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Title

Research and analysis of pharmaceutical residues in liquid effluents for their elimination by COFs

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ملخص :

إن الهدف من هذه الدراسة هو إزالة مخلفات الملوثات الصيدلانية من المياه باستخدام الأطر العضوية التساهمية (COF) ومقارنة النتائج المحصل عليها مع نتائج الإزالة بإستعمال مسحوق الكربون المنشط AC باعتبارها مكثفات. كما يعتبر أول تقرير عن إزالة المستحضرات الصيدلانية من المياه بواسطة COF. سبق هذه الدراسة مسح للمنتجات الصيدلانية في الجزائر ومقارنتها بالبيانات العالمية مع تحديد الأدوية المستخدمة على نطاق واسع في الجزائر، و التي من المحتمل أن تلوث البيئة المائية.

أجريت اختبارات تجارب الامتزاز بطريقة النظام الغير مستمر. أظهرت النتائج أن COF أكثر فعالية من مسحوق الكربون المنشط AC في التقاط المستحضرات الصيدلانية. أعطى COF أوقاتًا قصيرة للوصول إلى التوازن تتراوح ما بين 10 دقائق وساعة واحدة ، أي أقل من 3 ساعات التي تم الحصول عليها عن طريق الفحم المنشط AC.

نماذج مختلفة تم تطبيقها لدراسة الحركية و ايزوتارم الامتزاز على المواد المختارة بعد تسليط الضوء على تأثير بعض المعلمات مثل التركيز ودرجة الحموضة.

بين الإيبوبروفين السهل الانحلال في الدهون قدرة امتزاز عالية على COF مقارنة بالأسيتامينوفين والأمبسيلين. حيث تم الوصول إلى قدرة قيمتها 133 مغ غ$^{-1}$ ما تعادل 90٪ عند درجة الحموضة المحايدة وتحت درجة حرارة 21 درجة مئوية في الماء عالى النقاوة. كما يبين ايبوبروفين امتزاز جيد على AC مقارنة مع الفينوباربيتال.

أظهرت تحاليل امتصاص المواد الصيدلانية باستخدام COF في المياه الحقيقية أن الأيبوبروفين يتمتع بقدرة امتصاص أعلى مقارنة مع الفينوباربيتال وأسيتامينوفين و هذه القدرة على الإمتزاز تأثرت بخصائص هذه المياه.

كشفت النتائج أن COF لها جاذبية جيد للمواد الصيدلانية المحبة للدهون و الأقل استقطاب في الماء عالى النقاء والمياه الحقيقية المستخدمة في تجارب الإمتزاز التنافسي على COF ، مما يدل على أمكانية تصميم COF لها أكثر تخصص و موجهة بدقة لالتقاط هذه الملوثات من المياه.

الكلمات الافتتاحية: الامتزاز، الامتزاز الثنائى، الأطر العضوية التساهمية (COF) الفحم المنشط CAP (F400) الابيبروفان، الفينوباربيتال، الأسيتامينوفان، الأمبيسيلين، الحركية، الازوتارم.

Résumé:

L'objet de cette étude est d'éliminer les résidus de polluants pharmaceutiques présents dans les eaux en utilisant comme adsorbants les Structures Organiques Covalentes (SOF) et de comparer les résultats obtenus à ceux donnés par le charbon actif en poudre CAP. Elle présente le premier rapport sur l'élimination des produits pharmaceutiques de l'eau par les COF. Cette étude est précédée par une enquête sur l'utilisation des produits pharmaceutiques en Algérie dont les résultats ont été comparés aux données mondiales et ont permis la mise en évidence des produits pharmaceutiques largement utilisés en Algérie et susceptibles de contaminer le milieu aquatique.

Les tests d'adsorption ont été réalisés par des expérimentations en batch. Les résultats ont montré que les COF sont plus efficaces que le charbon actif pour capturer les produits pharmaceutiques. Ils ont donné des temps d'équilibre plus courts (10 minutes à une heure) que ceux donnés par le charbon actif (trois heures).

Divers modèles ont été appliqués à l'étude cinétique et aux isothermes d'adsorption des molécules sélectionnées sur les COF et le CAP après avoir mis en évidence l'effet de certains paramètres tels que la concentration et le pH.

L'ibuprofène lipophile a montré une capacité d'adsorption élevée sur les COF comparé à l'acétaminophène et à l'ampicilline. Elle a atteint une valeur de 133 mg g^{-1} équivalente à 90% à pH neutre et à température de 21°C dans de l'eau ultrapure. Il a montré également une bonne adsorption sur le charbon actif par rapport au phénobarbital.

Les analyses d'adsorption de produits pharmaceutiques par les COF dans les eaux réelles montrent que l'ibuprofène présente une capacité d'adsorption plus élevée que le phénobarbital et l'acétaminophène et cette capacité d'adsorption est affectée par les caractéristiques de ces eaux.

Cette étude a mis en évidence le bon attrait des COF pour les produits pharmaceutiques moins polaires à caractère lipophile dans les eaux ultrapures et dans les eaux réelles utilisées pour réaliser l'adsorption compétitive, ce qui suggère que les COF peuvent être préconçus pour la capture sélective des contaminants dans les eaux.

Mots clés: Adsorption, Coadsorption, COF, CAP (F400), Ibuprofène, Phénobarbital, Acétaminophène, Ampicilline, Cinétique, Isothermes.

Abstract:

The aim of this study is the capture of pharmaceutical pollutants from water using covalent organic frameworks (COF) and activated carbon (ACP) as adsorbents. It presents as well the first report on pharmaceutical removal from water by COF. This study is preceded by an investigation about pharmaceutical products in Algeria compared to data from the world with determination of the largely used pharmaceuticals in Algeria that may contaminate the aquatic environment.

The adsorption tests were carried out in batch experiments. The results showed that COF are more efficient in capturing pharmaceutical products than ACP. COF showed short times to reach equilibrium varying between 10 minutes and 1 hour, much less than the 3 hours obtained by ACP.

Various models have been applied to the kinetic study and the adsorption isotherms of the selected molecules on the COFs and CAP after highlighting the effect of certain parameters such as concentration and pH.

Lipophilic ibuprofen has shown a high adsorption capacity onto COF compared to acetaminophen and ampicillin. This capacity is reached a value of 133 mg g^{-1} equivalent of 90 % at neutral pH and temperature of 21°C in ultrapure water. Ibuprofen has also shown a good adsorption onto ACP compared to phenobarbital.

Analyzes of pharmaceuticals adsorption by COF in real waters show that ibuprofen has a higher adsorption capacity compared with phenobarbital and acetaminophen and this adsorption capacity is affected by the characteristics of these waters.

This study has highlighted the good appeal of FOCs for less polar lipophilic pharmaceuticals in ultrapure waters and in the real waters used to achieve competitive adsorption, which suggest that COFs may be preconceived for selective capture contaminants in the waters.

Key words: Adsorption, Coadsorption, COF, PAC (F400), Ibuprofen, Phenobarbital. Acetaminophen, Ampicillin, Kinetic, Isotherm.

Dedications

This dissertation is lovingly dedicated

To my dear mother, for her love and support throughout my life, and to my dear father, who taught me the love of knowledge and success, may Allah welcome him to his vast paradise. Thank you both for giving me the strength to reach my dreams.

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"Optimism is the faith that leads to achievement. Nothing can be done without hope and confidence."

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ABBREVIATIONS

A	Temkin isothermal constant (L g^{-1})
APS	Algeria Press Service
B	Constant related to the free energy of adsorption (L mg^{-1})
BD	Benzidine
BET	Brunauer–Emmett–Teller
b_T	Constant related to the heat of adsorption (J mol^{-1})
B_t	Reichenberg parameter
C_0	Initial concentrations of the solutions
C_e	Equilibrium concentration of the solute in the bulk solution (mg L^{-1})
COF	Covalent Organic Framework
F	q_t/q_e ratio (q_t : quantity adsorbed at time t, q_t : quantity adsorbed at the equilibrium),
h	Initial adsorption velocity
IR	Infrared
K_a	Acid dissociation constant
K_f	Freundlich constant
K_1	Rate constant of pseudo-first-order (min^{-1})
K_2	Rate constant of pseudo-second-order (min^{-1})
K_p	Intra-particle scattering rate constant (mg g^{-1} $min^{1/2}$)
LOD	Limit of detection
logK_{OW}	Partition coefficient
LOL	Limit of linearity
m	Mass
M	Molecular mass
Me	Methyl
MIS	Medical Industry Service
MOF	Metal−Organic Framework
NCIS	National Centre for Informatics and Statistics
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
ORP	Overall rate purchases
PAC	Powder Activated Carbon

pH	Hydrogen potential
pK_a	The acidity constant
PPCPs	Pharmaceuticals and Personal Care Products
Q_e	Amount of solute adsorbed per unit of weight of adsorbent at equilibrium
QI	Quantities of pharmaceutical products imported
Q_m	Maximum adsorption capacity (mg g^{-1})
R	Universal gas constant (8.314 J $mol^{-1}K^{-1}$)
SAXS	Small-angle X-ray scattering
SEM	Scanning Electron Microscopy
SNAPO	Algerian National Union of Officine Pharmacists
t	Time
T	Temperature
TGA	Thermogravimetric analysis
$T_{Melting}$	Melting point temperature
Tp	Triformylphloroglucinol
UNOP	National Union of Pharmacy Operators
V	Volume of solution.
WHF	World Heart Federation
WHO	World Health Organization
α	Initial adsorption rate in mg g^{-1} min^{-1}
1/β	Related to the number of available sites for adsorption in mg g^{-1}
λ	Wave length (nm)
1/n	Heterogeneity factor

INTRODUCTION AND OBJECTIVES

Introduction

Pharmaceuticals and Personal Care Products (PPCPs) are medication and products for healthcare and cosmetics, which help to prevent or treat human and animal diseases and to improve the quality of daily life **(Ebele et al., 2016)**. The contamination of the environment by the transfer of these pollutants, known as emerging pollutants (Pollutants are not regulated in water quality standards), to the aquatic environments is the result of the high quantities of drugs and these products used throughout the world **(Liu, 2013; Daughton and Ternes, 1999)**. Many studies report the presence of various PPCPs in different environmental compartments, such as river water, seawater and wastewater **(Nikolaou et al., 2007; Anekwe et al., 2017; Castiglioni et al., 2006)**, which explains the growing attention, in recent years, their removal from water has received.

Although pharmaceuticals exist in the environment at very low concentrations, they are considered as micropollutants since they are able to cause harm to humans, plants, and animals (**Margot et al., 2015; Evgenidou et al., 2015; Bergman et al., 2013)**. Thus, the removal of such micropollutants has become increasingly important **(Ebele et al., 2016)** and can be more difficult due to the presence of other substances at high concentrations, which may prevent good treatments **(Li et al., 2003; Pelekani and Snoeyink, 2001, Quinlivan et al., 2005)**.

The newly recognized environmental micropollutants are known to be of great scientific and public concern and are the subject of considerable attention with respect to their environmental fate, the circumstances of their contact with the organisms and their toxicological risks during the last decade **(Evgenidou et al., 2015; Kummerer, 2009**). In recent years, several studies conducted by scientists and ecologists have drawn the attention of the public to the presence of traces of pharmaceutical and cosmetic products in water **(Boxall et al., 2012; Tambosi et al., 2010)**. The negative effects of drugs are now known, and the risk of presence of these substances grows continuously, which calls for a great effort to protect the aquatic and terrestrial resources from these substances and improve the environmental management globally **(Kalyva, 2017)**.

This growing interest has resulted in a lot of deep and specialized research, where several treatment technologies for pharmaceutical removal have been extensively investigated, such as activated sludge systems **(Jelic., 2011; Nakada., 2006; Radjenović., 2009; Carvalho et al., 2013)**, electro-coagulation coupled with electro-flotation process **(Zaidi et Al., 2015)**,

membrane bioreactors **(Radjenović et al., 2009; Kovalova et al., 2012; Martinez et al., 2013)**, photocatalytic oxidation processes **(Rizzo et al., 2009; Martinez et al., 2013)**, advanced oxidation processes **(Klavarioti et al., 2008; Esplugas et al, 2007; An et al., 2010)**, magnetic ion-exchange resins **(Jiang et al, 2015)**, and adsorption **(Domínguez et al., 2011)**.

Independently of the technology used for the elimination of pharmaceuticals, adsorption is always involved **(Landry and Boyer, 2013)**, and many researchers have studied the removal of pharmaceuticals by activated carbon **(Baccar et al., 2013; Guedidi et al., 2013)**. Removal of pharmaceuticals using adsorption is one of the most effective methods currently used to remove contaminants from reclaimed water due to its low cost, simplicity of the materials used and the rapidity of the pollutant removal. This efficiency has been reported in diverse works on adsorption treatment and removal mechanisms **(Coimbra et al, 2015; Jiang et al., 2015)**, but apart the activated carbon, which remains quite expensive, the materials used for removal generally present problems of low adsorption capacity, low affinity between adsorbent/adsorbate and the long equilibration time. Therefore, there is a need to develop novel materials and adsorbents to improve the efficiency and selectivity of the materials for pollutant elimination.

Algeria, like many other countries, is a major consumer of pharmaceuticals. The Algerian health expenditure is steadily increasing due to the combination of several factors, including population growth and the evolution of the age pyramid **(MH-029, 2012)**. Moreover, this continued increase in the use of these substances makes their transition to water a reality, which requires research and control. The drug substances present in the environment in Algeria are mainly found in aquatic systems, particularly watercourses close to pharmaceutical factories **(Boughrara, 2009)**, which prove that there is probably a pollution of drinking water and a certain danger to human health **(Yaker, 2016)**.

The objective of this PhD thesis is to test different materials for effective, less expensive and easy-to-use treatments of water contaminated by pharmaceuticals. The removal efficiency rates of the materials used and the mechanisms which could be effective for eliminating the pharmaceutical compounds in the aquatic environment will be studied using pharmaceuticals belonging to different diagnostic groups, such as ibuprofen and acetaminophen (analgesics), phenobarbital (antiepileptic), and ampicillin (antibiotic).

