biodegradable behavior, which in comparison to non-biocatalytic technologies, biocatalysis appears as green and sustainable approach that follows almost the 12 principles of green chemistry (Haghighatian et al., 2020, Sheldon and Woodley 2018). Thus, biocatalysis can be considered as a more efficient approach to remove psychiatric drugs from aquatic systems.

2.5. Transformation products of psychiatric drugs and their detection/monitoring

Techniques such as ozonation and UV photolysis have shown excellent performance on the removal of psychiatric drugs (Ikehata et al., 2006; Naghdi et al., 2018); however, complete oxidation and mineralization are typically not achievable, thus, releasing transformation products (TPs) (Donner et al., 2013; Naghdi et al., 2018). Historically, research efforts on environmental monitoring of pharmaceutical residues have been focused on the parent compounds (Boix et al., 2016; L. Li et al., 2022; Wang et al., 2021; Yang & Carlson, 2004). However, the persistence and ecotoxicological effects of TPs –occasionally with higher toxicity than parent compounds– have led to an increased research interest in their detection (Boix et al., 2016; Ferrer & Thurman, 2012; Singh et al., 2021) and with it, the urgent need for powerful analytical methods since their detection/identification is challenging due to complex degradation mechanisms and because there are no analytical standards for most of TPs (Huntscha et al., 2012; Osawa et al., 2019).

Nevertheless, advances in environmental analysis by mass spectrometry technologies had enabled rapid, selective, and robust quantification of TPs and the detection of unknown compounds (Haddad & Kümmerer, 2014; Osawa et al., 2019). In this regard, TPs from psychiatric drugs have been effectively detected using different high-resolution mass spectrometry (HRMS) analyzers such as Orbitrap (Llorca et al., 2019) and quadrupole time-of-flight (QTOF) (Carpinteiro et al., 2017; Gonzalez-Gil et al., 2019; Osawa et al., 2019). Mass analyzers can be coupled to gas chromatography; however, a wider range of compounds with

different chemical properties and polarities can be properly analyzed through liquid chromatography (Aceña et al., 2015). Thus, as demonstrated in Table 5, liquid chromatography coupled to mass spectrometry is the preferred technique for pharmaceutical degradation experiments because of its high sensitivity and selectivity. Other techniques such as nuclear magnetic resonance (NMR) together with HRMS have been also performed on isolated TPs to conclusively identify the TPs' structures (Kråkström et al., 2020).

The feasibility of water treatment methods needs to consider the TPs in terms of abundance, stability, and ecotoxicity; which is highly dependent on the degradation pathway. For example, in the human body the metabolization of carbamazepine (CBZ) results in the formation of dihydroxy-carbamazepine and carbamazepine epoxide as the main metabolites (Kråkström et al., 2020). On the other hand, 15 different TPs derive from the ozonation of CBZ, such as 1-(2-benzaldehyde)-4-hydro-(1H,3H)-quinazoline-2-one (BQM) and 1-(2-benzaldehyde) -(1H,3H)-quinazoline-2,4-dione (BQD), which are the main representative products. Contrastingly, laccase-mediated degradation processes have demonstrated the formation of a lesser number of TPs (in the range of 2 – 5). The main TPs derived from laccase-mediated biodegradation of CBZ are 10,11-dihydro-10,11-epoxy-CBZ (CBZE), 10,11-dihydro-10,11-dihydroxy-CBZ (CBZD), and acridone (Alharbi et al., 2019; Ji et al., 2016; Naghdi et al., 2018; Tufail et al., 2021). Similar results were obtained by Pylypchuk et al. (2020) using peroxidase enzymes (horseradish peroxidase and lignin peroxidase).

The differences in the TPs and their abundance have a significant effect on the toxicity of the resulting solution. In this regard, Donner et al. (2013)

evaluated the toxicity of TPs formed during ultraviolet photolysis of CBZ. The ecotoxicity assays showed an increased ecotoxicity after CBZ degradation, demonstrating higher toxicity of the resulting TPs (Donner et al., 2013). Furthermore, the individual and mixture toxicity of four TPs of CBZ (CBZE, CBZD, BQD, and BQM) were tested in zebrafish (Danio rerio). The mixture presented comparable toxicity to that of CBZ, while the individual toxicity assessment suggested that BQM and BQD were the main ones responsible for the toxicity (Pohl et al., 2020). These results were in agreement with Alharbi et al. (2019), who compared the enzymatic method with advanced oxidation processes (ozonation, UV photolysis, and UV/H_2O_2 treatment) in terms of toxicity of treated solutions. Ozonation and UV photolysis of CBZ resulted in increased toxicity due to the formation of highly toxic TPs. However, the enzymatic degradation method produced a non-toxic effluent under the same toxicity assessment assay (Alharbi et al., 2016, 2019). Similarly, Tufail et al. (2021) evaluated the effect of adding an enzymatic pretreatment on the degradation of CBZ by ultraviolet photolysis. Interestingly, the non-enzymatic treatment produced twelve TPs, while the enzymatic treatment formed five TPs with lower abundance, suggesting a more complete degradation (Tufail et al., 2021). In this context, the merits of biocatalytic degradation are not only related to their low energy requirements and moderate conditions but also to the minimization of undesirable TPs due to the high specificity of enzymes (Naghdi et al., 2018).

On the other hand, the photocatalytic degradation of Venlafaxine (VFX) and the consequent formation of TPs have been investigated by different authors. Lambropoulou et al. (2017) detected more than 70 TPs from the photocatalytic

degradation of VFX using 800 mg/L of TiO2 catalyst. Whereas Osawa et al. (2019) elucidated the structures of five TPs derived from the photocatalytic degradation of VFX using 150 mg/L of modified cobalt-titanate nanowires as catalyst (Osawa et al., 2019). The remarkable differences in TPs formation could be attributed to the catalysts used, their concentration, among other operational parameters.

Typically, O-desmethylvenlafaxine (ODMVFX) and N-desmethylvenlafaxine (NDMVFX) are found as the main TPs of VFX' degradation (Lambropoulou et al., 2017; Llorca et al., 2019). ODMVFX is formed by the demethylation of the methoxy group of VFX, while the demethylation of the dimethylamino group of VFX results in the formation of NDMVFX. Recently, Llorca et al. (2019) evaluated the removal efficiency of three fungal treatments (Trametes versicolor, Ganoderma lucidum, and Pleurotus ostreatus) on VFX. Regardless of the fungal species, three TPs including ODMVFX and NDMVFX were reported. Similar VFX removal efficiencies (~70%) were achieved by T. versicolor and G. lucidum; however, the latter one produced more ODMVFX. Despite both TPs (ODMVFX and NDMVFX) do not possess higher toxicity effects than those presented by the parent compound (VFX), ODMVFX had a higher N-nitro-sodimethylamine formation potential with negative effects on human health and the environment. Therefore, T. versicolor was presented as a better alternative in comparison with G. lucidum, which generated more ODMVFX within their TPs (Llorca et al., 2019).

In this manner, a critical issue for promoting the large-scale application of degradation methods requires not only to ensure an efficient degradation of the

parent compounds but also to ensure their TPs are nontoxic. Finally, the detection of TPs derived from the degradation of other psychiatric drugs such Diazepam, Oxazepam, Nordazepam, Amitriptyline, Alprazolam, and Trazadone, are also found in the literature (Table 4) (Carpinteiro et al., 2017; Mitsika et al., 2021; Osawa et al., 2019).

Table 5. Detection and monitoring techniques for transformation products of psychiatric drugs.

Psychiatric Drug	Degradation method	Technique	Transformation products	Representative transformation products	Reference
Carbamazepine[2,3]	Electro-Fenton	LC-QTOF-MS/MS	7	CBZE	(J. Li et al., 2021)
Carbamazepine[2,3]	Ozonation	LC-QTOF-MS and NMR	15	BQM BQD	(Kråkström et al., 2020)
Carbamazepine[2,3]	UV/H_2O_2	HPLC-MS/MS	6	CBZE	(Lu & Hu, 2019)
Carbamazepine[2,3]	Biocatalytic (*Aspergillus oryzae* laccase)	LC-ESI-MS	5	NR	(Tufail et al., 2021)
Carbamazepine[2,3]	Biocatalytic (*Trametes versicolor* laccase)	LDTD-MS	2	CBZE CBZD	(Naghdi et al., 2018)
Carbamazepine[2,3]	Biocatalytic (*Trametes versicolor* laccase)	LC-LTQ-Orbitrap	3	CBZE CBZD Acridone	(Ji et al., 2016)
Carbamazepine[2,3]	Biocatalytic (*Trametes versicolor* laccase)	LC-ESI-MS	2	CBZE Acridone	(Alharbi et al., 2019)
Carbamazepine[2,3]	Biocatalytic (Horseradish peroxidase and lignin peroxidase)	NMR	2	CBZE CBZD	(Pylypchuk et al., 2020)
Venlafaxine[1]	Photodegradation	LC-LIT-Orbitrap	~70	ODMVFX NDMVFX	(Lambropoulou et al., 2017)
Venlafaxine[1]	Biodegradation (enzymes extracted from anaerobic sludge)	LC-QTOF-MS	0	NR	(Gonzalez-Gil et al., 2019)

Venlafaxine[1]	Biodegradation (*Trametes versicolor*, *Ganoderma lucidum*, and *Pleurotus ostreatus*)	LC-LTQ Orbitrap	3	ODMVFX NDMVFX	(Llorca et al., 2019)
Venlafaxine[1]	Photodegradation	UHPLC-QTOF-MS/MS	5	NR	
Amitriptyline[1,2,3]	Photodegradation	UHPLC-QTOF-MS/MS	8	NR	Osawa et al., 2019)
Trazadone[1]	Photodegradation	UHPLC-QTOF-MS/MS	7	NR	
Diazepam[2]	Chlorination	LC-QTOF-MS/MS	5	CMAB	
Oxazepam[2]	Chlorination	LC-QTOF-MS/MS	1	OXA-TP	(Carpinteiro et al., 2017)
Nordazepam[2]	Chlorination	LC-QTOF-MS/MS	4	Phenylquinazoline products	
Alprazolam[2]	Photo-Fenton	LC-(ESI)MS/MS	15	4-Hydroxyalprazolam	(Mitsika et al., 2021)
Diazepam[2]	Photo-Fenton	LC-(ESI)MS/MS	23	Nordiazepam Oxazepam Temazepam	