To reach this principal objective, three underlying objectives are set.

- A bibliographic and theoretical synthesis allows recalling, for this work, the necessary notions relating to pharmaceuticals, different methods of treatment of these micropollutants, and particularly adsorption. The different molecules selected are also presented as well as the adsorbents used.

This section presents the work that has been done in this field and the importance of this study in contributing to the elimination of pharmaceutical residues from water.

- The first experimental part consisted to a survey study on pharmaceuticals in Algeria, based on statistics drawn from the questionnaires addressed to four main categories of the health cycle: manufacturers, suppliers, pharmacists, and consumers with a general overview on pharmaceutical product consumption. This first step made it possible to situate the management of pharmaceutical products and to determine the drugs widely used in Algeria.
- The second purpose of this dissertation is to test new materials for an effective treatment, less expensive and easier to use, for water contaminated by pharmaceuticals. Tow molecules, TpBD-$(CF_3)_2$ and TpBD-Me_2 as part of new class of materials called Covalent Organic Framework (COFs) have been selected in this study. COFs have been studied for many applications such as optoelectronics, gas storage, and catalysis. COFs have also shown promise as adsorbents for organic dyes, CO_2, mercury, radionuclides, lanthanides, and marine toxin okadaic acid from seawater.

After selecting four pharmaceutical products between the most consumed in Algeria (ibuprofen, phenobarbital, ampicillin, and acetaminophen), the study of the elimination of these molecules residues from water by adsorption on the activated carbon, and then on the selected COFs was conducted by examining several aspects such as the adsorption capacity effect, concentration and pH on the adsorption following by the kinetics and the adsorption isotherms of these products in ultrapure water, tap water and finally study of adsorption of pharmaceuticals in real waters (lake, fountain, rivers) individually and as mixtures on the selected COFs will be studied.

PART I

BIBLIOGRAPHIC SYNTHESIS

CHAPTER I

PHARMACEUTICALS

I. Pharmaceuticals

Throughout history, humans have struggled to find medicines for various diseases and epidemics. In the past, drugs were not used for only physical therapy but were also associated with religious and spiritual healing. Pharmaceuticals have gone through several stages in their development, and their long history dates back to the early days of human civilization **(History, 2009).** The first drugs were likely discovered through accidents and observations **(Ban; 2006**). The early humans started to use different plants, animals, and mineral substances as drugs, and collecting more information for understanding their specific effects **(Davis, 1982; Petrovska, 2012**). Today, many scientific and technological advances in the fields of chemistry, genetics, biochemistry, biology and computing have transformed the pharmaceutical industry and flooded the market with new drugs.

I.1. Definition of drugs

Drugs are part group of Pharmaceuticals and Personal Care Products or PPCPs **(Ebele et al., 2017**). Drug is any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis, thanks to the active principles they contain **(Pan et al., 2013)**. A drug can be administered orally, by injection, rectally, cutaneously, and it can be in the form of cachet, ampoule, suppository, ointment or syrup, among others. The drug can be used to kill bacterias **(Trafton, 2017; Maddison, 2008)**, to relieve pain, to reduce a symptom or to overcome a deficiency. Some medicines require a medical prescription to be delivered, particularly because of their side effects, their toxicity or their addictive properties.

Active pharmaceutical ingredient: Any substance or mixture of substances intended to be used in the manufacture of a drug product, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or function of the body **(WHO, 2011)**.

Pharmaceutical excipients: are substances other than the active pharmaceutical ingredient (API) that have been appropriately evaluated for safety and are intentionally included in a drug delivery system **(Rowe, 2009)**.

Different types of drugs can be distinguished according to their use, components, and regulatory registration mode (Table 1) **(Vardanyan et al., 2006)**. On the environmental level,

drugs are emerging contaminants that at low doses can cause physiological effects in humans, animals and nature **(Ebeleet al., 2017)**.

Table 1 Four major categories of pharmaceutical products **(Plunkett, 2009).**

Categories	Psychiatric	Infections		Inflammation	Diverse
anesthetics	antidepressants	antibiotics	diuretics	antipyretics	bronchodilators
analgesics	anxiolytics	antivirals	anti-diuretic	antihistamines	vasopressors
sedatives	psychotropic	antiretrovirals	laxatives	anti-inflammatories	

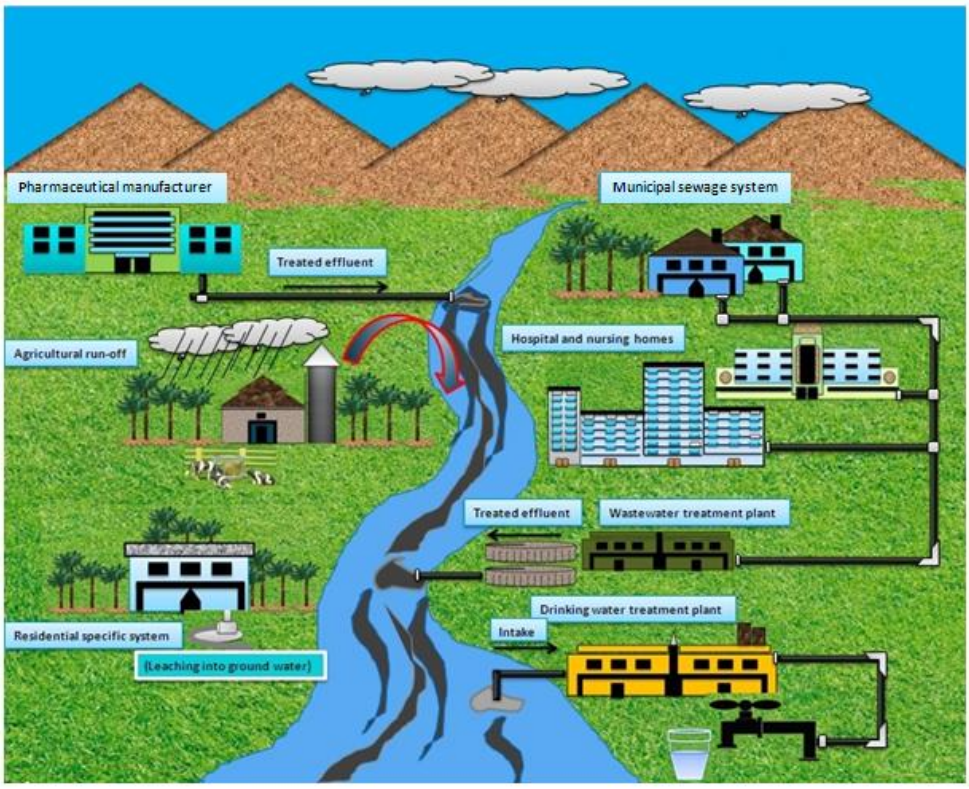

Figure 1 Illustration of sources of environmental contamination with PPCPs

I.2. Hazards, toxicity and effects of pharmaceutical pollutants on the environment

Pharmaceutical pollutants are frequently detected in effluents usually at levels from below 1 ng L^{-1} but they can up sometimes to a few µg L^{-1}, which makes their release in rivers and lakes an issue of growing concern (**Desbrow et al., 1998, Parrott et al., 2005)**. Indeed, several studies have reported about the limited degradability of pharmaceuticals by the conventional treatments applied in the wastewater treatment plants (WWTPs) **(Radjenovic et al., 2007; Carballa et al., 2005**), suggesting that upgrade and implementation of advanced treatment technologies are required to achieve high-quality treated effluents **(Radjenovic et al., 2009).**

Scientifically, drugs are created with the intent of causing a biological effect, and they often have similar types of physio-chemicals behaviors as characteristic of harmful xenobiotics (chemicals found but not produced in organisms or the environment), e.g. the ability to cross membranes. Drugs are designed as relatively persistent in order to avoid being inactivated before having their therapeutic effect (**Sanderson et al., 2003)**. Additionally, some of them, if not stored, handled or properly applied, may present certain risks to humans and animals and can have adverse effects on the environment (**Montague, 1998)**. On the other hand, these products in the soluble state present a danger of pollution by modifying the properties of water. They can also alter the natural environment and the species living there, such as different aquatic organisms (algae, daphnids and fish), and interfere with the proper functioning of the WWTPs by destroying their purifying flora (**Montague, 1998; Grosa et al., 2010)**, where the risks associated with the occurrence of those products in water resources are mostly unknown (Figure 1) **(Sanderson et al., 2003)**.

Many studies have proven the harmful effects of pharmaceuticals in the environment:

- Under the action of metabolism, the drug can give rise to metabolites having a hydrophilic structure different from the parent molecules (lipophilic). However, the persistent molecules pass through the purifying mechanisms of the WWTP to finally end up in the receiving environments, which may give rise to a risk to aquatic organisms in the event that the metabolites are active **(Halling-Sørensen et al., 1998)**.

- Sex hormones that are endocrine disruptors **(Emmanuel, 2003**) and antitumor drugs are important groups of medicines posing health and environmental risks (**Kümmerer, 2001**). Ethinylestradiol, the estrogen in many hormonal contraceptives, is at least in part responsible for the feminization of fish downstream from sewage treatment plants (**Desbrow et al., 1998; Parrott et al., 2005; Raloff, 1998)**.

- Antibiotic residues pose serious threats to public health if they are released into the environment without being processed **(Halling-Sørensen et al, 1998**). They can remain biologically active and pose a risk to the environment, especially because they can be concentrated in food chains. They can as well influence bacterial biomass in the environment, whether in water, soil, water treatment plants or drinking water distribution networks **(Haguenoer; 2010)**.

I.3. How drugs end up in water and methods of elimination

Pharmaceutical pollutants have recently raised great interest because of their direct impact on the environment, human and animal alike, in view of their occurrence in the aquatic environment and even in drinking water. The main source of these pollutants is sewage treatment plants effluents (**Alighardashi et al., 2008)**. Despite studies already conducted **(Jones et al., 2005; Ternes et al., 2004**), it still exists of many gray areas regarding the presence and fate of pharmaceutical substances in wastewater.

The knowledge of the physicochemical properties of pharmaceutical pollutants facilitates and helps to identify their inherent hazards, such as biological reactivity, physical hazards and environmental fate (degradation, persistence) **(NAP, 2014)**. Moreover, local physical and chemical factors such as pH, temperature, water hardness, suspended solids, and oxidation–reduction potential largely explain the environmental behavior of drugs in water. Several studies have shown that aerobic and anaerobic biodegradation by microorganisms is the main process for the elimination of these products in aquatic environments **(Garric et al., 2005)**.

I.4. Disposal methods for pharmaceuticals in water

The main role for which pharmaceuticals are manufactured is to have a biochemical activity in target organisms at relatively low concentrations. Therefore, an ecological and human health effect can be caused even at low part-per-trillion levels by some of these compounds (**Rodriguez-Mozaz et al., 2010; Kadam et al., 2016)**. Currently, wastewater treatment systems are not usually designed to remove medical or pharmaceutical waste, and thus the passage of many of these compounds to the wastewater effluents and consequently into the aquatic environment occur. Furthermore, using recycled wastewater for agricultural irrigation may lead to contamination of the soil with these substances, which may be transferred to plants and agricultural products and thus pose a threat to the environment, humans and animals (**Murdoch, 2015; Al-Farsi et al., 2017)**.

In order to solve this problem, researchers are looking for solutions and developing new methods, ways and technologies that allow the removal of pharmaceuticals from water. Below, some current innovative methods are presented that have proved effectiveness in treating water contaminated with pharmaceuticals.

I.4.1. Biodegradation

Biodegradation refers to the molecular degradation process of organic substances to simple molecules by the action of microorganisms, such as bacteria, fungi or yeast. Water and carbon dioxide are the final products of biodegradation (**Pérez et al., 2002)**.

Biodegradation is an important and very useful process in the wastewater treatment plant for the removal of toxic compounds and pollutants from the sewage by using two well-known processes: abiotic, such as photochemical reactions and hydrolysis, and biotic, i.e. biological degradation **(Kümmerer, 2009)**.

Biodegradation is one of the main routes of drug degradation, with some molecules biodegrading easily, others much less **(Montiel, 2006)**. Several studies treat the removal of pharmaceuticals pollutants using biodegradation by microorganisms **(Hervé Gauthier, 2008**), removal and degradation during membrane bioreactor treatment **(Schröder et al., 2012**), and degradation with advanced oxidation processes and ozone (**Quero-Pastora et al., 2014)**.

I.4.2. Membrane separation processes

Membrane separation processes (Figure 2) are defined as processes using a group of materials having some specific characteristics such as porosity, selectivity, electric charge, and ability to separate chemicals components from water **(Ortiz, 2011)**. Separation processes are already playing a key role in bio-pharmaceutical separation and purification operations via microfiltration, ultrafiltration and diafiltration. Currently, membrane filtration techniques such as reverse osmosis and nanofiltration are used to remove pharmaceutical pollutants from wastewater by coupling them to advanced bioreactors and oxidation processes **(Dengyue et al., 2017)**.