[1] (Antidepressant); [2] (Anxyolitic); [3] (Mood stabilizer); LC-QTOF-MS/MS (Liquid chromatography coupled to quadrupole Time-of-Flight Mass Spectrometry); NMR (Nuclear magnetic resonance); HPLC-MS/MS (High Performance Liquid Chromatography coupled with a Triple Quadrupole Mass Spectrometer; LC-ESI-MS (Liquid Chromatography-Electrospray Ionisation-Mass Spectrometer); LDTD-MS (Laser Diode Thermal Desorption–Tandem Mass Spectrometry); LC-LTQ Orbitrap (Liquid Chromatography System coupled to a Hybrid Linear Ion Trap – High Resolution Mass Spectrometer); LC-LIT-Orbitrap (Liquid Chromatography coupled to a Linear Ion Trap Orbitrap Mass Spectrometer); LC-QTOF-MS (Liquid Chromatography Quadrupole Time-of-Flight Mass Spectrometry); UHPLC-QTOF-MS/MS (Ultra-High Performance Liquid Chromatography coupled to Quadrupole time-of-flight Mass Spectrometry); LC-(ESI)MS/MS (Liquid Chromatography-Electrospray Ionization-Mass Spectrometry); CBZE (10,11-dihydro-10,11-epoxy-CBZ); BQM (1-(2-benzaldehyde)-4-hydro-(1H,3H)-quinazoline-2-one); BQD (1-(2-benzaldehyde)-(1H,3H)-quinazoline-2,4-dione); NR (Not reported); CBZD (10,11-dihydro-10,11-dihydroxy-CBZ); ODMVFX (O-desmethylvenlafaxine); NDMVFX (N-desmethylvenlafaxine); CMAB (5-Chloro-2-(methylamino)benzophenone); OXA-TP (6-chloro-3,4-dihydro-4-phenyl-2-quinazolinone).

2.6. Magnetic nanobiocatalysts

The synergistic integration of biocatalysis engineering with nanostructured materials has emerged as a new interface named nanobiocatalysis, which is an innovative area that focus on the incorporation of the enzymes into a nanostructured material (Ansari et al., 2012). As well known, isolated enzymes have important properties, such as high specificity, high reaction rate under mild reaction conditions of pH and temperature, low energy reactions, water solubility, and biodegradability (de Jesús Rostro-Alanis et al., 2016). However, the implementation of enzymes has some important issues that commonly are hampered by different factors, including high isolation and purification cost, lack of stability and short lifespan, inhibition by non-natural substrates, and difficult to operate due to its hard/low recovery and recycling process (Del Arco et al., 2020, Homaei et al., 2013, Rodríguez-Delgado et al., 2015). Fortunately, the nanobiocatalysis, has been allowed to overcome the most of previously mentioned obstacles by using different immobilization methods to attach the enzymes into nanostructured materials, providing stability, high catalytic behavior, and reusability, which leads to lower reaction times and allows to implement different bioreactors designs (Homaei et al., 2013, López et al., 2014).

Finding the proper immobilization method and a good solid support for enzyme immobilization is a critical step to design nanobiocatalysts. In the beginning of nanobiocatalysis, enzymes were immobilized by simple methods such as simple adsorption and covalent attachment, then with recent research on the field of biotechnology and nanotechnology, the application of different nanostructured materials, including mesoporous materials, electrospun nanofibers, carbonaceous

materials, and metallic materials, including magnetic and non-magnetic materials; has allowed taking advantage of the main characteristic of nanobiocatalysis, the high surface/volume ratio of nanomaterials, which improves some biocatalyst properties like enzyme loading into the solid support, leading to higher enzyme activity compared to free enzyme or enzyme immobilized into conventional materials (de Jesús del Rostro-Alanis et al., 2016, J. Kim et al., 2008).

The principal reason of the use of different nanostructured materials for the immobilization of enzymes is the feasibility of work on the control over size at nanometer scale, by the modification of pore size, thickness of nanofibers or nanotubes and particle size of nanoparticles (Kim et al., 2008). As one of the previously mentioned supports materials, magnetic nanomaterials are gaining remarkable ground over other type of supports owing to its important characteristic but principally to their magnetic behavior, which allows to easily recovery by the application of a magnetic field (Del Arco et al., 2020, Bilal et al., 2020). Metallic MNPs, such a Fe_3O_4, $MnFe_2O_4$, $FeFe_2O_4$, $CoFe_2O_4$ have a great interest for biocatalytic applications as supported carrier material for enzyme immobilization (Del Arco et al., 2020, Kudr et al., 2017). As mentioned above, the increasing interest is owed to some important properties like high specific area, elevated enzyme loading ability, controllable particle size, modifiable surface, small volume, and the most important, easily, and rapid separation from solutions in comparison of conventional materials, where centrifugation and filtration are the only option to separate and reuse the enzyme. Also, this material is commonly used because its good biocompatibility, non-toxic properties, and the interesting low process cost (López et al., 2014, Nicolás et al., 2014)]. The use of magnetic nanomaterials has

been applied in different fields of investigation Table 6, such as food industry, biosensors, biodiesel production, pharmaceutical industry, and bioremediation of environmental pollutants.

2.6.1. General outlook of magnetic/modified nanobiocatalysts, advantages and drawbacks

The implementation of MNPs as enzyme nanocarriers for enzyme immobilization implies several advantages that lead to enhanced properties of free enzyme biocatalysts. Thus, MNPs have gained interest in research as versatile carriers, owing to its easy recovery by the application of magnetic field, which may avoid some of the most reported drawbacks of the use of immobilization biocatalysts, such as biocatalysis reusability and deterioration of biocatalyst by mechanical agitation commonly caused by centrifugation process (Del Arco et al., 2020, Bilal et al., 2018). Even though magnetic-based supports are commonly based on iron oxide materials, such as Fe_3O_4 (magnetite) α- Fe_3O_4 (hematite) and γ- Fe_3O_4 (maghemite), alloy-based matrices ($CoPt_3$ and FePt) and pure metals (Fe and Co), owing to its excellent biocompatibility and non-toxicity properties. Magnetite (Fe_3O_4) is considered the most interesting magnetic carrier for enzyme immobilization in biocatalysis applications due to its high magnetization rate, excellent biocompatibility and null or low toxicity (Del Arco et al., 2020, Bilal et al., 2019). Table 6 indeed, provides an update outlook for different MNPs implemented for enzyme immobilization, its improved properties, and its respective applications. For example, it has been proved that the immobilization of different enzymes such as, chymotrypsin (Huang et al., 2018), peroxidases (Almulaiky and Al-Harbi, 2019,

Grebennikova et al., 2020), lipase B (Xie and Zant, 2018, Hosseini et al., 2019, Rathankumar et al., 2021) [31,34,39], and laccases (Deng et al., 2015, Pang et al., 2011, Silveira et al., 2020) [27,28,35], onto free or modified MNPs , have improved some properties, such as the increment of adsorption rate of substrates, higher enzymatic activity, resistance to broader pH values, higher thermal and storage stability, higher recovery, and reutilization rate, and higher biocatalytic activity (Deng et al., 2015, Pang et al., 2011, Guo et al., 2019, Li et al., 2018, Xie et al., 2018, Almulaiky and Al-Harbi, 2019, Torres et al., 2018, Hosseini et al., 2019, Silveira et al., 2020, Sarno et al., 2020, Xie and Huang 2020, Esmi et al., 2021, Rathankumar et al., 2021, Huang et al., 2018, Grebennikova et al., 2020). Different materials have been implemented to modify the surface of MNPs to add extra characteristics that increment enzyme immobilization efficacy. Pang et al., Guo J. et al. and Almulaiky and Al-Harbi used the elasticity of polymers (chitosan, polydopamine, and carboxymethyl cellulose, respectively) to trap the enzyme between the polymer and the magnetic material, providing higher storage stability (Pang et al., 2011, Guo et al., 2019, Almulaiky and Al-Harbi, 2019).

However, despite the important advantages provided by MNPs to biocatalysis, the implementation of these materials as host carriers for enzyme immobilization might present some drawbacks, such as problems to be implemented at industrial level due to high fabrication cost of nanomaterials (Bilal et al., 2018), aggregation phenomena that commonly increase the size and heterogeneity of the biocatalyst, which involves operational dilemmas, such as the alteration of physiochemical properties, low reproducibility and mass transfer limitations (Del Arco et al., 2020, Cipolatti et al., 2016). Comparison of all mentioned advantages

and drawbacks for the application of MNPs as enzyme host carriers are shown in Table 7.

2.7. Design of the magnetic nanobiocatalysts

There are different physical and chemical properties that biocatalysts might target to improve, from size, pore size, and shape, which are related to synthesis method; and selectivity, stability, and kinetic activity of the enzyme, related to surface modification of MNPs, and immobilization method (Su et al., 2020). In general, for subsequent applications of MNPs as biocatalyst, it is necessary to develop a specialized formulation that improves the physical, chemical, and enzymatic properties (Singh et al, 2020). In this section, as is shown in Figure 4, the discussion of the different approaches to get a magnetic nanobiocatalyst, the most common synthesis routes for MNPs, such as co-precipitation, sol-gel synthesis, hydrothermal synthesis, thermal decomposition, mechanochemical, microemulsion, and some others like pyrolysis, electrochemical synthesis, and microorganism or bacterial synthesis. Moreover, due to the incompetence of naked MNPs for direct immobilization of enzymes, different surface modification/functionalization, e.g., silica coated modification, organic polymer modification, MOF modification, or carbonaceous modification are also discussed. And finally, the different immobilization methods of enzymes, which can be adsorption, entrapment, encapsulation, cross-linking, and covalent immobilization.

Table 6. Enzymes immobilized on magnetic nanoparticles and their biotechnological applications.