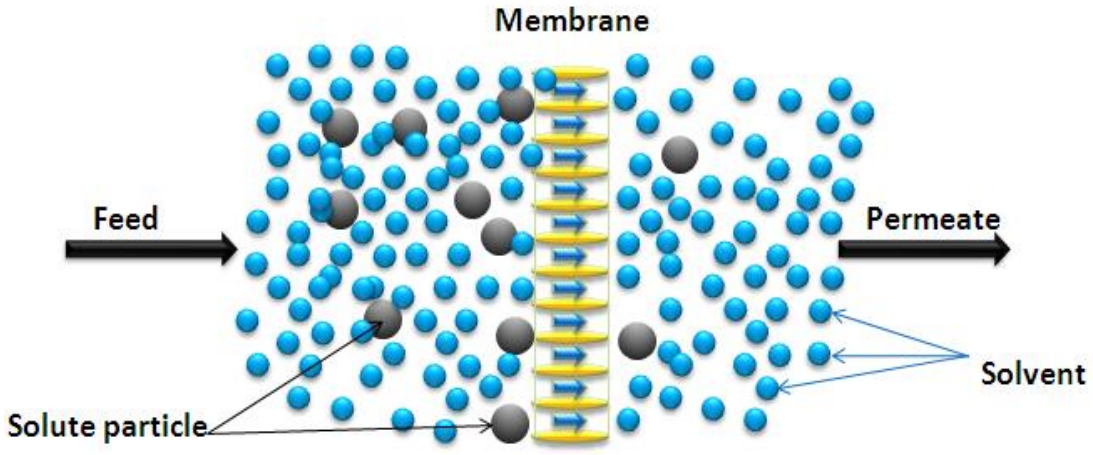

Figure 2 Membrane separation processes **(MEIS, 2017).**

I.5. Definition, structure, physicochemical properties and toxicity of the products studied

The physicochemical characteristics of the selected molecules for this study are relevant to understand their stability and persistence in the environment and to make it possible to interpret their behavior during their elimination from water. The most important parameters are defined below.

- **Solubility** is defined as the upper limit of solute that can be dissolved in a given amount of solvent (water) at equilibrium.
- **The acidity constant pK_a** is the negative decimal logarithm of the acid dissociation constant (K_a) of a solution. pK_a = –logK_a. The lower the pK_a value, the stronger the acid.
- **Partition coefficient logK_{ow}** is the ratio of the concentration of a solute between water and octanol commonly used as a measure of hydrophobicity. The ratio is essentially independent of concentration and is usually expressed in logarithmic terms. If logK_{ow} is positive and very high, the molecule is much more soluble in octanol than in water, which reflects its lipophilic character, and vice versa. A value of logK_{ow}= 0 means that the molecule is distributed equally between the two phases; thus, its concentration in octanol will be equal to its concentration in water.

The products chosen for this study are ibuprofen, ampicillin, acetaminophen, and phenobarbital. The choice of these pharmaceuticals is based on their high use in Algeria and the severity of their hazard to humans and the environment. Each compound will be briefly described in the following.

I.5.1. Phenobarbital

Definition: Phenobarbital (phenylethylbarbituricacid) or phenobarbitone is a barbiturate drug first synthesized in 1911 by the German chemist Emil Fischer **(Kwan & Brodie, 2004; López-Muñoz et al., 2005)**. The antiepileptic properties of phenobarbital were discovered in 1912 by the German physician Alfred Hauptmann **(Kumbier et al., 2004; López-Muñoz et al., 2005)**. Phenobarbital and other barbituric acid derivatives have been used therapeutically for over 65 years and remain widely used orally in the chronic treatment of several seizure disorders. They are frequently administered by intravenous route in the acute treatment of status epilepticus **(Nelson et al., 1982)**.

Structure and physicochemical properties: Phenobarbital is a white microcrystalline powder, with no odor, bitter taste, a melting point of 176°C and a molecular weight of 232.23

g mol^{-1}. It has a low solubility in water (1 g L^{-1}) but it is soluble in organic solvents such as chloroform, acetone, methanol, diethylether, and ethanol (**Wilensky et al., 1982**). It is also soluble in aqueous alkaline solutions. Its chemical structure is shown in Figure 3.

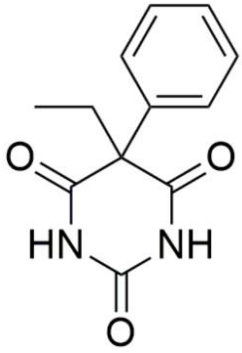

Figure 3 Chemical structure of phenobarbital

Due to tautomerism, phenobarbital is a weak acid; with pK_{a1} = 7.2, pK_{a2} = 11.8. Phenobarbital is mostly undissociated form **(Lechat et al., 1982)**. The weak acid character has interesting consequences:

- Phenobarbital salts can be prepared for intravenous administration.
- Phenobarbital can be precipitated by acids and extracted by solvents.
- Despite its solubility in saline solutions, phenobarbital has the inconvenience of being unstable; it breaks down to give urea.

Toxicity: The main undesirable effect of phenobarbital is drowsiness, which can have serious consequences in the exercise of professional activities and when driving a vehicle; dizziness, loss of appetite, headache, nausea and vomiting, problems with memory or concentration, and confusion (especially in children or older adults). The drug can pass through breast milk to the fetus and causes addiction **(Lautieri, 2018)**. Phenobarbital is also harmful to aquatic organisms, and it may cause long-term adverse effects on the environment (**Kiran et al., 2002)**.

I.5.2. Ibuprofen

Definition: Ibuprofen belongs to the class of nonsteroidal anti-inflammatory drugs (NSAIDs) (**Paxéus, 2004)** patented for the first time in England in 1964. Ibuprofen marketing has started afterwards by prescription in the 70s in the entire world, where it was recommended for the treatment of musculoskeletal pain and inflammation as well as other painful conditions **(Rainsford, 1999a)**. Ibuprofen has several established therapeutic uses. It is used for acute pain of mild or moderate intensity in adults and children (**Beaver, 2003; Autret-Leca, 2003)**.

It is also used as a symptomatic treatment for mild to moderate fever in adults and children (**Beaver; 2003, Autret-Leca; 2003)**. On the other hand, its antiproliferative and pro-apoptotic properties suggest that this product could have a clinical use for the chemoprevention of certain cancers (**Terry et al., 2004; Yeh et al., 2004)**.

Structure and physicochemical properties: Ibuprofen is characterized by a low solubility in water (21 mg L^{-1}) and a high logK_{ow} of 3.97, indicating that this substance is lipophilic. Ibuprofen is a carboxylic acid with a pK_a of 4.91, which explains its presence in the form of negatively charged ions in waters with a pH greater than 5 (**Abdulla al., 2014; Jingjie et al., 2014)**. Its chemical structure is shown in Figure 4.

Toxicity: Like other NSAIDs, ibuprofen is associated with a number of side effects: gastrointestinal, effects on the liver, kidney, nervous system, hematologic, hypersensitivity, dermatological and ocular effects. The toxicity of ibuprofen is related to the inhibition of prostaglandin synthesis **(Volans et al, 2003)**.

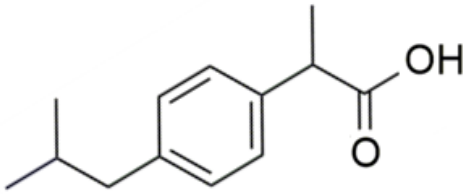

Figure 4 Chemical structure of ibuprofen

I.5.3. Acetaminophen

Definition: ***para***-Acetylaminophenol known as acetaminophen in the United States and paracetamol in Europe **(Howard et al., 2009; Rhonda, 2001),** is one of the most widely used drugs in the world **(Parashar, 2015)** for acute musculoskeletal pains and acute headache **(Tzortzopoulou, FDA, 2012),** fever reduction and pain relief **(FDA, 2012),** and to reduce nausea and vomiting **(Apfel et al., 2013)**.

Due to its wide use in the world, acetaminophen has become one of the most widely studied in many fields of pharmaceutical sciences for studying its toxicology, pharmacokinetics and its metabolism **(Prescott, 1996)**.

Structure and physicochemical properties: Acetaminophen is a white, crystalline powder, odorless, and with a bitter taste. It has a melting point of around 170°C and a molecular weight of 151.17 g mol^{-1}. The compound is miscible with water, methanol and ethanol **(Foye et al., 1995)**. Its chemical structure is shown in Figure 5.

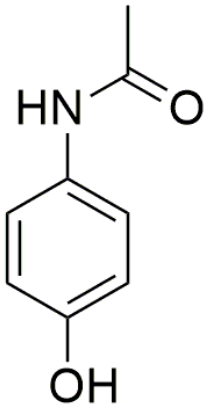

Figure 5 Chemical structure of acetaminophen

Acetaminophen has a very high solubility in solvents of medium polarity, and very low solubility in nonpolar and chlorinated hydrocarbons. Its solubility in water is 14 g L^{-1} at 25°C **(Roger et al.,1999)** and it has a pK_a = 9.0–9.5 and logK_{ow} = 0.46.

Toxicity: Acetaminophen is one of the most common causes of poisoning worldwide **(Kennon et al., 2008**), and has toxicity effects independent of the type of administration, intravenous, intramuscular, rectal and oral, with similar symptoms whether biochemical, hematological or histological, that provides a good understanding of its toxicity **(Kelvin et al., 2015)**.

Acetaminophen poisoning is the number one cause of acute liver failure in the world (**Hinson et al., 2004; Farrell, 1994; Lee et al., 1997**) and causes cell death (**Gibson et al., 1996)**. In addition to liver, however, many organ systems may fail under acute overdose such as renal, cardiac, and central nervous systems (**Thomas, 1993**).

I.5.4. Ampicillin

Definition: Ampicillin is a β-lactam antibiotic belonging to the penicillin family. It has been widely used for treating bacterial infections since 1961 **(Ashnagar et al., 2007; Pacifici, 2017)**. It penetrates the cell wall more efficiently than penicillin G, enabling it to kill many gram-negative bacilli. Ampicillin kills susceptible bacteria by interference with cell wall biosynthesis, therefore lysing the bacteria by autolysis **(Kohanski et al., 2010; Munita et al., 2016; Jordan, 2008)**. Ampicillin has been widely used for treatment of bacterial meningitis (infection of the central nervous system) in children (**Mathies et al., 1965; Theodoridou et al., 2013)**.

Structure and physicochemical properties: Ampicillin is a white, crystalline powder. It is odorless or has a faint odor characteristic of the penicillins, with a melting point of 208°C and

a water solubility of 10 g L^{-1}. Its dissociation constant pK_a = 2.5, 7.3 and log K_{ow} = 1.35. Its chemical structure is shown in Figure 6.

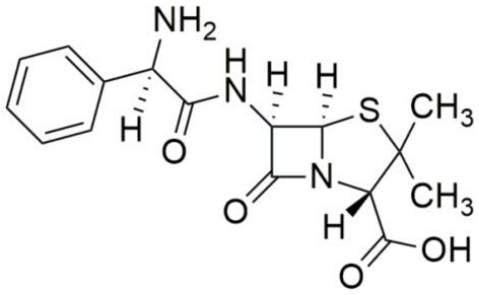

Figure 6 Chemical structure of ampicillin

Toxicity: Ampicillin may cause adverse effects that are commonly associated with Clostridium difficile, diarrhea, and macular rash resembling measles or rubella **(Farrington, 2012)** and candida vaginitis **(Raynor, 1997)**. There are also some types of allergic reactions caused by ampicillin. Moreover, a study by **Dunnick et al** (1989) shows that toxic lesions of the stomach were seen in rats and mice after ampicillin trihydrate administration.

Ampicillin toxicity, harmful effects and symptoms can be of two types depending on the duration of exposure. First, a short-term exposure can result in shortness of breath, and it can also cause skin rash after an allergic reaction, upset stomach (high-level exposure), and hypersensitivity reactions in allergic persons. Second, at long-term exposure, ampicillin may cause allergy, often accompanied with hives, which can lead to a fatal reaction (aplastic anemia), and a liver-damaging reaction **(Pohanish et al., 2012)**.

The physicochemical properties of the four molecules are summarized in Table 2.

Table 2 Physico-chemical properties of the pharmaceuticals used in this study, (source **ChemSpider**)

	Ibuprofen	Phenobarbital	Ampicillin	Acetaminophen
formula	$C_{13}H_{18}O_2$	$C_{12}H_{12}N_2O_3$	$C_{16}H_{19}N_3O_4S$	$C_8H_9NO_2$
molecular weight (g mol^{-1})	206.28	232.23	349.41	151.17
Solubility in water at 25°C (g L^{-1})	0.021	1	10,1	14
Polar Surface Area(Å^2)	37.3	75.3	138	49.3
log*D*	3.97	1.47	1.35	0.46
Melting point(°C)	75	174	208	169–172
pK_a	4.91	7.3; 11.8	2.5; 7.3	9.0; 9.5

CHAPTER II

ADSORPTION

II. Adsorption

II.1. Definition

Adsorption is a surface phenomenon, where the adsorbent is a substance adhering another substance on its surface. The substance that accumulates on the surface of the adsorbent is called the adsorbate **(Sparks, 2005)**. Adsorption can be a chemical or a physical process, or a combination of the tow, which occurs at the common boundary of two phases, such as liquid–solid, gas–solid, gas–liquid, or liquid–liquid **(Fomkin, 2009; LeVan et al., 1999)**. gas–solid and liquid–solid adsorption are processes in which a solid is used for removing substances from either gaseous or liquid solutions, respectively. The gas–liquid or liquid–liquid adsorption are processes in which a liquid is used for removing substances from either gaseous or liquid solutions.

Adsorption is a phenomenon resulting from the surface energy, which determines the mechanism and is at the same time similar to the surface tension. The bonds between atoms in this process may be of physical (van der Waals forces) or chemical (ionic, covalent, or metallic) nature (**Tilak et al, 2016)**. The basic phenomenon involved is a mass transfer from the gaseous or liquid phase to the surface of the adsorbent material to which the adsorbate tends to bind, the binding energy being materialized by heat of adsorption specific to the considered system **(Degremont, 1989)**.

The solid superficial properties (hydrophobicity or hydrophilicity) capable of modifying the equilibrium state of the medium (dispersion, flocculation) **(Butt, 2003)**. As indicated in Figure 7, adsorbate molecules diffuse into the porous spaces and channels of the adsorbate.

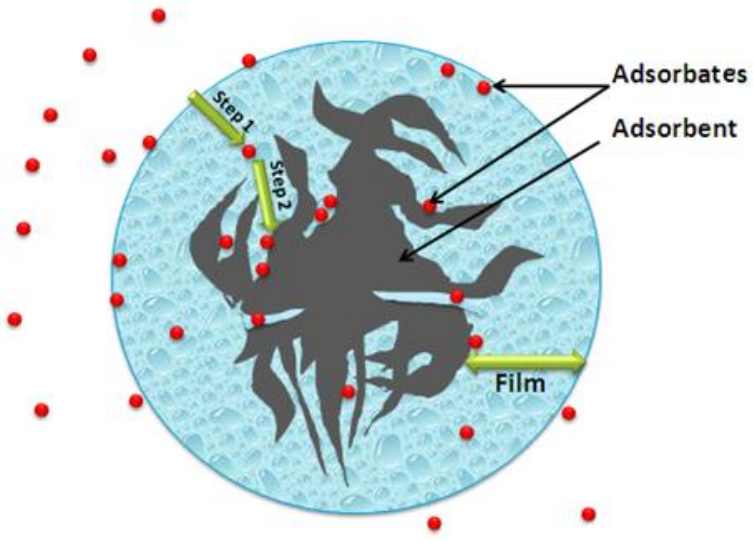

Figure 7 Adsorption of an adsorptive molecule onto the internal surface of a porous adsorbent **(Butt, 2003)**.

The adsorption process (Figure 8) has always been an effective and very useful technique to treat domestic and industrial effluents **(Naeem and Zafar, 2009)**. However, it is relatively expensive in terms of the materials used as adsorbents. The most common adsorbent used in this process is activated carbon (**Tsoung, 1992; Naeem and Zafar, 2009)**, either in powder form or in grains, where the molecules penetrate and settle in its pores according to the mechanism of the adsorption process (**Baccar et al., 2012; Mellah & al., 2014)**.

Desorption is the inverse process of adsorption, where adsorbed molecules break off from the adsorbent. Both natural and artificial adsorbents exist (**Tabelin et al., 2013)**, as exemplified by natural adsorbents such as the minerals, zeolites of different types, clays, or synthetic materials including Al_2O_3 and SiO_2 (**Tsoung, 1992; Naeem and Zafar, 2009)**.

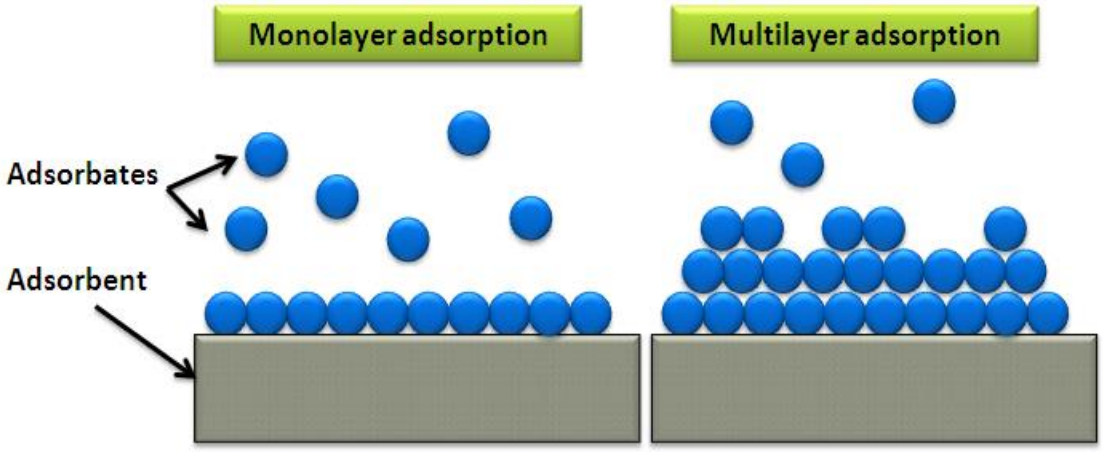

Figure 8 The adsorption process **(Butt, 2003)**.

II.2. Different types of adsorption

There are two types of adsorption: physical adsorption or physisorption and chemical adsorption or chemisorption (Figure 9; Table 3).

II.2.1. Physical adsorption

Physical adsorption (Figure 9) is a reversible phenomenon that results from the attraction between adsorbent functionalities composing the surface of the solid and molecules of the solute of the fluid phase. These attractive forces are physical in nature, including the so-called van der Waals forces, corresponding to weak energies of the order of a few kilocalories per mole **(Ruthven, 1984; Kaustubha et al, 2005)**. This phenomenon consists essentially of the condensation of molecules on the surface of the solid and is therefore favored by a lowering of the temperature (**Arris, 2008)**.

II.2.2. Chemical Adsorption

Chemisorption (Figure 9) is adsorption involving the formation of strong covalent, ionic, or metallic bonds between the surface of the adsorbent and the adsorbate **(Robert, 1997; Nevskaia, 2001)**. The reaction of the chemisorption process is irreversible and generally caused by charge transfer, with the adsorbed molecules undergoing changes in their chemical structure. The liberated heat is in the order of 20 to 50 kcal mol^{-1}, much higher than in physical adsorption **(Robert, 1997)**. The criteria for distinguishing between physical and chemical adsorption are mentioned in Table 3.

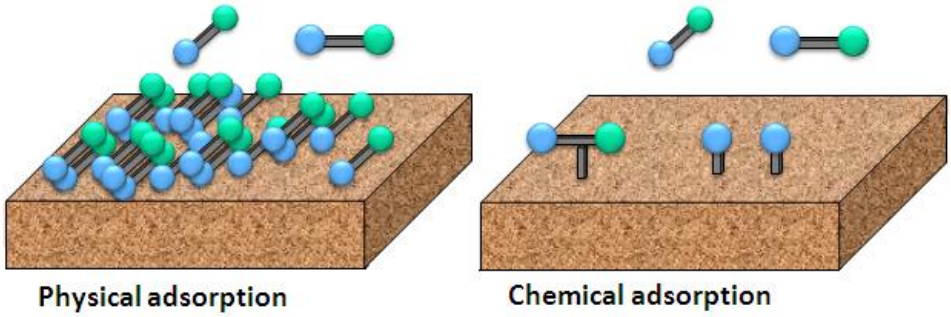

Figure 9 Types of adsorption **(Deng, 2019)**.

Table 3 Criteria for distinguishing between physical and chemical adsorption **(Deng, 2019)**.

Parameter	Physical Adsorption	Chemical Adsorption
Heat of adsorption	Some kcal mol^{-1}	Some tens of kcal mol^{-1}
Nature	Van Der Waals	Covalent/ionic
Specificity	Non-specific process	Specific process
Temperature	Relatively low compared to the boiling point of the adsorbate	Higher than the boiling point of the adsorbate
Reversibility	Reversible	Irreversible
Nature of the layers	Monolayer or multilayer formation	Monolayer formation

II.3. Factors affecting adsorption

The adsorption equilibrium between an adsorbent and an adsorbate depends on numerous factors, the main ones being**:**

Temperature: Adsorption increases at low temperature conditions. The adsorption process is exothermic in nature. According to Le Chatelier's principle, low temperature conditions favor the forward direction **(Boucif, 2009)**. $A + B \Leftrightarrow AB + Heat$

Pressure: The adsorption increases with increasing of pressure until reaching saturation level. Thereafter no more adsorption takes place no matter how high the pressure is applied **(Boucif, 2009)**.

pH: Adsorption is maximal at the isoelectric point and is influenced by the residence time **(Edeline, 1996)**.

Surface area of adsorbent: More active centers are present when the adsorbent surface area is large and the adsorption may be faster **(Edeline, 1996)**.

Activation of a solid adsorbent: Sub-dividing the solid adsorbent into fine particles for increasing its effective area or heating the solid adsorbent for opening its pores will increase the adsorption **(Singhal, 2011)**.

The structure of the carbon chain: molecules containing unsaturated bonds are more easily adsorbed than saturated molecules (electronic exchanges) **(Gendrault Derveaux, 2004)**.

II.4. Principles of the adsorption process

In practice, adsorption is often performed as an operation, either in batch or continuous mode, in a column packed with porous sorbents. Under such circumstances, mass transfer effects are inevitable. The complete course of adsorption includes mass transfer which is done in three steps (**Ho et al., 2008; Cardot, 1999; Hammache, 2006**):

Step 1: Film diffusion (external diffusion), which is the transport of the adsorbate from the bulk phase to the external surface of the adsorbent.

Step 2: Pore diffusion (intraparticle diffusion (IPD)), which is the transport of the adsorbate from the external surface into the pores.

Step 3: Surface reaction, which is the attachment of the adsorbate to the internal surface of the sorbent.

II.5. Adsorption Isotherm

Adsorption isotherms refer to chains of adsorption measurements performed at a given temperature and whose results are plotted as a relationship between adsorbed and non-adsorbed amounts. The form of the isotherm gives a lot of informations concerning the nature of the adsorption process **(Flatt et al., 2012)**. An isotherm is a curve that represents the variation of the amount of solute adsorbed per unit mass of adsorbent as a function of the equilibrium concentration (C_e). The amount adsorbed can be calculated, based on the following equation:

$$q_e = \frac{(C_0 - C_e)V}{m} \qquad (1)$$

Where q_e is the adsorption capacity in equilibrium, C_0 is the initial concentration of the adsorbate in solution, m is the mass of the adsorbent and V is the volume of the solution.

Different mathematical models have been established to represent the adsorption equilibrium. The models described below (Figure 10) are the most commonly used.

The shape of the isotherm varies according to the adsorbate–adsorbent pair studied. Solute adsorption isotherms have been classified by Giles et al. **(Giles et al., 1960)** in four main classes (Figure 10):

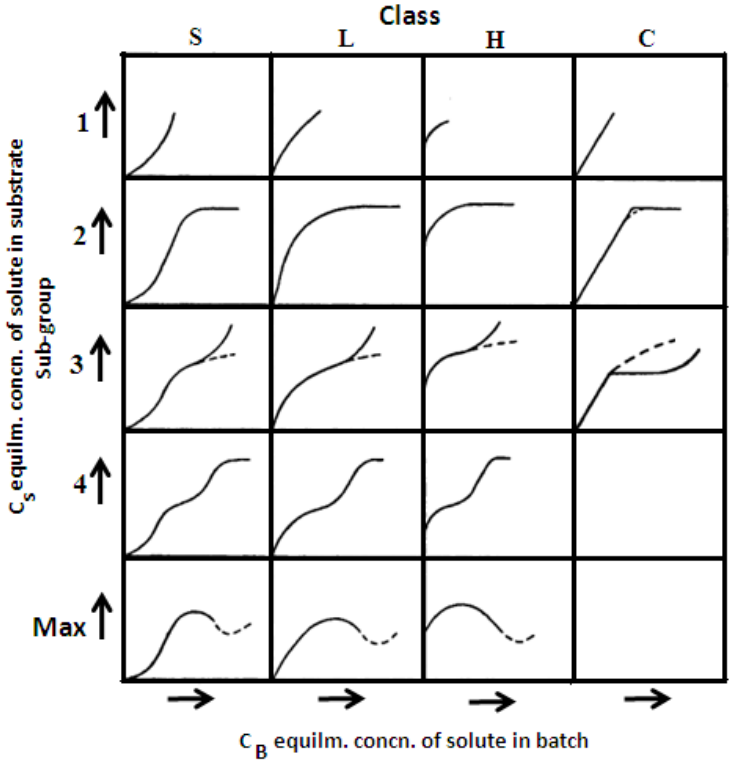

Figure 10 System of isotherm classification **(Giles et al., 1960)**.

S: These curves indicate that the orientation of adsorbed molecules is vertical at the surface.

L: Normal or Langmuir, these isotherm curves usually indicate that the molecules are adsorbed flat on the surface, or sometimes the ions are vertically adsorbed.

H: Curves (high affinity) in this case are often concerned with solutes adsorbed as ionic micelles and the exchange between high affinity ions with low affinity ions.

C: Linear curves are given by solutes which penetrate into the solid more readily than the solvent.

II.5.1. Langmuir model

The Langmuir model **(Langmuir, 1960**) assumes uniform energies of adsorption onto the surface and no transmigration of adsorbate in the plane of the surface. The model is based also on monolayer and finite adsorption site assumptions, and therefore a saturation value is

reached beyond which no further adsorption takes place. It also assumes that there is no interaction between the molecules adsorbed at neighboring sites. The Langmuir equation may be written as:

$$q_e = \frac{x}{m} = q_m * \frac{b.C_e}{1 + b.C_e} \qquad (2)$$

where q_e is the amount of solute adsorbed per unit weight of adsorbent at equilibrium (mg g^{-1}), C_e the equilibrium concentration of the solute in the bulk solution (mg L^{-1}), q_m the maximum adsorption capacity (mg g^{-1}), and b is the constant related to the free energy of adsorption (L mg^{-1}). Eq. (2) can be linearized to:

$$\frac{C_e}{q_e} = \frac{C_e}{q_m} + \frac{1}{q_m b} \qquad (3)$$

II.5.2. Freundlich isotherm

Freundlich isotherm **(Freundlich, 1906)** is an empirical equation for multilayer, heterogeneous adsorption sites. The Freundlich equation is commonly given by:

$$q_e = K_f C_e^{1/n} \qquad (4)$$

where q_e is the amount of solute adsorbed per unit weight of adsorbent (mg g^{-1}), C_e is the equilibrium concentration of solute in the bulk solution (mg L^{-1}), K_f is the Freundlich constant indicative of the relative adsorption capacity of the adsorbent (mg g^{-1}), and $1/n$ is the heterogeneity factor.

II.5.3. Temkin isotherm

The derivation of the Temkin isotherm assumes that the lowering of the adsorption heat is linear rather than logarithmic, as applied in the Freundlich equation. The Temkin isotherm was generally presented by the following equation **(Temkin, 1940)**:

$$q_e = \left(\frac{RT}{b_T}\right) \log A + \left(\frac{RT}{b_T}\right) \log C_e \qquad (5)$$

Where: T is the temperature (K); R is the universal gas constant (8.314 J $mol^{-1}K^{-1}$); b_T is the constant relative to the heat of adsorption (J mol^{-1}), and A is the Temkin isothermal constant (L g^{-1}).