Enzyme	Nanomaterial	Immobilization method	Improved properties	Application	Reference
Lipase B	Fe_3O_4	Cross-link and covalent	Higher stability at different reaction media, high conversion rate of olive oil to biodiesel, higher thermal stability, and reutilization	Biodiesel and biosurfactants production	Del Arco et al., 2020
Lipase B	Fe_3O_4	Cross-link	Higher enzymatic activity, resistant to degradation by short alcohols, reutilization	Synthesis of ethyl oleate	Nicolás P. et al., 2014
Glucose Oxidize	Fe_3O_4 /TiO_2	Adsorption	Increment of adsorption rate: 26.069 m2/mol	Degradation of organic pollutants	Zolfaghari et al., 2019
Laccase	Fe3O4/SiO_2	Entrapment	Higher resistance to broader pH values and stability than free enzyme, high catalytic activity	Enzymatic catalysis and biosensing	Deng et al., 2015
Laccase	Fe_3O_4/MMWCNTs/Chitosan	Entrapment	Low detection limit (3.34x10-8 mol/L), reutilization of the biosensor, high linear range (10-7-0.165 x10-3 mol/L) and reusability.	Biosensing	Pang et al., 2011
Lignin peroxidase	Fe_3O_4/SiO_2/poly dopamine	Entrapment	Higher thermal stability and storage stability than free enzyme, complete degradation of various organic pollutants and reusability	Degradation of organic pollutants	Guo et al., 2019
Penicillin G acylase	Fe_3O_4/ SiO_2-NH2	Cross-link	High activity (394.74 U/g), high thermal stability and reusability.	Industrial production of penicillin	Li et al., 2018

Lipase B	Fe_3O_4	Adsorption	Hydrophobic interaction, high catalytic, strong magnetic responsiveness, catalytic activity toward trans free plastic fats, and reusability.	Production of trans-free plastic fats	Xie and Zang 2018
Peroxidase	Carboxymethyl cellulose/ Fe_3O_4	Entrapment	High thermal stability and storage stability, retain of 44 % the initial activity, wide range of temperature and pH reaction mediums, and reusability.	Industrial applications	Almulaiky and Al-Harbi 2019
Soybean Peroxidase	Activate Carbon/ Fe_3O_4	Adsorption	High operational stability, magnetic and adsorption properties, reusability.	Synthesis of nanobiocatalysts	Torres et al., 2018
Lipase B	Fe_3O_4/Chitosan	Covalent	High biocatalytic and separation properties, high storage stability and reusability.	Synthesis of biobased oligo-esters	Hosseini et al., 2019
Laccase	Fe_3O_4/Chitosan	Cross-link	Increment of thermal stability of the enzyme by 1.33, high activity (139 U/g), and reusability	Decolorization of methyl orange dye	Silveira et al., 2020
Horseadish peroxidase	GO/ Fe_3O_4/AuCA	Adsorption	Increment of storage stability and higher removal rate than free enzyme catalyst	Removal of pollutants from wastewaters	Sarno and Iuliano 2020
Lipase	Fe_3O_4/poly(GMA-co-MAA)	Covalent	High binding efficiency (88.7 %) and activity recovery (67.3 %), high catalytic activity to the transesterification of soybean oil with biodiesel yield of 92.8%, and reusability.	Biodiesel production	Xie and Huang 2020

Lipase	Fe_3O_4/Mesoporous silica	Covalent	Covalent bonding increase enzyme loading from 67.8 to 82.4 %, and improvement of reusability and thermal stability	Biodiesel production	Esmi et al., 2021
Naringinase and Lipase B	Fe_3O_4/Chitosan	Cross-link	High activity (925 U/g naringinase, 825 U/g lipase), and reusability	Environmental applications	Rathankumar et al., 2021
Chymotrypsin	Fe_3O_4/ Chitin Nanofiber	Cross-link	Thermal stability, retention of 70.7 % activity after exposition under high temperatures (60C), and reusability	Synthesis of nanobiocatlysts	Huang et al., 2018
Peroxidase	Fe_3O_4	Covalent	Higher thermal stability than free enzyme, increment of the activity and higher reaction rate	Oxidation of 2,3,6-trimethylphenol	Grebennikova et al., 2020

Table 7. Magnetic nanoparticles as host carriers for enzymatic immobilization, advantages, and drawbacks.

Advantages	Disadvantages
High surface area	High cost for synthesis of biomaterials
Insolubility	High cost for enzyme isolation
Large surface/volume ratio	Aggregation phenomena
High mass transfer	Not ease to implemented at industrial scale
Reusability	Low reproducibility
High biocatalytic activity	
Resistance to broader pH values	
High storage stability	
High thermal stability	

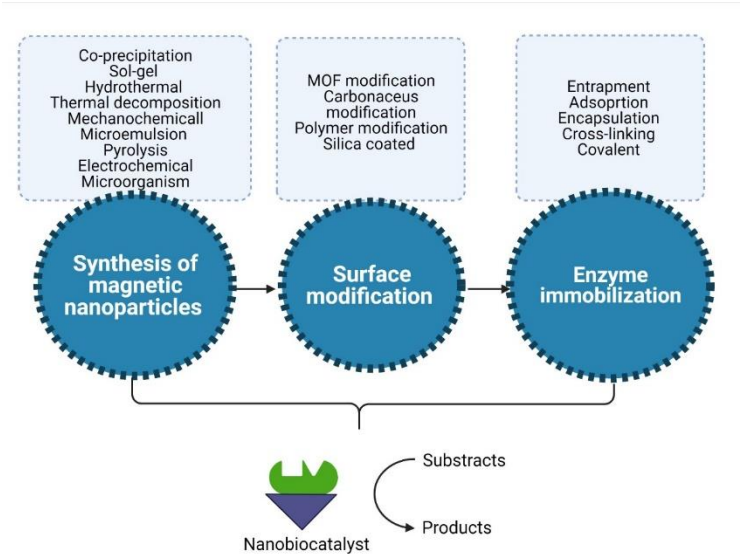

Figure 4. Design and development of magnetic nanobiocatalysts.

2.7.1. Synthesis of magnetic nanoparticles

Until now, there are different popular methods to synthesize shape-controllable, monodisperse and stable MNPs, such as co-precipitation, sol- gel process, hydrothermal synthesis, thermal decomposition, solvothermal, microemulsion, pyrolysis, electrochemical, and synthesis from microorganisms (Singh et al., 2020, Silveira et al., 2020, Majidi et al., 2016, Xie and Huang 2020).

Co-precipitation synthesis

Chemical precipitation or co-precipitation is the simplest and most common route to obtain controlled and high magnetic MNPs due to the reaction between a source of metal, such as iron salts for the synthesis of magnetite, and a base that allows precipitation under inert atmosphere at room temperature or at elevated temperature (A Lu et al., 2007). The chemical precipitation of magnetite depends on the type of salt used, such as chlorides, sulfates, nitrates, etc, the ratio of Fe^{3+}/ Fe^{2+}, the pH, and temperature (Chen et al., 2018). Typically, chemical precipitation method begins with the dropwise addition of one reagent to another under continuous stirring, while the molar ratio of Fe^{3+}/ Fe^{2+} is kept stoichiometry according to the molar ratio (2:1). Then, the mixture is adjusted to a specific pH (8-14), and temperature (25-100°C), and after purification it is recovered by the application of magnetic field (Cipolatti et al., 2016, Majidi et al., 2016). The co-precipitation process is then shown in the following Equation 1.

$$\boldsymbol{Fe^{2+} + 2Fe^{3+} + 8OH^{-} \rightarrow Fe(OH)_2 + 2Fe(OH)_3 \rightarrow Fe_3O_4 + 4H_2O} \quad (1)$$

Chemical co-precipitation is a widely used method since a large amount of MNPs can be synthesized at a reasonable cost, good reproducibility, and high magnetization. Unfortunately, particles prepared by co-precipitation tend to produce

particles with extensive polydisperse distribution of particle size and are non-stable under ambient conditions (A Lu et al., 2007). Even so, it has been demonstrated that by variation of pH and ionic strength of the medium, it is possible to control the mean size of particles in nanometric range (2-15 nm) (Majidi et al., 2016). For example, Yussoff et al. studied the role of pH in the control of spherical particle size for the synthesis of magnetite (Yusoff et al., 2017). The size of nanoparticles was reduced with the increase of pH from 11.33 to 12.15, and then the size increment once the pH is greater than 12.15. In addition, Sirivat and Paradee also investigated the relation of $[OH^-]$ concentration with size (Sirivat and Paradee 2019). It was observed that pH influences the control of nucleation and growth of the magnetite nanoparticles, which directly affect the particle size and magnetic properties. For example, for pH <11, particle size decreased with increasing pH, but for pH>11, particle size is unchanged, which suggests that optimum pH to synthesize Fe_3O_4 should be in the range of 9.7-10.6. Moreover, the effect of temperature in the synthesis of magnetite nanoparticles via co-precipitation process was studied by T. Saragi et al. The variation of temperature in ranges between 25°C-80°C led to conclude that due to correlation of chemical reaction acceleration and temperature, the size of the synthetized MNPs increase from 10.14-13.13 nm when temperature increases (Saragi et al., 2018).

Hydrothermal synthesis

Hydrothermal method is one of the most widely used methods for the synthesis of nanomaterials, it can be defined as a reaction of chemicals in aqueous solution at elevated temperatures (up to boiling point of water) and pressure (Szcześ and Chibowski 2017). The hydrothermal method can be simplified as a precipitation

reaction in which an aqueous mixture of precursors is heated inside an autoclave at high temperatures, and consequently, at high pressure which increments because of the temperature (Pu'ad et al., 2020). Compared with the "low-temperature" coprecipitation procedures that usually produce poor crystalline nanoparticles, hydrothermal synthesis shows regular stoichiometric and highly crystalline nanoparticles, which is possible because of the synergistic effect of temperature and pressure that provides a one-step process to produce highly crystalline materials without further post-treatment (Huang et al., 2019). However, hydrothermal synthesis presents a high-cost process development disadvantage, due to elevated temperatures and pressure needing expensive equipment (Pu'ad et al., 2020, Huang et al., 2019). The synthesis of MNPs by hydrothermal method has been previously reported, for example, Torres- Gómez et al. synthesized a pure phase magnetite using a hydrothermal method at different temperatures, 120 °C, 140 °C, and 160 °C (Torres-Gómez et al., 2019). According to TEM and SEM studies of the synthetized nanoparticles, it was observed that the shape of the nanoparticles changes from spheres, to octahedrons, and cube-like shapes when temperature increase from 120°C to 140° C, and 160 °C, respectively, which allows to implement this method for different applications according to the desired morphology. In another study, it was also reported that temperature might help to change the morphology of the desired nanoparticles, in this case, cobalt doped magnetite cubic nanoparticles were synthetized at 150 °C (Sadat-Shojai et al., 2013).