II.6. Kinetics of adsorption

The kinetic equations of the chemical reaction show the dependence of the reaction rate on the concentration of the reactants. The study of adsorption kinetics is important because it provides valuable informations on the mechanism of the reaction (**Iakovleva et al., 2013)**. It permits to highlight the specificity of the physicochemical interactions between the solute and the adsorbent and to obtain the initial adsorption rate, as well as the equilibrium time, the material transfer coefficient, and the diffusion coefficient **(Hammache, 2006)**.

According to De Laat **(De Laat, 1988**), the adsorption rate of the solute is determined either by the transfer rate of the adsorbate through the boundary layer (first stage) and/or by the solute diffusion rate inside the grain (second step). The adsorption kinetics are not yet satisfactorily described. Various kinetic models are applied in the kinetics.

II.6.1. Pseudo-first-order kinetic model

The Lagergren differential equation governing the pseudo-first-order adsorption kinetics is the most widely used (**Lagergren, 1898)**:

$$\frac{dq_t}{dt} = K_1(q_e - q_t) \qquad (6)$$

where q_e and q_t are the amounts of solute adsorbed in mg g^{-1} at equilibrium and at time t, respectively, and K_1 is the pseudo-first-order rate constant (min^{-1}).

The equation allows the determination of the adsorption rate constant of the solutes. The linearized form of this equation is obtained by integration between the initial moment (t_0=0) and the specific time t:

$$\log(q_e - q_t) = \log(q_e) - \frac{K_1 t}{2.303} \qquad (7)$$

II.6.2. Pseudo-second-order kinetic model

The differential equation governing the second-order adsorption kinetics is of the following form **(Quek et al, 1998, Repo; 2011)**:

$$\frac{dq_t}{dt} = K_2(qe - qt)^2 \qquad (8)$$

where k_2 (g mg^{-1} min^{-1}) is the pseudo-second-order rate constant.

Integration of this equation leads to:

$$\frac{1}{q_e - q_t} = \frac{1}{q_e} + K_2\, t \qquad (9)$$

It is mostly used in the following linearized form:

$$\frac{t}{q_t} = \frac{1}{K_2 q_e^2} + \frac{1}{q_e} t \qquad (10)$$

The initial adsorption velocity *h* is given in this case by the equation:

$$h = K_2\, q_e^2 \qquad (11)$$

II.6.3. Intraparticle diffusion

Since the two previous models cannot describe the diffusion mechanism, Weber and Morris proposed a theoretical model based on intraparticle scattering, described by the function **(Akhtar et al., 2007; Sarvinder et al., 2004)**

$$q_t = K_p t^{1/2} \qquad (12)$$

where q_t is the adsorbed quantity per unit mass of adsorbent at time *t* (mg g^{-1}) and K_p is the intraparticle scattering rate constant (mg g^{-1} $min^{1/2}$)

II.6.4. Reichenberg model

The Reichenberg equation is applied to distinguish the diffusion process from that of adsorption through the film in the particle diffusion mechanism **(Reichenberg, 1953)**. The latter is expressed as follows:

$$F = \frac{Q_t}{Q_e} = (1 - 6|\pi^2)\exp(-B_t) \qquad (13)$$

$$B_t = -0.4977 - \log(1 - F) \qquad (14)$$

where B_t is the Reichenberg parameter and *F* is the fractional attainment of equilibrium.

If the curve B_t as a function of time is linear and passes through the origin, then the rate of adsorption is governed by diffusion. In other words, it is governed by the diffusion through the film.

II.6.5. Elovich equation in chemisorptions kinetics

The equation generally known as the Elovich equation, first suggested by Roginsky and Zeldovich, has been widely used to treat chemisorption data **(Low, 1960; Taylor et al., 1952)**. The velocity of chemisorption or activated adsorption generally obeys the Elovich's empirical relation, especially when chemisorption is slow **(Popiel, 1967)**. The equation is:

$$Q_t = \frac{1}{\beta \log(\alpha\beta)} + \frac{1}{\beta \log(t)} \qquad (15)$$

where α is the initial adsorption rate in mg g^{-1} min^{-1}, and $1/\beta$ is related to the number of available sites for adsorption in mg g^{-1}.

CHAPTER III

ADSORBENTS

III. Adsorbents

III.1. Overview

Several materials are used as adsorbents in water treatment such as activated alumina (Al_2O_3), activated carbon, zeolites, silica gel, polymers and resins **(Masschelin, 1996)**. Below are presented the definitions and the applications as well as the advantages and disadvantages of these adsorbents.

III.1.1. Activated alumina

Activated alumina is a commercial porous solid form of aluminum oxide, Al_2O_3 with specific surface area of 200–300 $m^2\ g^{-1}$ **(Jekel et al., 2006)**. Its most important application is the adsorption of water and desiccation of compressed air and other gases and liquid streams. This adsorbent is often used to purify gas streams by the selective adsorption of specific molecules. The main advantage using activated alumina is its high surface area, high efficiency when used as water filter, high resistance to abrasion, and maintaining of its shape when in contact with water. Alumina does not shrink, swell or soften when immersed in water. Activated alumina use has several disadvantages. The process cycle of alumina columns is generally complicated and requires careful monitoring by a trained operator **(DEGJP, 1996)**. Defluoridation using activated alumina presents a risk of toxicity by aluminium **(George et al., 2012)**. Adsorption on activated alumina depends on its pH and the pH of the solution (**Kasprzyk-Hordern, 2004)**.

III.1.2. Activated carbon

Activated carbon is a carbonaceous, highly porous adsorptive medium that has a complex framework composed mainly of carbon atoms. It has a large specific surface which gives it a high adsorbent capacity. It is most available in three shapes: powder, granular, and extruded. The fields of application of activated carbon materials are many and varied: in medicine, it is used in the treatment of some forms of acute poisoning by reducing the absorption of toxic agents. In the food industry, it is used for water discoloration of sweeteners (glucose, sucrose), organic acids, amino acids, and vitamins. In the chemical industry it is used for hydrogen storage, support for catalytic metals, removal of hydrocarbons from water, extraction of gold from ores, treatment of liquid effluents, and gas treatments (VOCs= Volatile Organic Compounds). Active charcoal has several advantages, such as the possibility of regenerating the same carbon charge several times and the flexibility of operation. As For disadvantages, activated carbon cannot be regenerated when mixed with hydroxide sludge

(lenntech), it is very expensive, non-selective **(Crini et al., 2010)**, and, for reuse, it needs to be treated with a solvent, which adds to the cost. Other principal disadvantages of activated carbon are fouling by Natural Organic Matter (NOM). NOM competes with other organic pollutants for adsorption sites and prohibits them from entering the micropores by stopping them **(Hassan, 2007)**.

III.1.3. Zeolites

Zeolites are microporous aluminosilicate minerals commonly used as commercial adsorbents and catalysts, with internal surface of 100–850 m^2 g^{-1} **(Deng; 2016)**. Zeolites occur naturally but are also produced industrially on a large scale. They are mainly used in hydrocarbon transformations **(Perot et al., 1990)**, and also to adsorb gaseous molecules such as SO_2, NH_3, H_2S, and HCl, and in water purification to remove substances such as Cs^+, Sr^{2+}, and NH_4^+. In addition, it is used to fix catalysts as ion exchangers, and removal of Hg, NO_X and SO_X to protect the environment and control pollution.

Zeolites have advantages such as energy saving during gas separation, recovery of solar energy, and raw material economy (**Grés, 1979)**. Zeolites are natural and ecological filters for swimming pools, for example. As solid catalysts, zeolites offer numerous advantages over liquid catalysts: less or no corrosion, no waste or disposal problems, high thermostability, and easy set-up of continuous processes **(Perot et al., 1990)**. However, zeolites have some inconveniences: the selectivity can be very high because of their pore structure. The sensitivity of zeolites to the deactivation by coke: comparatively small amounts of coke are able to stop incoming of the reactant to the active sites **(Perot et al., 1990)**. In addition, the natural zeolite extract contains many toxic minerals and when it moves through the human body, it can cause dehydration. In addition the aluminum of the zeolite liquid can penetrate the blood.

III.1.4. Silica gel

Silica gel is an amorphous and porous form of silicon dioxide (silica), consisting of an irregular tridimensional framework of alternating silicon and oxygen atoms with nanometer-scale voids and pores. It is a desiccant with great moisture absorption properties. Currently, silica gel is used in several industries and for several applications such as energy storage, adjuvant in industrial and domestic use, dew point control of natural gas, dietary supplement, food preservation, and chromatography. Silica gel holds many advantages such as the almost indeterminate shelf life if stocked under airtight conditions. It has the capacity to adsorb up to

40% of its own weight in water vapor (35% greater than typical desiccant clays). It is a very inert material, non-toxic and non-flammable. Silica gel can be regenerated and reused if required. Despite its advantages, silica gel has many inconveniences and numerous harmful effects, especially the form that contains cobalt chloride. Silica gel has the potential to harm humans, as example asbestos is very harmful if breathed **(Luus, 2007)**, and ingesting silica gel causes dehydration and discomfort, respiratory effects, irritation and redness when contact with the eyes occurs. Industrially, silica gel is considered a more selective solid sorbent than activated carbon, and its most important disadvantage is its high hydrophilicity and its ability to absorb water vapor and displace collected components **(Mansdorf et al., 1998; Rose et al., 2010)**.

III.1.5. Polymers and resins

Polymers and plastic resins are macromolecules comprised of repeating organic or synthetic molecules. They are widely used as raw materials in plastic molding and fabrication operations. Polymers and resins are used for water purification, retrieval and purification of steroids and amino acids, separation of fatty acids from water and toluene, separation of aromatics from aliphatics, retrieval of proteins and enzymes, removal of colors from syrups and removal of organics from hydrogen peroxide **(Deng; 2016)**. In the industry polymers and resins are used for vibration damping (pumps, rotating machines), safety (anti-slip floors), anti-acid protection, protection against corrosion and chemical attack. They are also used for textiles and packaging and building equipment **(Fried; 2008)**. There are also biodegradable polymers used in the biomedical field, especially in chirurgy.

Polymers and resins have several advantages related to their physical and chemical properties such as thermal and surface properties, permeability and electrical properties. Polymers and resins are cheap to make and some polymers can be recycled, melted down, and transformed into something else, which saves valuable natural resources. Polymers can reduce the use of wood, so fewer trees will have to be felled. Polymers can be produced from plant seed oils which are able to reduce the use of petrochemical-based polymers. Such oil-based polymers are renewable, biodegradable, and environmentally friendly **(Garrison et al., 2016)**.

Polymers and resins also have several disadvantages. Most of them are not biodegradable and may remain in the environment for a long time after disposal. Some plastics are toxic, and their use may cause health problems. In addition, it is hard to live near polymer-producing industries because of the release of harmful chemicals during polymer production.

Additionally, burning polymers can release toxic fumes **(Thompson et al., 2009; Hopewell et al., 2009).**

III.1.6. Metal Organic Framework

Metal−Organic Frameworks (MOFs) are a class of crystalline materials made by linking inorganic and organic units by coordinative bonds in order to form a complex structure at an atomic precision, which can be one-, two-, or three-dimensional (Figure 11) **(Yuan et al., 2018; Furukawa et al., 2013)**. Recently, their properties have attracted enormous attention with respect to the capture of diverse hazardous cationic and anionic species, materials for gas storage, gas/vapor separation, catalysis, luminescence, and drug delivery among others **(Kumar et al., 2017; Kuppler et al., 2009)**.

Metal–Organic Frameworks are tested for water treatment for purification and removal of pharmaceutical pollutants from aqueous solutions because of their large specific surfaces **(Seo et al., 2016; Song et al., 2017)**. However, the low hydrolytic stability of some MOF derivatives in water can hinder their use in environmental applications.

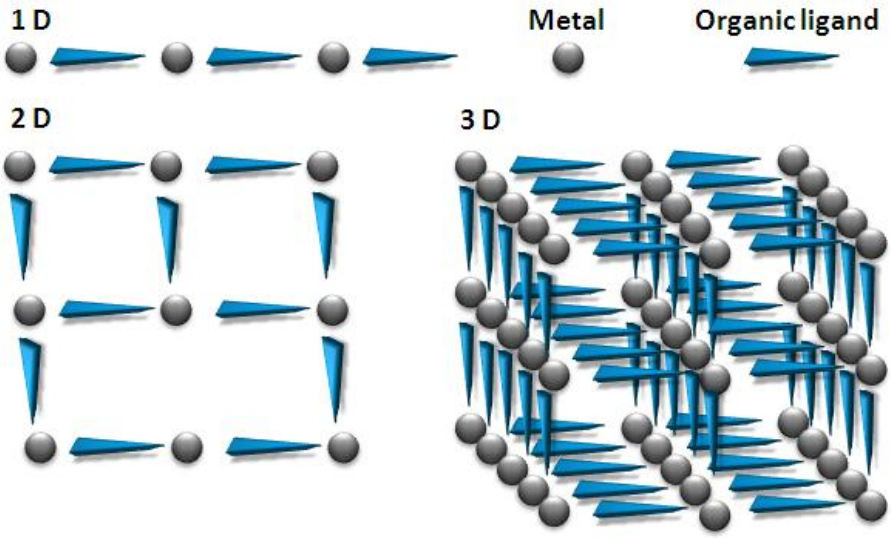

Figure 11 Metal−organic framework (MOF) structures **(Yuan et al., 2018)**

III.2. Covalent Organic Framework

Covalent Organic Frameworks (COFs) are a class of porous crystalline materials obtained by the self-assembly of molecular building blocks into enlarged structures with periodic skeletons and ordered pores **(Lohse et al; 2018)**. COFs are rigid frameworks with exceptional thermal stabilities, usually up to temperatures around 400°C, and low densities. They feature permanent porosity with specific surface areas surpassing those of well-known zeolites and porous silicates (**Côté et al; 2005)**.

III.2.1. Fabrication

The dynamic covalent chemistry principles helped to create and synthesize COFs through the use of reversible condensation reactions such as boronic acid trimerization, boronate ester formation, and Schiff-base reactions **(Thote et al., 2016)**. COF materials are formed by strong covalent linkages between C, Si, B, N, and O. Their ordered porous architectures can be two-dimensional (2D) or three dimensional (3D) **(Lohse et al; 2018).**

III.2.2. Application

Recently, COFs have been explored for many applications because of their properties, such as ordered channel structure and pores, large surface area, low density, and high stability, which attributes them several advantages which give them the primer character for other applications in the future **(Lohse et al; 2018)**. COFs have for example been tested for optoelectronics **(Medina et al., 2017; Mandal et al., 2017)**, gas storage **(Zhu et al., 2017)**, and catalysis **(Ding et al., 2011; Zhi et al., 2018)**.

COFs have also shown promise as adsorbents for organic dyes **(Fang et al., 2014; Ning et al., 2017)**, CO_2 **(Sharma et al., 2017)**, mercury **(Ding et al., 2016; Sun et al., 2017)**, radionuclides **(Sun et al., 2018)**, and lanthanides **(Yusranet al., 2017)**, as carriers for drug delivery, **(Fang et al., 2015; Vyas et al., 2016)**, and isolation of industrially relevant compounds **(Lohse et al., 2016)**. Recently, Salonen et al. demonstrated that COFs can be used to efficiently capture the marine toxin okadaic acid from seawater **(Salonen et al., 2017)**.

PART II

INVESTIGATION ON PHARMACEUTICAL PRODUCTS IN ALGERIA

I. Introduction

Since many years, Algerian authorities have focused on increasing the local production of pharmaceutical products in order to reduce import costs and to increase their control of the internal market in terms of regulation, provision of medicines and the development of the health sector and to eliminate dependence and income diversification and to achieve autarky and go to export. Furthermore, the speed of the population growth in Algeria (in 2018, the population of Algeria was 42 million based on the latest United Nations estimates **(Algeria Population; 2018)**) hampers the pharmaceutical sector development program and makes the market expand more and more over the time.

The Algerian pharmaceutical industry made phenomenal progress in this last decade (UNOP), in which the local production has experienced in recent years a very sustained growth from $ 473 million in 2008 to almost $ 2 billion in 2017. This performance is due to the strong support given by the Algerian public authorities to the industry through the 2008 decision on "the ban of the export of locally produced medicines". For the manager, this progress was made possible thanks to the considerable efforts made by investors in this field. Despite the efforts, the momentum of the national drug industry may be slowed with the accumulation of constraints in recent years. The financial crisis and the decline in the value of the dinar are impacting prices, and the lack of readjustment of margins weakens producers **(UNOP, 2017).**

The consumption of pharmaceutical products in general and drugs especially is the number one item of expenditure in the health sector. It represents a serious challenge for the health system and policy because of the growth of the drug market due to the large increase in the demand of care in general, and more particularly, through medicines that increase the life level and the improvement of the management of certain pathologies, and by epidemiological, demographic transition and health insurance supply.

With an average growth of over 10% per year, the Algerian pharmaceutical market is the second African market (3.45 billion $ in 2012) **(IMS Health, 2013)**. However, structurally, it remains an importer: local production units focus on generics and on pharmaceutical formulations that cover only part of the needs (mainly in the liquid, paste, and dryforms). Moreover, despite its investment in the local production, Algeria remains highly dependent on the global drug market. It imports, on average, 55 % of the drugs consumed **(Algerian (Ministry of Health, December 2015)**.

According to the statistics provided by Customs, the national drug market is estimated at $ 3 billion, in which $ 1.85 billion come from imports and the rest is a local production. The private sector provides about 84% of the pharmaceutical products, while 16% is insured by the public sector.

The present work aims at giving recent statistics with a general overview on the pharmaceutical product consumption in Algeria based on statistical data from various sectors in connection with importation and manufacture. A questionnaire was delivered for representatives of the four main categories of the healthcare cycle: manufacturers, suppliers, pharmacists, and consumers, and the results of the analysis of the questionnaire are presented hereafter.

II. Overview of the consumption of pharmaceuticals in Algeria

II.1. Exploitation of questionnaire responses sent to pharmacists, manufacturers, suppliers, and consumers

At the time when the survey was conducted in the period (2013–2016), 200 pharmacists, manufacturers, suppliers, and consumers were listed in the cities of Tlemcen, Tiaret, Algiers, Constantine, Batna, and Biskra. About 30% of the suppliers and manufacturers gave general informations orally. Of the 100 pharmacists that were contacted, 40% responded to the survey and further 40% were surveyed orally.

225 questionnaires were addressed to consumers from different regions in cities such as downtown, local, communities, rural. 40% of the investigated consumers are living downtown, 27% in local, 22 % in communities, and 11% in rural areas (Figure 12).

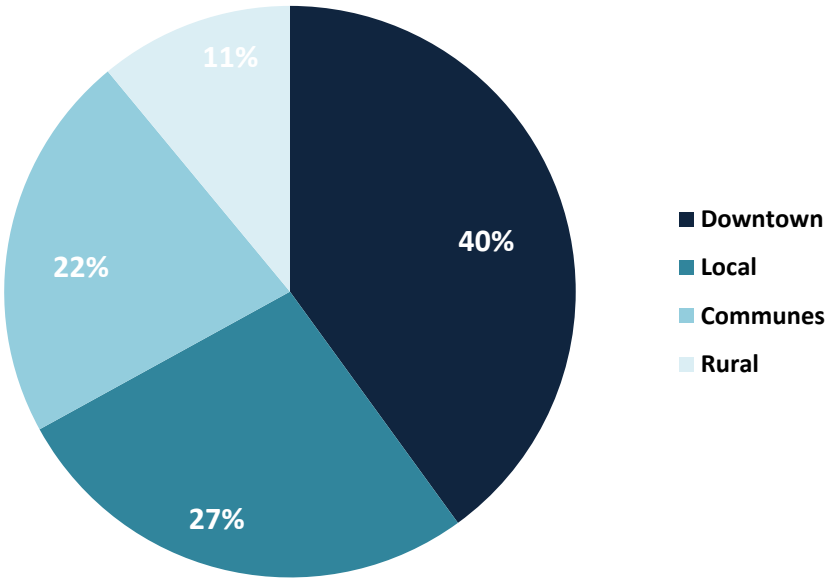

Figure 12 Distribution of the surveyed consumers based on their location

II.1.1 Pharmacists

Out of the 80 pharmacists that responded to the survey, 50% of their pharmacies are located in downtown, 25% are local pharmacies, and 15% in the surrounding communities of cities and 10% in rural areas (Figure 13).

The strong rise in the consumption of pharmaceutical products was confirmed by all pharmacists that responded to the survey, which is reflected by the fact that many drug classes, such as antibiotics, analgesics, and anti-inflammatory drugs, are found in water **(Soufan, 2011).**

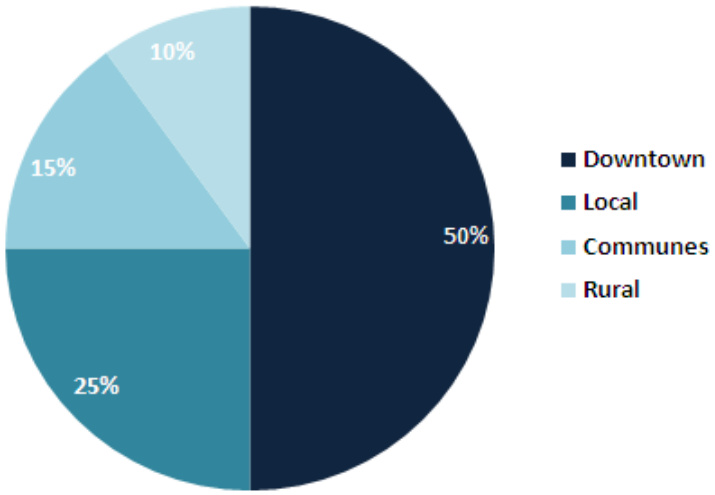

Figure 13 Distribution of the surveyed pharmacists based on their location.

II.1.2 Management of obsolete products

Pharmaceuticals are special products, with their manufacture, import, marketing, and dispensation governed by strict laws and regulations. When no longer used, i.e. obsolete, damaged, or removed from the market, they should not be discarded as simple garbage, because pharmaceutical waste is considered hazardous, and is governed by the Basel Convention **(UNFPA, 2013)**. Their destruction requires special precautions to protect the population as well as the environment **(AMM, 2011).**

Part of the survey was designated to study the fate of obsolete pharmaceuticals in pharmacies and at the consumer level.

1. At pharmacies

The clearing of obsolete pharmaceuticals by pharmacies, as extracted from the survey results, is represented by Figure 14. By analyzing the graph, one sees that 67% of expired pharmaceutical products are generally incinerated according to the answers provided by the pharmacists. This is confirmed by the national waste management policy of care establishment **(SNAPO; APS, February 2016)**, which has already been developed to target specific waste of the health sector including expired drugs. As part of the implementation of this policy and the process of improving the quality of care and research for better health of the population, the availability of a guide for the destruction of pharmaceutical products and drugs especially is essential. Indeed, pharmaceutical waste is hazardous and its destruction requires special precautions to minimize the risks for both the population and the environment.

According to the statistics of the Environment Ministry, no less than 12,000 tons of expired pharmaceutical products are stored in 500 sites scattered across 42 cities in Algeria **(SNAPO)**, reflecting the high rate of storage (Figure 14) found in the questionnaire results from the pharmacies. The pharmacists could choose more than one option, which explains that the percentage is higher than 100%.

A Large population is located in six Algerian cities, where they produce 95% of the pharmaceutical waste. About half of the stored hazardous waste or 1 million tons, are located in ten cities of the East, while a third is in the West and the rest in the central regions. The financial losses generated by the maintenance of this waste are estimated at $60 million, i.e. 0.15% of the gross domestic product.

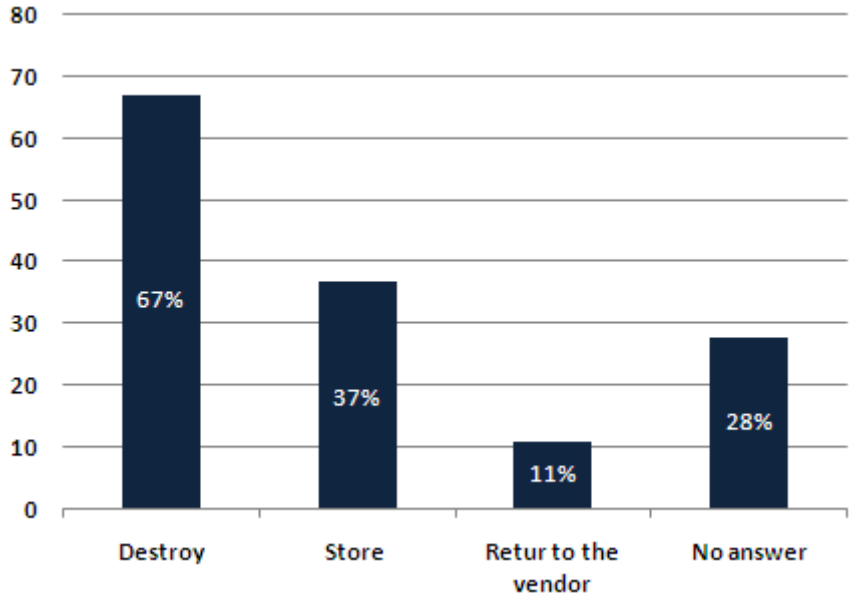

Figure 14 Clearing obsolete pharmaceuticals by pharmacies

The waste disposal requires the use of incinerators and modern technical means and must be conducted under conditions in compliance with environmental standards to protect the public health and natural resources **(SNAPO)**.

2. At the consumer level

The fate of the expired pharmaceutical products disposed of by consumers is presented in Figure 15, which shows that 64% are thrown away with the trash and 32% thrown in the toilets. A part of the pharmaceutical products are destroyed with 17%, stored with 12% or returned to the pharmacy with 8%. The large amount thrown out using inadequate procedures implies the presence of a threat to the environment and a risk to human health. The consumers could choose more than one option, which explains that the percentage is higher than 100%.

The potential risks associated with the presence of low concentrations of pharmaceutical compounds in the environment are largely unknown and are currently under debate **(Manal Soufan, 2011)**. However, several studies have revealed cases of feminization of certain fishes in freshwater and marine environments (eg. Sumpter and Johnson 2005 cited by **(Schlenk, 2008)**. These endocrine disruption phenomena could stem from the exposure of some fishes to synthetic female hormones or other industrial or agricultural compounds in the environment **(Schlenk, 2008)**.