Sol-gel synthesis

The sol-gel process, or chemical solution deposition is a wet chemical technique based on the conversion of a sol (inorganic colloidal suspension) formed by

organometallic precursors, to a gel through a hydrolysis-condensation process (Szcześ and Chibowski 2017). In case of MNPs synthesis, the reaction between the metallic precursors goes slowly, and the thermal treatment is critical for the generation of pure nanoparticles it allows to remove the organic residues, gaseous products, and water molecules from the porous gel (Huang et al., 2019, Sadat-Shojai et al., 2013). Recently, Dissanayake et al. synthesized a low-cost magnetite nano-spheres via sol gel synthesis using laterite as a source of iron (Dissanayake et al., 2020). The synthesis route consisted in the extraction of iron (III) from laterite, then the addition of ethylene glycol at 120 °C until the formation of tick gel and its further calcination at 500 °C for one hour. The characterization of the MNPs synthetized via XRD and SEM confirmed the formation of spherical nanoparticles of magnetite with 50 nm, suggesting then a process that can be easily scaled-up to industrial level because of its low cost and basic chemical phenomena (Dissanayake et al., 2020).

Thermal decomposition

Thermal decomposition is one of the simple methods used for the synthesis of MNPs. This synthesis consists in the reaction at high temperatures between one organometallic precursor, including acetylacetonates, [$\boldsymbol{M(acac)_n}$], (M=Fe, Mn, Co, Ni, Cr, n=2 or 3, acac=acetylacetonate), metal cupferronates or carbonyls; with a high-boiling organic solvents containing stabilizing surfactants (A Lu et al., 2007). Surfactant's function is to decelerate the nucleation process and affect the adsorption of additives on the nuclei and growth of the nanocrystal, which may restrain the growth of particles and favor the formation of MNPs (Koo et al., 2019). The synthesized nanoparticles via thermal decomposition are characterized by its high saturation of magnetization, and highly crystalline and well controlled defined

size and shape, properties that are usually controlled by the variations in temperature, proportion of reactants, and reaction time (Chen et al., 2018, Koo et al., 2019, Wu et al., 2019). For example, studies have showed that variation of temperature and time might contribute to the formation of highly square-like shaped nanoparticles with high magnetization (24 emu/g) (Shahjuee et al., 2019). Moreover, it has been observed that smaller particles could be formed at lower reaction temperatures and shorter reaction times (Maity et al. 2008).

Other synthesis techniques

Some other techniques have been reported for the synthesis of MNPs, such as mechanochemical synthesis (Bedoya et al., 2021), microemulsion (Najafi and Nematipour 2017), electrochemical synthesis (Karimzadeh 2018), and green synthesis (Sari and Yulizar 2017, Azadi et al., 2018, Basavaiah et al., 2018, Karade et al., 2017, Rahmawati et al., 2018). Mechanochemical method is based on collisions occurring in milling bars that create mechanical energy, which promotes chemical reactions and structural changes on the precursor materials Pu'ad et al., 2020). In microemulsion, the formation of MNPs occurs at nanoscale domains, in which nanoparticles will be formed by the addition of solvents into a micelle mixture of oil, water, surfactant and metallic precursor (Murray et al., 1995). The electrochemical synthesis is based on the principle of electrodeposition, which is an electrochemical phenomenon associated with the reduction or deposition of electroactive species on the cathode surface by the application of electrical current in the presence of one electrolyte (Nasirpouri et al., 2020, Wang and Wu 2017). Finally, it is said that a synthesis has a green approach when it is characterized for the use of safe reagents, various from natural renewable resources, which appears

to overcome the two major drawbacks limiting application of nanoparticles in biotechnology, toxicity, and biocompatibility (Ghosh 2019, Mitbe et al., 2018).

2.7.2. Surface modification

Typically, as mentioned before, magnetic nanoparticles tend to present some important drawbacks, such as aggregation effect, non-coercivity and remanence at room temperature, easy oxidation in the air which leads to loss of magnetism and dispersibility (Wu et al., 2019). In consequence, these factors result in the inability of naked magnetic nanoparticles for direct attachment of enzymes (Bilal et al., 2018). In this context, for the different potential application of magnetic nanoparticles can be controlled by surface modification/coating of the nanoparticles by different techniques, e.g., silica coated modification, organic polymer modification, MOF modification, or carbonaceous modification, which will prevent aggregation and precipitation while enhanced biocompatibility and chemical stability (Cipolatti et al., 2016, Dheyab et al., 2020).

- **Silica- coating:** silica-coating surface modification of magnetic nanoparticles consists in the formation of core-shell particles, which are a class of materials that are composed of a core (inner material) and a shell (outer layer), where in case of silica shell (@SiO_2), the magnetic nanoparticles with commonly spherical morphology are the inner material (Su et al., 2020). The surface modification with silica coating take place with the synthesis and isolation of naked magnetic nanoparticles, and then these nanoparticles are directly coated with silica shells, for example via sol-gel process with the hydrolyzation of tetramethyl orthosilicate (TEOS) under alkaline conditions

(Esmaeili-Shahri and Es'haghi 2015). In general, the surface modification using silica coating is applied because it improves chemical stability by protecting magnetic cores from aggregation and oxidation, increase the hydrophilicity and biocompatibility characteristics, and finally introduce a proper feasibility for enzyme immobilization, usually implemented covalent immobilization by attachment via functionalization with aminosilane and epoxy silane coupling agents (Bilal et al., 2018, Su et al., 2020).

- **Polymeric surface modification:** One of the advantages of magnetic nanoparticles are the easy chemical modification, which is pretended to solve aggregation and stability problems (Wu et al., 2019). The polymeric surface modification consists in the *in situ* or *ex-situ* modification, where *in-situ* modification is based on the incorporation of the organic polymer as a surfactant in the synthesis of the magnetic nanoparticles, whereas in *ex-situ* modification, a polymeric coating is formed on the magnetic nanoparticle by the polymerization of monomers (Bilal et al., 2018). The organic polymeric modification is primarily used in order to get advantage on the properties of these materials including flexibility, toughness, elasticity, dielectric properties, good permeability, wide pH stability and biocompatibility of certain polymers for different biomedical applications, such as chitosan and poly(ethylene glycol), which in addition of the inorganic materials properties, improve chemical stability, reduce toxicity and prevent the aggregation phenomena (Shanmugam et al., 2020, Rosman et al., 2018, Torres-Cartas et al., 2021, Mahdieh et al., 2017).

- **Metal Organic Framework coating:** Metal Organic Frameworks (MOFs) are crystalline porous solids composed of a three-dimensional network of metal ions cores and organic multidentate linkers that are characterized by several properties, including large surface area, porosity, easy recovery, tunable surface, structural and functional diversity, and chemical and thermal stability (Ruiz et al., 2018, Leus et al., 2010). Due to these properties, MOFs appeared to be a versatile support for enzyme immobilization, in addition by the combination of MOFs properties with magnetic nanoparticles properties, it might be possible to synthesize high crystalline three-dimensional materials with multivariate morphology, high recovery while aggregation phenomena and instability of magnetic nanoparticles is avoided (Ruiz et al., 2018). As a general procedure, the surface coating modification with MOFs consists in the reaction between organic ligands and metal ions in the presence of carboxylated magnetite (Bilal et al., 2018). Different applications have been achieved combining the properties of MOFs and magnetic nanoparticles, such as magnetite nanoparticles modified with copper-based MOF for drug delivery application (Hashemipour and Panahi 2017) or functionalized magnetite nanoparticles with MOF-199 for heavy metals treatment (Ghorbani-Kalhor 2016).
- **Carbonaceous surface modification:** as an emerging and innovative materials with proper catalytic effect for the immobilization of enzymes, carbonaceous materials, which are commonly obtained via heat from different sources, including coal, liquefied coal, coke, petroleum, resins, carbon blacks, paraffins, olefins, pitch, tar, polycyclic aromatic compounds and polymers; are

materials with important characteristics, including durability, high surface area, optical properties, electrical activity and chemical and thermal stability (Bilal et al., 2020, Hao Tian 2005). Carbonaceous materials can have different nanostructured derivatives, such as carbon nanotubes (CNTs), graphene (G) and its derivatives, including graphene oxide (GO) and reduced graphene oxide (rGO). When carbonaceous materials characteristic are combined with magnetic nanoparticles, both important characteristics can be exploited to apply as a new thermal and high catalytic material for enzyme immobilization, such as Rafiee-Pour et al. that combined the carbon nanotubes principal characteristics (e.g., nonporous structure, large surface area and biocompatibility) with the high catalytic and easy recovery characteristics of magnetite to synthesize a highly crystalline material for the immobilization of catalase as a potential application in drug delivery systems or industries, such as dyeing, cosmetics, leather production, paper production, etc (Rafiee-Pour et al., 2019, Siddiqui et al., 2019).

2.7.3. Enzyme immobilization

As we discussed before the use of nanomagnetic materials as a host carrier for enzyme immobilization will help to enhanced important characteristics that usually are limited using free- nonstable enzyme, such as the increment of adsorption rate of substrates, higher enzymatic activity, resistance to broader pH values, higher thermal and storage stability, higher recovery, and reutilization rate, and higher biocatalytic activity. Enzymes can be immobilized by different methods as mentioned before, which are visualized in Figure 5. The different immobilization

methods are a) physical adsorption, b) covalent binding, c) cross-linking, and e) entrapment/encapsulation (Rodríguez-Delgado et al., 2015, Alvarado-Ramirez et al., 2021, Nguyen and Kim 2017)

- Physical adsorption (Figure 5a) immobilization is the simplest immobilization method. This method is based on the formation of weak bonds by ionic interactions, Van der Waal´s forces, electrostatic or hydrophobic forces (Alvarado-Ramírez et al., 2021). Adsorption methodology is normally used for the construction of biosensors due to low cost, simple, and fast operation process, however, it might present some drawbacks such as loosely bound to the support by weak physical bonding and low storage stability (Sheldon and van Pelt 2013). To achieve physical adsorption, typically the enzyme is dissolved in solution at pH controlled and then the solid support is added and fixed for a period of time (Nguyen and Kim 2017).
- Covalent immobilization (Figure 5b) is widely utilized immobilization method due to it provides strong bindings between enzymes and supports, high uniformity and good control of the immobilized enzyme amount (Kim et al., 2008, Nguyen et al., 2017). Covalent immobilization consists in a two-step process, where the first one is an activation of the support's surface by multifunctional reagents, such as glutaraldehyde and carbodiimide, that act as a linker for the second step, which is a covalent coupling to the activated support by the coupling of functional groups of the enzyme, usually amino, carboxylic, phenolic, sulfhydryl, thiol, imidazole, indole and hydroxyl groups (Novick and Rozzel 2005). Other important characteristics of this method is that it presents high stability, which means that the enzyme have resistance

to the effects of temperature, pH, and other ambient conditions Rodríguez-Delgado et al., 2015). However, covalent bonding has the disadvantage that if the enzyme is irreversible deactivated, both the enzyme and the support are unusable, moreover, even though enzyme immobilization tends to increase, the enzyme activity might decrease, and in comparison, to adsorption process, covalent immobilization is performed in longer incubation times (Nguyen and Kim 2017, Marrazza 2014).

- Cross linking immobilization (Figure 5c) consists in the implementation of bifunctional reagents that generate intramolecular cross-linkages between the enzyme molecules by covalent bonds. Normally, the bifunctional reagents, which include glutaraldehyde, dialdehydes diiminoesters, diisocyanates and diamines activated by carbodiimide (Rodríguez-Delgado et al., 2015, Nguyen and Kim 2017), react with amino groups of the enzyme proteins and creates a three-dimensional complex structure. Even though this method had disadvantages as loss of activity, and poor reproducibility, the complex-enzyme-support formed is resistant to extreme conditions of pH and temperature, which improves reusability (Elnashar 2011).
- Encapsulation and entrapment (Figure 5d and 5e) immobilization are similar methods for the immobilization of enzymes into nanomaterials. These processes are commonly performed in two steps, first the enzyme is mixed into a monomer solution, and then the solution goes into a polymeric reaction and the enzyme is physically confined/entrapment within the polymer lattice network without chemical interaction (Nguyen and Kim 2017). In addition, encapsulation is a kind of entrapment method in which enzymes are

entrapped in a spherical semipermeable membrane, which can be polymeric, lipoidal, lipoprotein based or non-ionic materials (Elnashar 2011). Some important advantages of the application of this method include high enzyme loading, improvement of enzyme stability, less enzyme leaching and denaturation, and the capability to optimize the microenvironment for the enzyme by modifying the encapsulating material to have proper reaction conditions (Rodríguez- Delgado et al., 2015, Nguyen and Kim 2017). However, there are mass transfer resistance limitations, which means that substrates might have problems to reach inside the gel matrix into the enzyme (Nguyen and Kim 2017, Elnashar 2011).

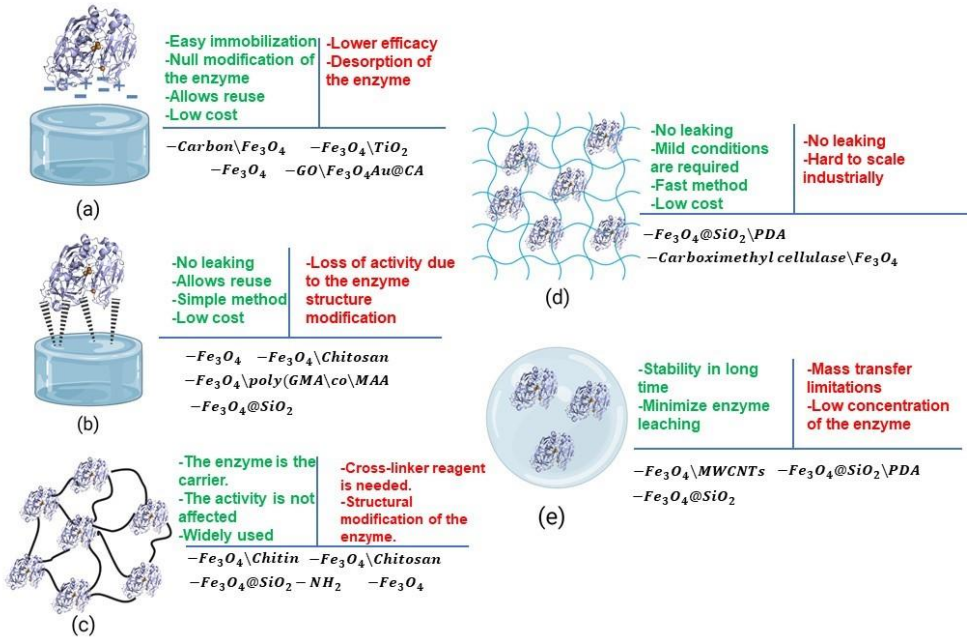

Figure 5. Immobilization methods a) physical adsorption, b) covalent binding, c) cross-link, d) entrapment and e) encapsulation; and its advantages (green), disadvantages (red) and magnetic materials implemented in literature for enzyme immobilization.

3. MATERIALS AND METHODS

3.1. Chemicals and other materials

2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammoniumsalt (ABTS, purity ≥98%), venlafaxine hydrochloride (≥99%), sodium phosphate monobasic monohydrate (≥98%), sodium phosphate dibasic heptahydrate (≥98%), citric acid anhydrous (≥99%) iron (II) sulfate heptahydrate (≥99%),nitric acid (≥99%), (, anhydrous iron (III) chloride (≥99%), ammonia hydroxide (≥99%), methanol (HPLC grade), and carbon nanofibers (≥98%, D × L 100 nm × 20-200 μm) were purchased from Sigma-Aldrich (Monterrey, Mexico). HPLC grade water was prepared in the laboratory using milli-Q/Milli-RO system (Millipore, USA).

3.2. Laccase source

Extracellular laccase was derived from the native white-rot fungus cultures of *P.sanguineus* CS43 (culture collection Universidad Autónoma de Nuevo León, Mexico) (Hernández-Luna et al., 2008). Laccases from the white-rot fungus culture were obtained from a previously reported procedure in which laccase production was carried out in tomato juice medium (36.8%), 3 mM $CuSO_4$, and 1% v/v soybean oil (Ramirez-Cavazos et al., 2014).

3.3. Synthesis of magnetic carbon nanofibers (mCNFs)

To functionalize with iron oxide nanoparticles, a method reported by Wu et al., 2015 with some modifications was applied (Figure 6). The method consisted in the acidic treatment of the CNF followed by a chemical coprecipitation method. Firstly, 1 g of CNF were mixed with 100 mL of nitric acid and treated at 80 °C for 6 h under vigorous magnetic stirring. After the acidic treatment, the mixture was washed several times with deionizing water until reaching pH value ~7. Then, the sample were centrifugated and dried in a vacuum oven at 60 °C and 700 mmHg. After this treatment, CNFs are expected to possess oxygen containing functional groups on their surface and are detonated by CNFox

The CNFs were further magnetically modified by a facile coprecipitation method (Tang et al., 2021, He et al. 2021). Firstly, 0.450 g of the CNFox were dispersed in 200 mL of distilled water by ultraprobe sonication for 15 min, into which 0.450 g of $FeCl_3$ was added and kept other 15 min in sonication and heated at 65 °C under a nitrogen (N_2) atmosphere. Then, 0.231 g of $FeSO_4$-$7H_2O$ was added, and the mixture was maintained in sonication during 30 min at 50 °C under nitrogen atmosphere, and the pH was adjusted to reach pH value ~10 by adding dropwise 15 mL of 8 M NH_4OH aqueous solution to precipitate ferric and ferrous salts. Finally, the magnetic carbon nanofibers (mCNFs) were obtained by magnetic separation, washed with distilled water and ethanol util reach neutral pH, and dried under vacuum at 60 °C.

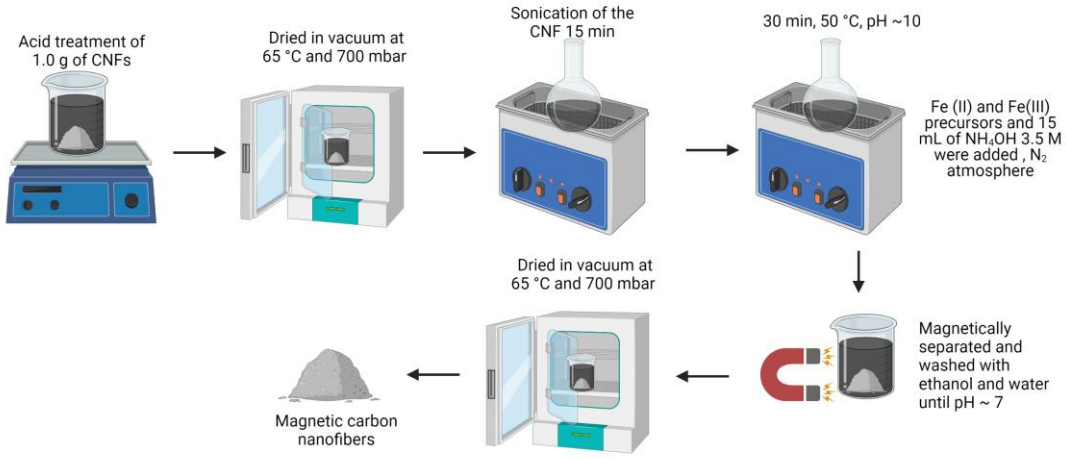

Figure 6. Schematic representation of the ynthesis methodology of the mCNF

3.4. Immobilization of laccases

The laccases were immobilized onto the mCNFs by physical adsorption as follows (Gonzalez-Coronel et al., 2017) (Figure 7). 10 mg of the mCNFs were suspended in 3 mL PBS buffer solution (pH 7) by 15 min in ultraprobe sonication, and then 23 U/mL of laccases were added to the suspension and the solution was mechanically stirred during 2 h at 25 °C. Next, the immobilized enzyme (mCNFs/Lcc) was magnetically separated and washed with the same buffer to remove all the unbounded enzyme. Finally, the immobilized enzymes onto mCNFs were stored at 4°C until needed.

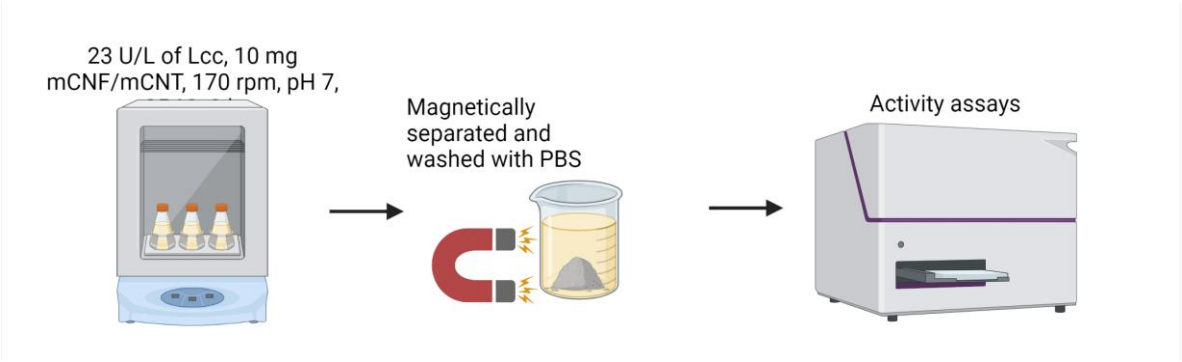

Figure 7. Schematic representation of the immobilization of laccases into the mCNF

3.5. Physicochemical characterization of mCNFs

3.5.1. Characterization of mCNFs by Scanning Electron Miscroscopy

The morphology of the modified nanoparticles was studied by taking a series of Scanning Electron Microscopy (SEM; EVO MA25, Zeiss, Germany) images. Before SEM, all the samples were sputtered with a thin gold layer to avoid their charging. Three samples were analyzed by SEM, the CNF, CNFox and the mCNF.