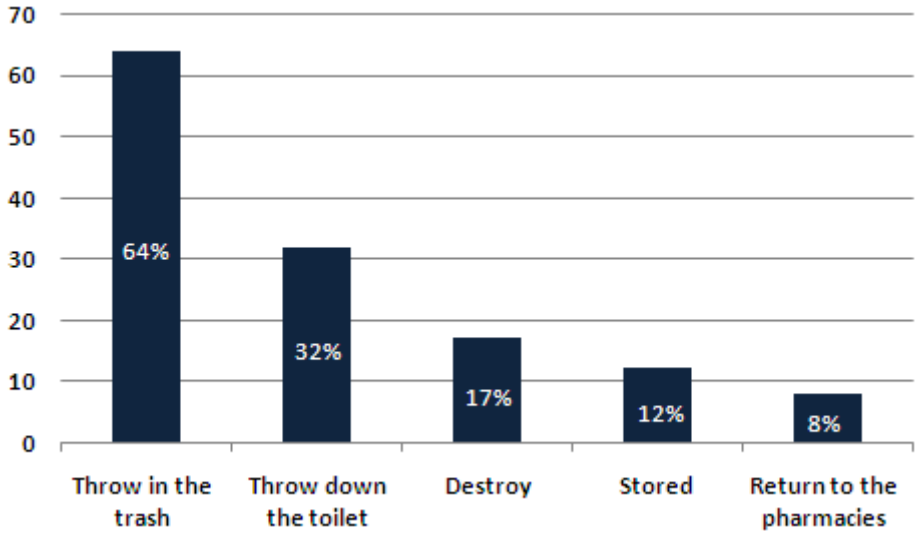

Figure 15 Clearing unnecessary pharmaceuticals by consumers

As per Health Canada, when pharmaceuticals are discarded in the sink or latrine, chemical compounds can end up in the water supply or the ground **(Health Canada, 2016)**. The presence of these drug pollutants in the environment is a matter of national and international importance. In spite of the very low concentrations of these substances in the soil, they could be sufficient to harm the environment and human health. Potential adverse effects of cumulative exposure over the long term, in trace of mixtures amounts of pharmaceutical products on vulnerable populations such as pregnant women, infants and children, are of particular concern.

II.1.3 The most consumed pharmaceutical products in Algeria

Pharmaceutical products widely consumed in Algeria can be divided into 11 groups according to the percentage of pharmaceuticals largely sold by pharmacies (Table 4). Paracetamol (acetaminophen) is on the top of the list as the drug the most sold in Algeria with a rate of sale of 34%, followed by ibuprofen (17%), amoxicillin (14%) and each of diclofenac, clofenal, and metformin with 9% (Table 4). From import bill digits ($2.23 billion in 2012,

$2.34 billion in 2013, $1.85 billion in 2014 and $1.96 billion in 2015) of pharmaceutical products in Algeria, it can be deduced that significant quantities of these products are consumed in the last years.

Table 4 Widely consumed drugs in Algeria.

Group	Consumption rate (%)	Drugs
1	34	Paracetamol and its derivatives
2	17	Ibuprofen
3	14	Amoxicillin
4	9	Diclofenac, Clofenal, Metformin
5	7	Clamoxyl
6	6	Rhumafed , Voltaren, Omeprazole, Antag
7	5	Humex , Gripex
8	4	Amlor, Aspegic, Syntole, Smekta
9	3	Oxaciline, Augmentin, ranitidine, Aspirin, Vitamine C
10	2	Betadine, Denoral, Celebrex, Alvity, Biotine, Duphalac, Marvelon, Methionine, Cityne, Solumedrole, Glucophage, Malacur
11	1	Magnesium, Alvityl, Ranitex, Cutacnyl, Votrex, Nasacort, Biocalyptol, Antadys, Artiz, Pénicilline, Ritadole, Corticoid, Depredates, Fervex, Amoclane, Pepsane, Phosphalugel, Kefentech, Modestamine, Maxidrole, Desomedine, Cephadar

II.2. Import of pharmaceutical products in Algeria

The national drug market is estimated to be $3 billion, including $1.85 billion of import, while the rest came from the local production, with 84% returning to the private sector and 16% to the public.

Currently, the local production covers only 60% of the national market, but should reach, if the goals are achieved, 70% in 2019. If the investment projects in the field of the pharmaceutical industry materialize, they will put Algeria in position of strength, not only to cover the national market but mainly for export, according to the National Union of Pharmaceutical Operators (UNOP). The pharmaceutical industry has experienced in the recent years an exceptional increase in investments since 151 new production units are currently in the construction phase in addition to the already operational 50.

II.2.1. Purchase of pharmaceutical products per year

The results in Table 5 show the variation of the overall rate of purchases (ORP) and are presented by Figure 16 and 17 during the period 2011–2015, where we can see an augmentation of ORP from $1.96 billion in 2011 to $2.23 billion in 2012. This is followed by a little stabilization in the period 2012–2013 and a decline to $1.85 billion in 2014, followed also by a little stabilization in the period 2014–2015. ORP is predicted to reach $5.7 billion in

2018. The same explanation concerns the variation of imported quantities (IQ). The high rest quantity was purchased in 2012 with 35540 tons and the lowest quantity in 2011 with 24468 tons (UNOP, SNAPO).

Table 5 Procurement of drugs and pharmaceuticals in Algeria (2011–2015).

Algerian purchases of pharmaceuticals						
Period	2011	2012	2013	2014	2015	Reach2018
ORP (Bn USD)	1,96	2,23	2,34	1,85	1,96	5,7
Increase / Decrease ORP %	16,86	13,6	1,96	25	-22	unavailable
(IQ) (tons)	24468	35540	33389	25386	27000	unavailable
Increase /Decrease on IQ %	2.2	45	-6,74	-4,1	15,32	unavailable

ORP is the overall rate of purchases and IQ is the imported quantities

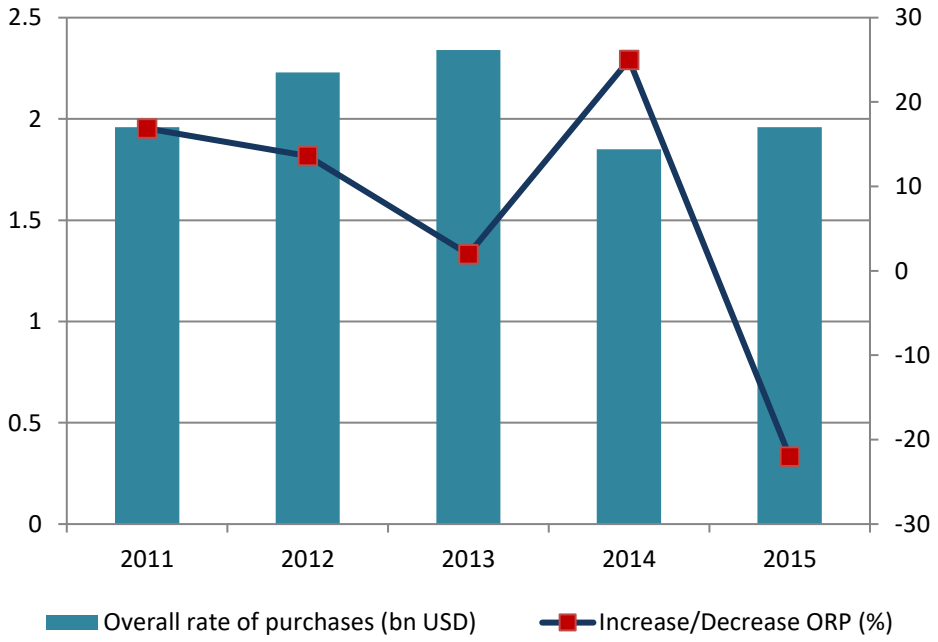

Figure 16 Overall rates of purchases in bn USD of pharmaceutical products between 2011 and 2015 in Algeria.

The decline in the value of drug imports in some periods was mainly due to better price negotiations with foreign laboratories **(Maghrebemergent, 2016)**. Para-pharmaceutical products, which represent only 3% of the total imports, also contributed to the decline of the import bill **(APS, December 2013)**. According to the Ministry of Health, Population and

Hospital Reform, a new methodology for fixing prices was adopted, based on the comparison of international prices, to obtain the best deals for Algeria **(APS, 2015)**.

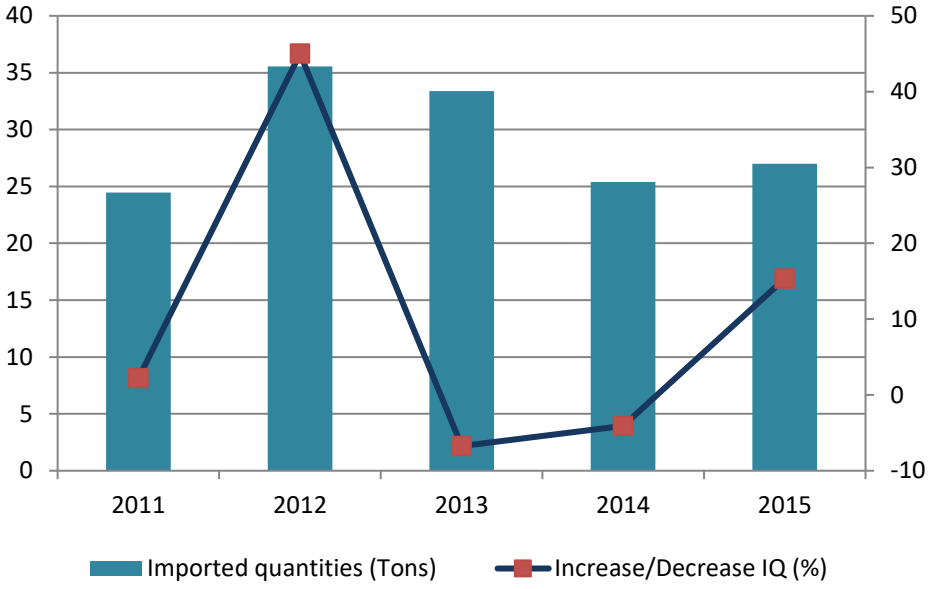

Figure 17 Quantities of pharmaceutical products imported in tons between 2011 and 2015 in Algeria **(APS, 2015)**.

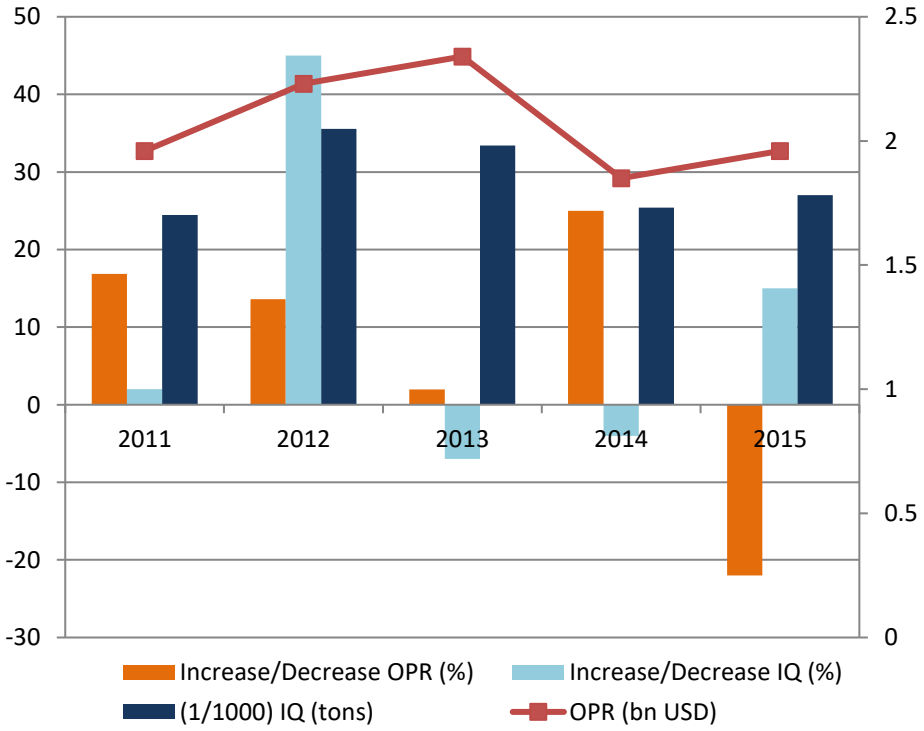

Figure 18 Overall rates of purchases in billion USD and quantities of pharmaceutical products imported in tons during the period 2011–2015 in Algeria **(APS, 2015)**.

The new purchasing methodology of Algeria has resulted in a decrease of purchasing of pharmaceuticals, and therefore, the Ministry ensures that the prices in Algeria remain the

cheapest in the region of North Africa **(APS, 2015)**. In addition, the new managerial approach in the Algerian pharmaceutical industry and state spending to develop this sector by encouraging innovation and exploitation, has contributed to the reduction of the drug import bill. This has been very noticeable since 2008 and a decline is expected to continue until the end of 2020.

Since 2008, Algeria has experienced frequent drug shortages in hospitals and pharmacies. These shortages are due in part to the government's desire to reduce the bill for drug imports but without substituting imported drugs by locally manufactured products. In 2010, the bill of Algerian drug imports fell by nearly 5%, the most important since the decision by the government in January 2009 to ban the importation of drugs that are also locally manufactured, because there are drugs imported even they are manufactured locally. To be exact, the import bill of medicines fell to $1.66 billion in 2010 from $1.74 billion in 2009 and $1.86 billion in 2008 **(CNIS, APS, 2011)**.

II.2.2. Algerian purchases of pharmaceuticals and medicinal products for human and veterinary use in Algeria in the period 2010–2015

Algeria has reduced import expenditures of pharmaceuticals by 39% during the first four months of 2015 according to figures published by the Algerian Customs **(Conseil de la Concurrence, 2019)**. This decline has concerned medicinal products for human use, pharmaceuticals, consumables, and medicinal products for veterinary use (Table 6 and Figure 19).

The bill for medicinal products for human use, which represented almost 94% of the overall import volume of pharmaceutical products, amounted to $440.34 million for a quantity of 6707 tons, compared to $742.52 million during the first four months of 2014 to 8057 tons **(Conseil de la Concurrence, 2019)**.The import bill of Algeria in pharmaceutical products totaled nearly $2.6 billion in 2014, compared to $2.3 billion in 2013. According to a study by the American Statistics Institute on the drug market in the world, Algerian drug consumption is expected to reach $5.7 billion by 2018. This expected increase is due to several factors including population growth, increasing life expectancy, and changes in the epidemiological situation of the Algerian society **(Djelouat et al., 2018; APS, décembre 2013)**.

Table 6 Purchases of pharmaceuticals and medicinal products for human and veterinary use in Algeria in the period 2010–2015 **(Douane, CNIS, UNOP)**.