3.5.2. Characterization by Energy-dispersive X-ray spectroscopy

The chemical composition of the mCNFs was analyzed by Energy-dispersive X-ray spectroscopy (EDS; XFlash6I10, Bruker, Germany). Before the analysis, all samples were sputtered with a thin gold layer to avoid their charging. Three samples were analyzed by SEM, the CNF, CNFox and the mCNF.

3.5.3. Characterization by Fourier transform spectroscopy

Moreover, Fourier transform infrared spectroscopy (Frontier, Perkin Elmer, Germany) was implemented to analyze the structural changes in the chemical composition of the mCNFs and the immobilized laccases. An ATR additament was implemented for the directly analysis. Four samples were anlysed, the CNF, CNFox, mCNF and mCNF/Lcc.

3.5.4. Characterization by X-ray diffraction

The crystal phase of the magnetic nanoparticles, the CNF and mCNF was studied by XRD spectroscopy (Riggku MiniFlex600, USA). Before analysis, all samples were dried in vacuum and no further treatment was necessary.

3.6. Characterization of immobilized enzymes

3.6.1. Laccase activity assay

Enzyme activity was determined spectrophotometrically by following the oxidation of 0.5 mm of the substrate 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammoniumsalt (ABTS). The oxidation of the ABTS (0.5 mm) in 0.1 M citrate/0.2 phosphate buffer (pH 3) at 25 °C was monitored by following the increase in absorbance at 420 nm (ε= 36 $mm^{-1}cm^{-1}$) using a plate spectrophotometer (Specifications). One unit (U) of laccase activity was defined as the amount of enzyme required to oxidize 1 μmol of ABTS per minute (Gonzalez-Coronel et al., 2017).

Thus, the percentage of the enzyme loading immobilization (%L) was calculated from the formula:

$$(\%\boldsymbol{L}) = \left(\frac{\boldsymbol{A_{i-}A_F}}{\boldsymbol{A_i}}\right) * \mathbf{100} \qquad (\mathbf{2})$$

Where A_i is the activity of the added immobilized enzyme and A_F is the activity recovered in the supernatant of the immobilization procedure.

3.6.2. pH and storage stability

For evaluating of pH stability, 10 mg of immobilized enzyme were added to separate containers with 3 mL of buffers with different pH values (3 to 7) and kept for 24 h at 25 °C and 200 rpm. The storage stability of the immobilized laccase was evaluated by keeping the samples at 4 °C for one month and measuring their laccase their laccase activity for one month period. The measuring procedure was performed in triplicates and the averages along with their standard errors are presented in figures.

3.7. Biodegradation of venlafaxine

For the detection of VFX in water, HPLC-DAD (Altus, Perkin Elmer, Germany) was implemented by using a reverse phase Agilent 4.6x150 mm Zorbax Eclipse XDB-C18 5 Micron column equilibrated with mobile phase methanol: 0.05M potassium dihydrogen (70:30, v/v; pH 6.2). Mobile phase flow rate was maintained at 1 mL /min and the sample injection was 10 µL. To prepare the calibration curve a stock solution of 1000 µg/mL in methanol was prepared, then appropriate aliquots of the stock solution were taken to prepare 10 mL of 2 µg/mL, 5 µg/mL, 10 µg/mL, 15 µg/mL, 20 µg/mL, and 30 µg/mL. Before running the samples, the mobile phase was filtered and sonicated for 15 minutes, and the solutions were also filtered through 0.22 µm filter.

Once prepared the curve of calibration, a solution of 30 µg/mL of VFX was mixed during 18 h with 5 mL of the mCNF/Lcc suspension. After 18 h, the mCNF/Lcc system was separated from the solution by magnetic separation, and the solution was filtered through the 0.22 µm filter before analyzing by HPLC-DAD.

4. RESULTS AND DISCUSSION

4.1. Characterization of support

4.1.1. SEM characterization

SEM imaging was applied to characterize the morphology of the modified nanomaterials. Fig.8a and b shows the SEM images of the CNFs and the CNFox, respectively. Both images show smoothed bare fiber walls without any nanoparticle attached to the surface, however, CNFox exhibits more agglomerate fibers which can be observed in the image as cumulus of intertwined fibers. In contrasts, the

formation of magnetic nanoparticles through the surface of the nanofibers can be confirmed in Fig. 8c. According to Han et al., 2018, iron nanoparticles can be observed in SEM microscopy as bright spots. Thus, it can be easily seen that there are randomly distributed bright particles over the surface of the nanofibers, which are given by the formation of iron oxides nanoparticles. Moreover, it is important to point out that magnetic nanoparticles are not covering the whole surface of the nanomaterial, but they are randomly distributed and tend to form clusters.

The nanofibers obtained in this work are from different size between 88 nm- to 270 nm. In comparison, Xiang et al. synthetized iron carbon nanofibers (CNF-Fe) with magnetic properties by implementation of carbonization at 1000 °C during 1 h (Xiang et al. 2014). In this work, the magnetic fibers were reported to have diameters between 410 and 540 nm, which is larger than then the reported in our work. In these terms, the fibers synthesized in this work reach the nanometer scale whereas the prepared by Xiang et al. might not be considered as nanofibers.

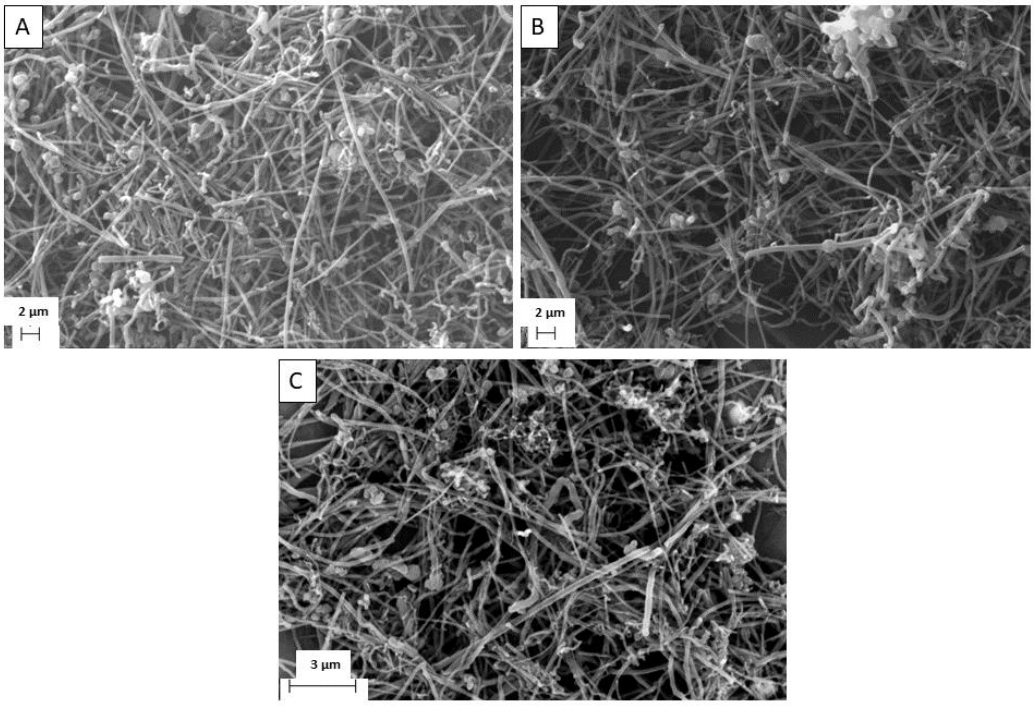

Figure 8. SEM image of (a) CNFs, (b) CNFox, and (c) mCNF

4.1.2. EDS characterization

Table 8. Chemical composition of CNF, CNFox, and mCNF obtained from EDS characterization

	CNFs	CNFox	mCNF
Carbon (%)	84.01	71.58	45.64
Oxygen (%)	15.99	28.42	35.61
Iron (%)	0	0	18.75

By the application of EDS characterization, it was possible to evaluate the oxidation rate of the CNF, as it was expected, after the acidic treatment of the CNF to obtain CNFox, the percentage of elemental oxygen in the material increased from 15.99 % to 28.42 %, which confirmed the chemical oxidation of the material.

Moreover, the addition of the iron oxides magnetic nanoparticles was confirmed by the increment of elemental oxygen from 28.42 %, corresponding to CNFox, to 35.61 %, and by the apparition of a new signal belonging to elemental iron with an elemental composition of 18.75 %.

The percentage of elemental iron attached to the surface of the CNF to form mCNF was higher than the reported for Zuo et al. (Zuo et al., 2019). In this work, magnetic CNF were synthetized by carbonization (280°C- 1000 °C, 5 h) to form Fe (II) and Fe (III) oxides with magnetic properties. According to the results, the content of iron was about 15.87% and 17.35%, which is lower than the 18.75 % obtained in this work, whit the difference that this mCNF were synthetized in 30 min using ultrasonic bath conditions.

4.1.3. FTIR characterization

Fourier transform infrared spectrum (FTIR) was implemented to determine the structural characterization of both free and immobilized enzymes onto the magnetic nanoparticles. Figure 9 shows the FTIR spectrums of the commercial CNF, modifications, and the immobilized laccases in a wave range of 400-4000 cm^{-1}. As it is expected, no significant signal was founded for the CNF (black) due to the absence of functional groups. Moreover, after the acidic treatment, no signal was detected by FTIR analysis, probably due to the low concentration of oxygen based functional groups, however, the formation oxidation of the CNF was confirmed by the EDS analysis, which confirmed the increment in elemental oxygen percentage from 16.00 % to 28.42 %. The functionalization of the oxidized CNF with magnetic nanoparticles was also confirmed by the FTIR spectra of this sample (blue). The

mCNF show two characteristic bands, one at 485 cm^{-1} attributed to the F-O bound characteristic of iron oxide nanoparticles. Moreover, the laccase immobilization was further characterized by FTIR analysis (green), after immobilization, signals attributed the addition of the enzyme, such as -NH- (820 cm^{-1}), C-N (1050 cm^{-1}), -CO-NH2 (1638 cm^{-1}) and C-H (2820 cm^{-1}) are observed.

In comparison with some reported literature, it was possible to confirm the attachment of the magnetic nanoparticles to the carbon nanofibers. For example, Wu S. et al. also confirmed the presence of iron nanoparticles with the presence of one absorption band at 597 cm^{-1}, moreover, their results also confirmed that after the acidic treatment, no characteristic bands are observed due to the low oxidation level Wu S. et al., 2015. Moreover, Samui et al. reported FTIR analysis of laccases, their results showed similar bands observed in this work for the characterization of laccases, for example, the spectrum also showed an amide I band at 1642 cm^{-1} due to C=O stretching, an amide III band around 1420– 1210 cm^{-1} due to CN stretching and NH bending, amide V and VI bands at 800–500 cm^{-1} due to out of plane NH and C=O bending, and a band at 1165–948 cm^{-1} characteristic of protein in laccase (Samui and Sahu 2018).

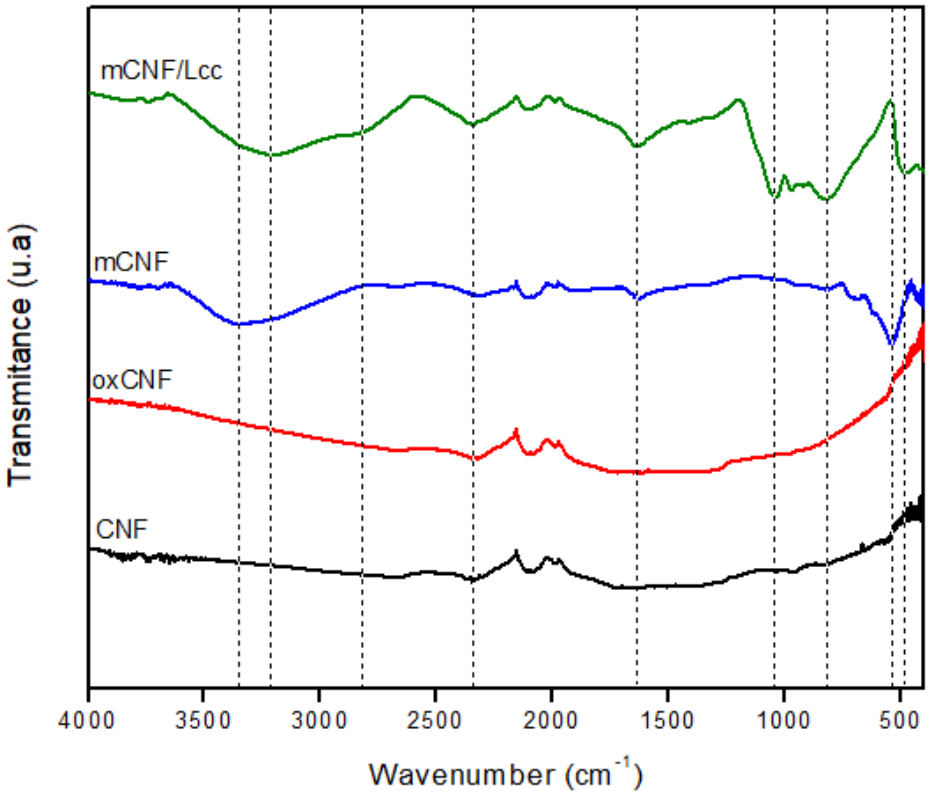

Figure 9. FTIR spectra of (black line)CNF, (red line) oxCNF, (blue line) mCNFs and (green line)Lcc/mCNFs4.1.4.

4.1.4. XRD characterization

XRD spectrums are shown in Figure 10, in which a comparison between the magnetic nanoparticles (B), the CNF (C) and the mCNF (D) can be observed. First, by the comparison of one computerized pattern of magnetite (Fe_3O_4) (A) with the obtained spectrum of the magnetic nanoparticles, it can be observed that both spectrums perfectly match, and characteristic planes are observed, including the 220, 311, 400, 422 and 511. Thus, the crystalline phase formed during the co-precipitation method was magnetite. Moreover, the results of the analysis of the non-modified CNF, showed the presence of the two characteristic planes of graphite 002 and 100, which can be also observed in the mCNF spectrum, as well than the

magnetite planes 220 and 311. In these terms, we can confirm by XRD the modification of the CNF with magnetite nanoparticles.

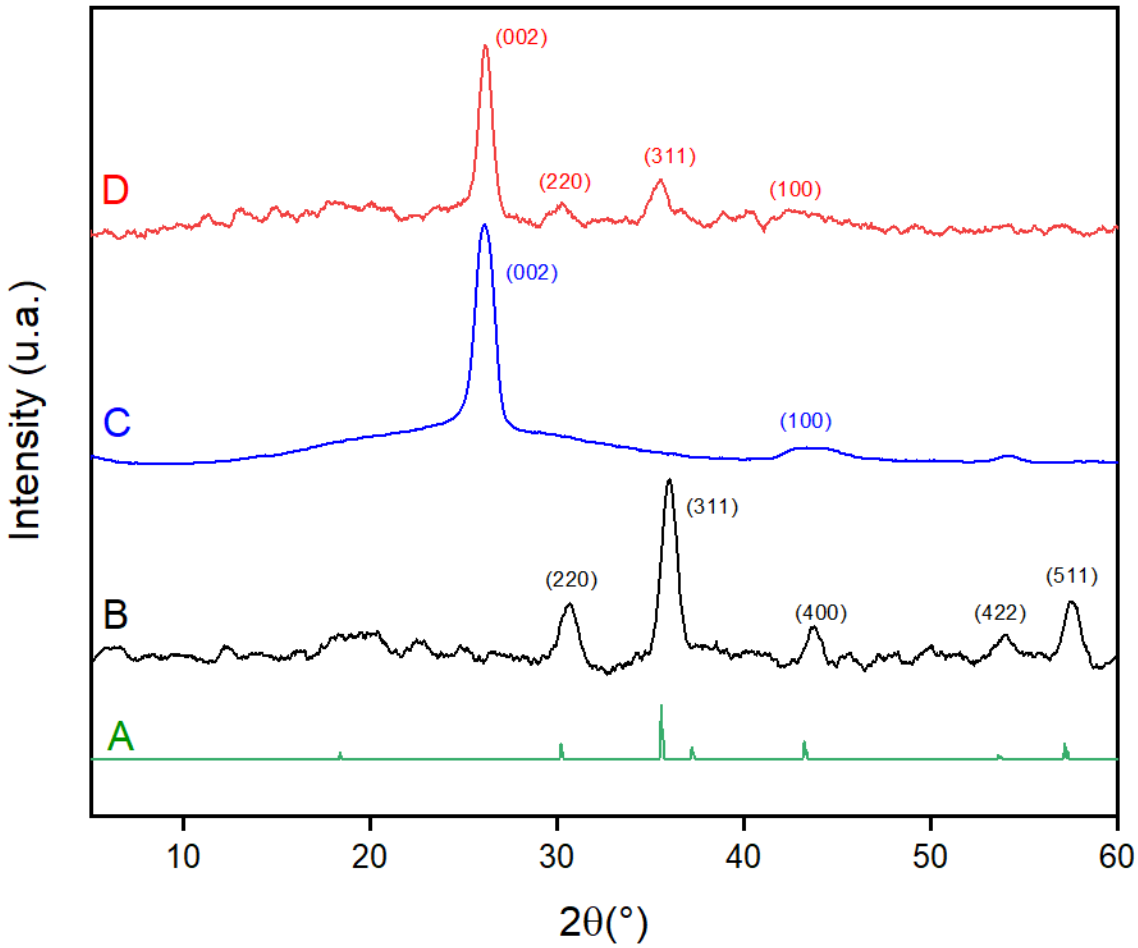

Figure 10. XRD spectrums of pattern of magnetite (A), synthetized magnetite (B), CNF (C), and mCNF (D).

4.2. Enzyme immobilization

Initially, a purified cocktail of laccases from *P. sanguineous* CS43, which were extracted following the optimized conditions determined in a previous study (Ramirez-Cavazos et al., 2014). The activity assay of the purified laccase was 117,154 U/L. Thus, by the addition of 200 µL of the purified laccases, about 23 U/L

were added to 10 mg of the mCNF. Table 9 shows the results of the immobilization of laccases onto the mCNF per triplicate.

Table 9. Percentage ff immobilization of laccases onto mCNF

Immobilization	mCNFs	Activity added (U/mL)	Activity immobilized (U/mL)	% Immobilization
1	10 mg	23.00	16.66	72.45
2	10 mg	23.00	17.14	74.53
3	10 mg	23.00	16.73	72.74
				73.24 ±1.28

As can be seen, in terms of laccase immobilization into the mCNF, 23 U/mL of laccases were used to immobilize and only around 27 % was recovered after 4 washes of the immobilized material, which means that the remaining activity was immobilized into the nanomaterial. The conditions of the immobilization of laccases from P. sanguineous were pH 7, 25 °C and 2 h of mechanical stirring, which led to obtain about 73.24 ±1.28 % of immobilization. Moreover, different magnetically modified nanomaterials have been applied for the immobilization of enzymes, including laccases. Table 10 shows a comparison of some magnetic nanomaterials used enzyme immobilization, including the results obtained in this work.

Table 10. Immobilization of enzymes onto magnetic nanomaterials

Magnetic material	Enzyme	Immobilization technique	% Of immobilization	Ref
Fe_3O_4@SiO_2	Laccases	Entrapment	43.28	Deng et al., 2015
Fe_3O_4@Chitosan	Laccases	Covalent	51.80	Zhang et al., 2020
Fe_3O_4@SiO_2@PDA	Lignin peroxidase	Entrapment	56.37	Guo et al., 2019
mCNF	Laccases	Adsorption	73.24	Present work

Different magnetic nanomaterials have been applied for the immobilization of enzymes, including metal based, polymeric materials, and carbon-based nanomaterials (this work). As can been seen, the mCNF showed higher % of immobilization than other modified magnetic nanomaterials, including polymers (chitosan and polydopamine) and silica, which all of them presented % of immobilization <60 %. In contrast, as mentioned below, the laccases from *P. sanguineous* implemented in our research reached 74.24 % of immobilization. CNF are characterized by their high surface area and its ability to be oxidized to form functional groups, which might help to the adsorption of laccases onto the surface (Ruiz-Cornejo et al., 2020).

4.3. Storage and pH stability of immobilized laccase

The activities of the immobilized laccases using ABTS as substrate were determined at pH ranging from 3.0 to 7.0 (Figure 10a). The results are shown in relative activity, been 100 % as the pH at which the enzyme-system expressed maximum laccase activity. According to previous reported results by Gonzalez-Coronel et al., the maximum relative activity of the free enzyme laccase is achieved at pH 2 (Gozalez-Coronel et al., 2017). Moreover, in comparison with free laccases, immobilized enzyme system exhibits highest enzymatic activities at pH values between 5.0 and

7.0, been 5.0 the maximum for the mCNF-laccase system. Therefore, these results suggest that the immobilized system provide favorable microenvironments and higher stability to changes in pH. As can be seen, free laccases exhibit a decrease in the activity at higher pH values, which could be due to the change in the ionic form of the enzyme active site and due to variations in folding of three-dimensional structure of the protein (Bagewadi et al., 2017). In contrast, when laccases are immobilized, an increment of activity is observed in a range between 3 and 5, and even though between 5-7 a decrease in activity is observed, this is lower than the free enzyme, since the free laccase at pH 7 exhibit less than 5 % of the relativity activity and the immobilized laccase shows around 64 %. These results also suggest that the binding of laccases on the mCNF gives it higher probability to avoid pH induced confirmational changes (Mohidem et al., 2009, Bagewadi et al., 2017). In this context, by the immobilization of laccases into CNF, wider pH range is provided, which makes possible to apply this biocatalytic systems even at pH 7 with relatively high activity (close to 70 % of the highest one). Similar results of pH variations and stability have been reported for other magnetic modified nanoparticles, including Fe_3O_4@Chitosan (Zhang et al., 2020), Fe_3O_4@ SiO2@ Kit-6 (Amin et al., 2018), and single magnetic nanoparticles, such as Fe_2O_3 and Fe_3O_4 (Patel et al., 2021).

Moreover, after determining the pH optimum of the immobilized laccases, the mCNF/Lcc system were stored for 30 days at 4 °C and the residual activity was measured every 7 days within the period. Figure 10b shows the residual activity of the immobilized system stored at 4±1 °C, in which can be seen that mCNF/Lcc retained more than 75 % of the initial activity. Similar results are reported for the immobilization of laccases after one month stored, for example, Taheran et al.,

immobilized the laccases into polyacrylonitrile-biochar and the activity retained was 71 % (Taheran et al., 2017).

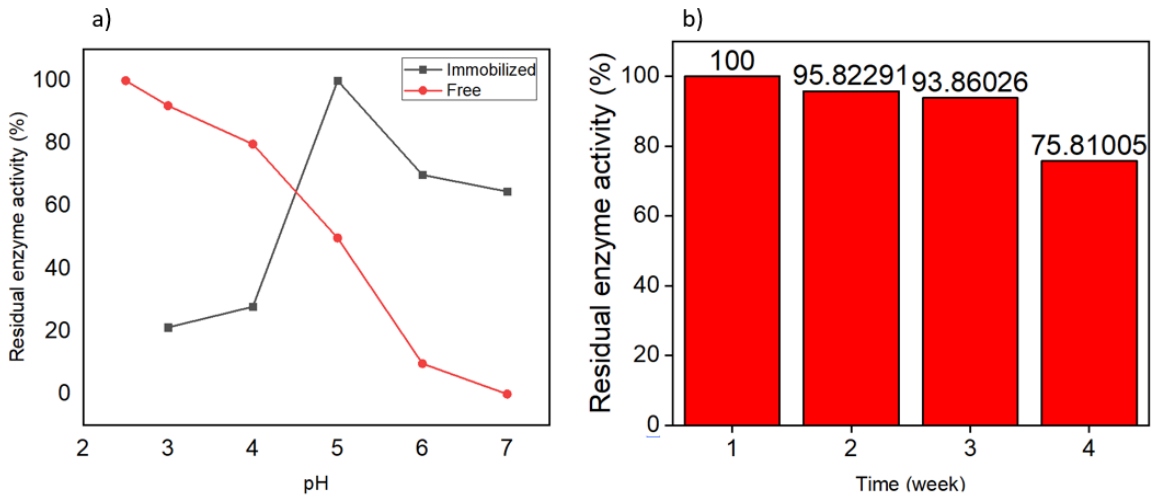

Figure 11. pH stability in a range between 2.5-7 (a) and storage stability stored at 4 °C (b)

4.4. Biodegradation of venlafaxine

Figure 12 shows the results of the calibration curve of the VFX made by HPLC-DAD, as can be seen, the calibration curve presents high linearity (R=0.999) with a equation of relation of Area(μV*sec)=20378[VFX] +17025. The retention time of the VFX in the instrumental analysis was 1.91 min. After the 18 h that the VFX was in contact with the nanobiocatalyst, the sample was measured by HPLC and the resulted area represented 9.31 μg/mL of the initial 30 μg/mL of VFX, which means that the % of remotion of the VFX was around 68.96 %. This results, represent a considerable improvement in comparison with the only reported nanobiocatalyst used for the remotion of VFX in water, which was published by Morsi et al., 2021 and only reach around 11 % of VFX remotion.

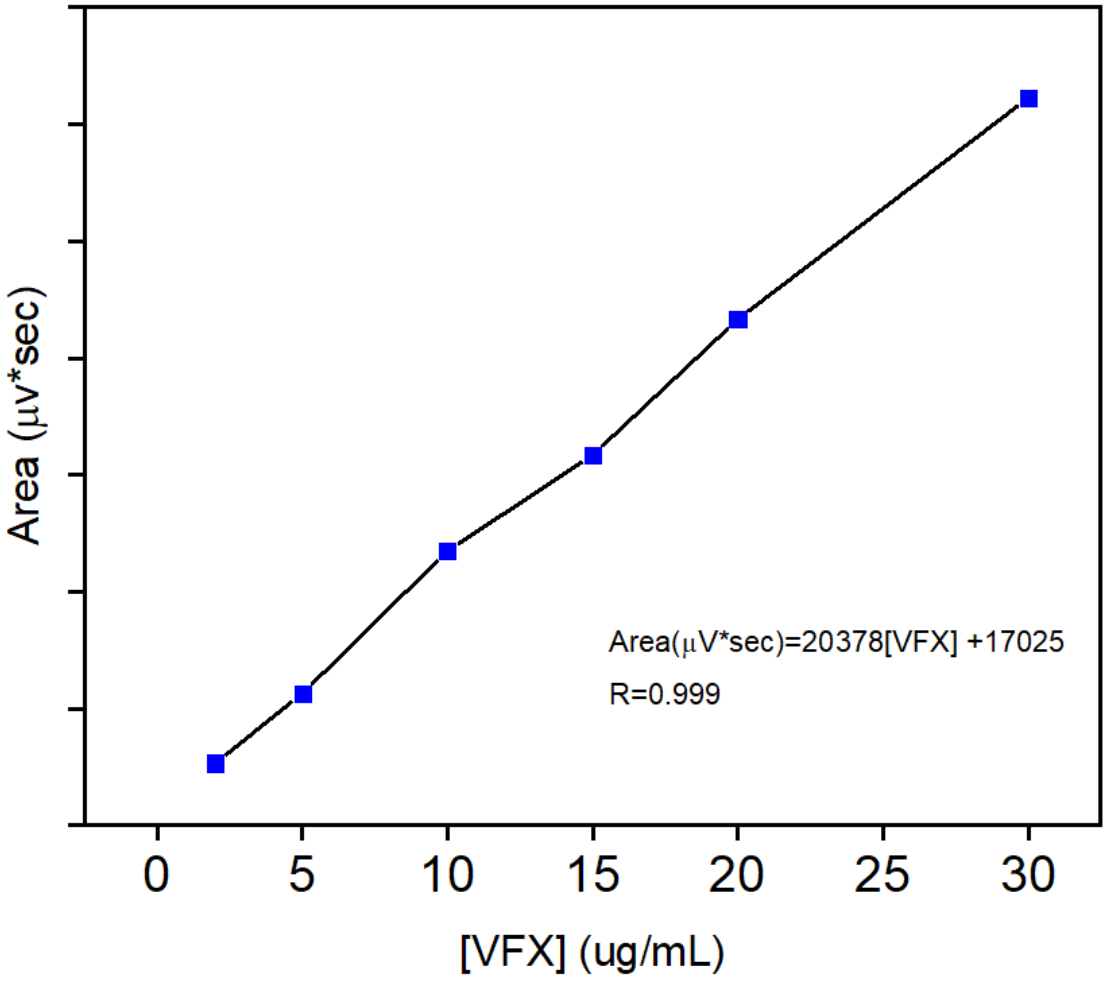

Figure 12. Calibration curve of VFX by HPLC-DAD

5. CONCLUSIONS

In the present study, a native laccase from *P. sanguineous* CS43 was successfully immobilized onto magnetically modified CNF for its potential use as biocatalyst of psychiatric drugs. In this thesis proposal, we designed a magnetic biocatalyst from CNF, which were subjected to an acidic treatment and after those magnetic nanoparticles were added by co-precipitation synthesis. The results confirmed the modification of the CNF by magnetic nanoparticles. The fiber type with

magnetic nanoparticles added to the surface- morphology of the nanostructured material was confirmed by SEM images of the non-modified CNF and the mCNF. Moreover, EDS results revealed the % in mass of every compound in the samples, in which after the modification of CNF, iron from the MNPs is observed. Moreover, FTIR analysis also confirmed the addition of the MNPs to the CNF by the presence of one Fe-O signal. In comparison with other techniques used by different authors, by the implementation of ultrasonic bath, it was possible to modify the CNF in 30 min at 65 °C, whereas other authors report the same synthesis with similar results at higher temperatures and more than 3 hours.

After immobilization of the laccases into the nanostructured material, the results obtained showed that, even though there was reduction in the activity of the immobilized enzyme, the stability of the laccase was improved. The mCNF retained around 73 % of the enzymes implemented for the immobilization process and the immobilized enzymes showed higher stability to pH changes in comparison to free enzyme, which is owned by the immobilization of the enzyme into the nanostructured system. Moreover, the immobilized enzyme retained around the 75 % of its initial activity after one month stored at 4 °C. Finally, the nanobiocatalysis system proved to be able to remove around 69 % of the psychiatric drug VFX from waters, which confirmed the highly catalytic property this material.

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