IMPORTATION						
Usage	**Period**	**Import Percentage (%)**	**Overall rate of purchases**	**Increase / Decrease ORP %**	**Imported quantities (tons)**	**Increase / Decrease IQ %**
Human Medicines	2010	96	$1,61 billion	-5,5	-	-
	2011	-	$1,87 billion	16,55	22608	-
	2012	-	$2,13 billion	13.15	33362	47,57
	2013	-	$2,19billion	2,38	31539	-6,2
	2014	93,17	$2,41 billion	9,96	30780	- 2,4
	2015	95	$1,65 billion	-24,2	21962,54	-16,35
Pharmaceutical products	2010	2,63	$44,62 million	24,37	-	-
	2011	-	$57,03 million	27,8	1349	-
	2012	-	$73,91 million	26	1616	-
	2013	-	$63,56 million	- 14,5	1246	- 23
	2014	-	$72,53 million	13,95	1406	-
	2015	-	$59,75 million	-2,89	1462,63	20
Veterinary medicines	2010	1,16	$19,31 million	23,8	-	-
	2011	-	$21,59 million	11,86	510,9	-
	2012	-	$25,72 million	17.32	560,9	-
	2013	-	$29,75 million	15,57	603	-
	2014	-	$35,85 million	19,68	564	-
	2015	-	$27,22 million	-13	635,72	31

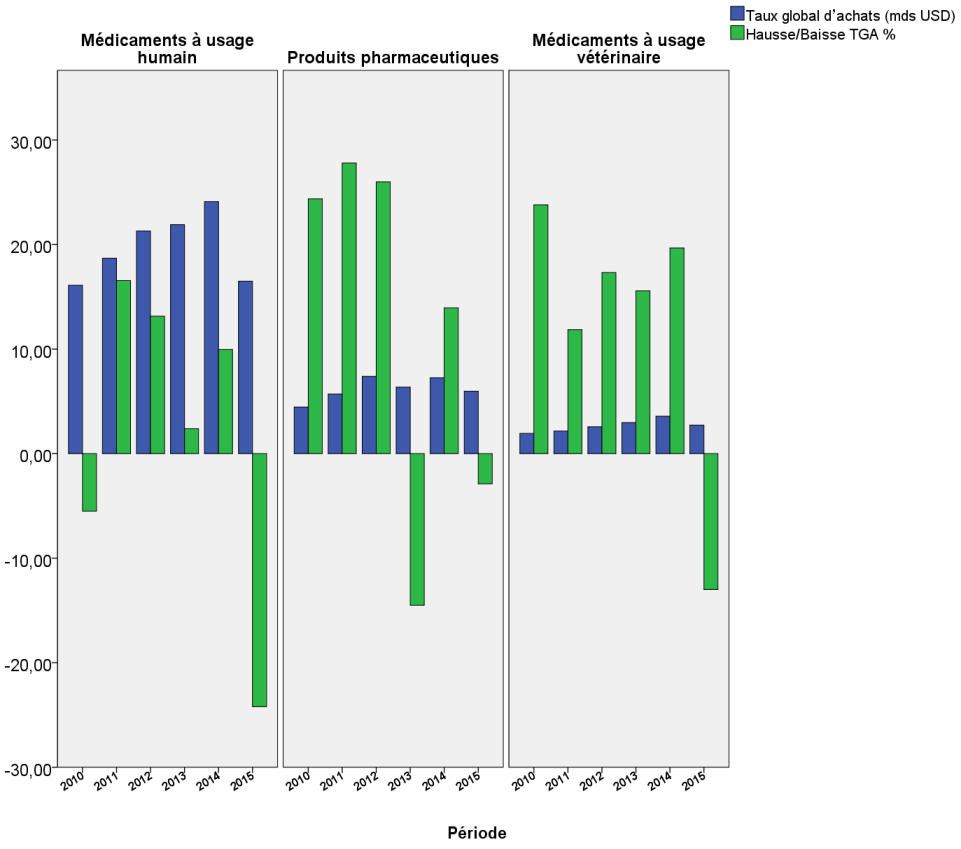

Figure 19 Purchases of pharmaceuticals, medicinal products for human and veterinary use in Algeria in the period 2010–2015 **(Douane, CNIS, UNOP)**.

Algeria's importation of pharmaceutical products reached $1.6 billion during the first ten months of 2013, compared to $1.8 billion in the same period of 2012, down with 11%, as reported by the Algerian Customs **(CNIS, Janvier 2015)**. The quantities of imported pharmaceuticals observed the same downward trend, from 29,096 tons during the first ten months of 2012 to 26,196 tons in the same period in 2013, a decrease of 13%, according to the National Centre for Informatics and Statistics (NCIS) of Customs **(APS, décembre 2013)**.

In 2011, the percentage of pharmaceutical product import covered a large part of the national consumption. The rest was local production, both private as well as public (Table 7).

The following table shows these figures very clearly **(Douane, MSPRH cited by UNOP)**:

Table 7 Import and local production of pharmaceuticals in Algeria in 2011.

2011	bn USD	Percentage %
Import value (source customs)	1.85	64
Local production value (source MSPRH)	1.05	36
Market Size	2.9	100

The following graph (Figure 20) illustrates very clearly the difference between importation and local production of pharmaceuticals in 2011 as well as the market size.

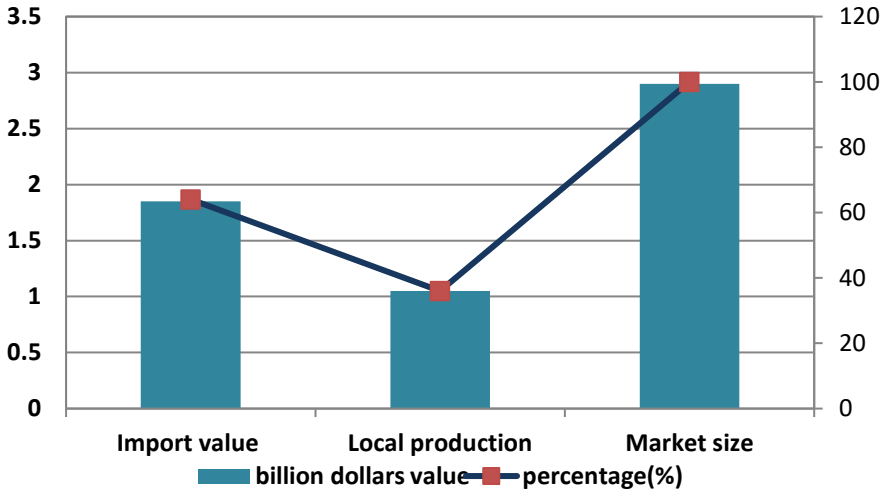

Figure 20 Import and local production of pharmaceuticals in 2011.

The rise of the invoice for medicines in 2011 is the result of significant quantities imported between June and October by the 60 operators present on the national market **(CNIS, UNOP, 2012)**.

Algeria has also banned the import of 120 locally produced drugs. This list can be extended even to other products to encourage local production and influence laboratories to invest more in this market.

Data of the national market of pharmaceuticals, such as the national output and its division between the public and the private sector, is represented in Table 8. This data show the values of $1.05 billion for the Algerian national production, which represents 36% of the total market, where the public sector participates by $0.17 billion about 16% from the local production and 6% from the total market. The private sector contributes by $0.88 billion with about 84% from the local production and 30% from the total market **(UNOP, 2013)** that can be explained by the state encouragement towards the private sector to exploit and develop the pharmaceutical products field.

Table 8 Size of the Algerian pharmaceutical market in 2011**(UNOP, 2013)**.

(Source MSPRH)	Value bn (USD)	% National Prod	% Total market
National Production	1,05	100	36
Public sector	0,17	16	6
Private sector	0,88	84	30

The objective of Algeria is to produce locally 70% of its pharmaceutical needs with the contribution of foreign laboratories in the local production by their units in Algeria by the end of 2019. In order to achieve this objective, the state has taken important steps to establish an efficient pharmaceutical industry to ensure the meeting the growing needs of the population, in particular by encouraging investment and industrial partnerships **(CNIS, 2013)**. Concerning invention in the pharmaceutical field, which can give a push to the local fabrication of new products also destined for export, Algeria has an increasing rate between the period 1995–2005 with a PIPP (index of intellectual property rights in pharmaceutical inventions) growing to 0.68 in 2005 from 0.57 in 1995 as shown in Table 9 .

Table 9 Index of intellectual property rights in pharmaceutical inventions in 1995 and 2005 (**Liu et al, 2015)**.

	1995	2005
Algeria	0.57	0.68
USA	4.48	4.51
Nigeria	0.68	2.46
Egypt	0.39	1.31
Spain	2.58	3.18
France	2.38	2.92
Germany	2.58	3.18
Finland	1.72	3.18
Portugal	1.87	2.92
China	1.69	3.00
Japan	3.18	3.18

II.2.3. Global pharmaceutical market

According to the annual World Preview report of Evaluate Pharma, a market research company, the global growth rate of the pharma industry is rising at a quicker pace over the period 2016–2022. It will arrive to 6.3% in 2022, and the overall market will reach $1.12 trillion in 2022 (Figure 21).

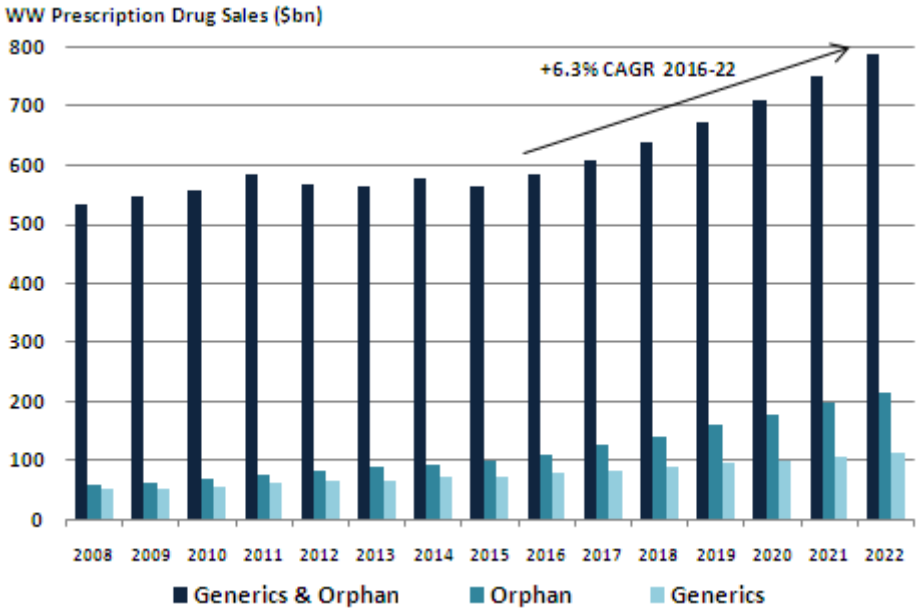

Figure 21 Worldwide total prescription drug sales (2008–2022) (**EvaluatePharma, 2016)**

CAGR (The Compound Annual Growth Rate) is the mean annual growth rate of an investment over a specified period of time longer than one year.

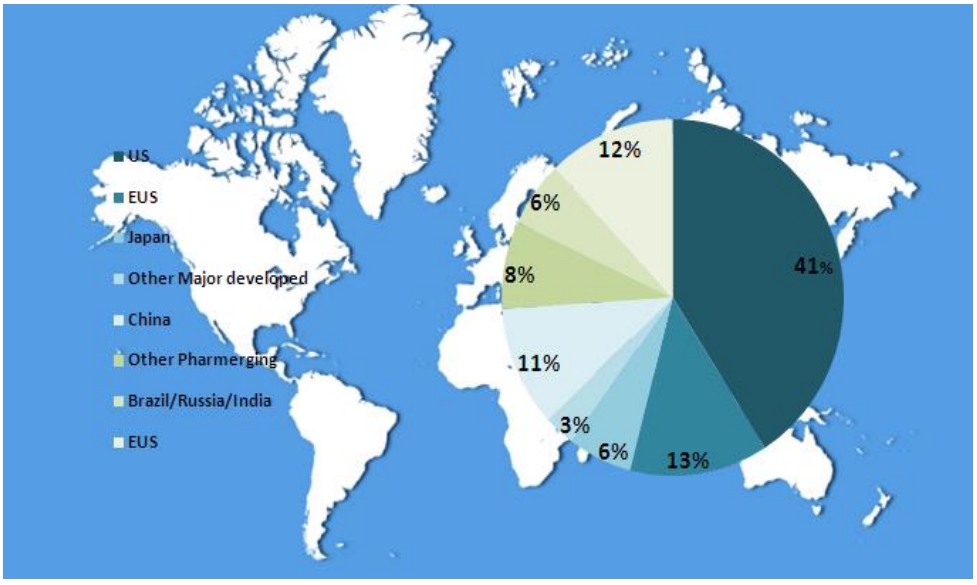

Figure 22 Medicine spending in 2020 USD by geography. The image is taken from: **IMS Market Prognosis, 2015)**.

In 2014, the total pharmaceutical revenues worldwide had exceeded $1 trillion for the first time **(Statista, 2018)**. Figure 22 shows the forecasted medicine spending worldwide in 2020 by region. The U.S. and the European Union are predicted to be responsible for 54% of spending. Brazil, Russia, and India together are predicted to amount to 6%, Japan 6%, and China 11% **(Statista, 2018)**.

II.2.4. World pharmaceutical market by region from 2009 to 2014

The statistics show the projected growth rates in the world pharmaceutical market by regions from 2009 to 2014, (Figure 23), highlighting the high percentage for Europe (non-EU) with 18%, followed by Japan with 14% and North America by 13%; the African pharmaceutical market is expected to grow during this period by 8% and the EU by 3% **(Statista, 2018)**. Commonwealth of Independent States (CIS): Azerbaijan, Armenia, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, Turkmenistan, Uzbekistan, and Ukraine.

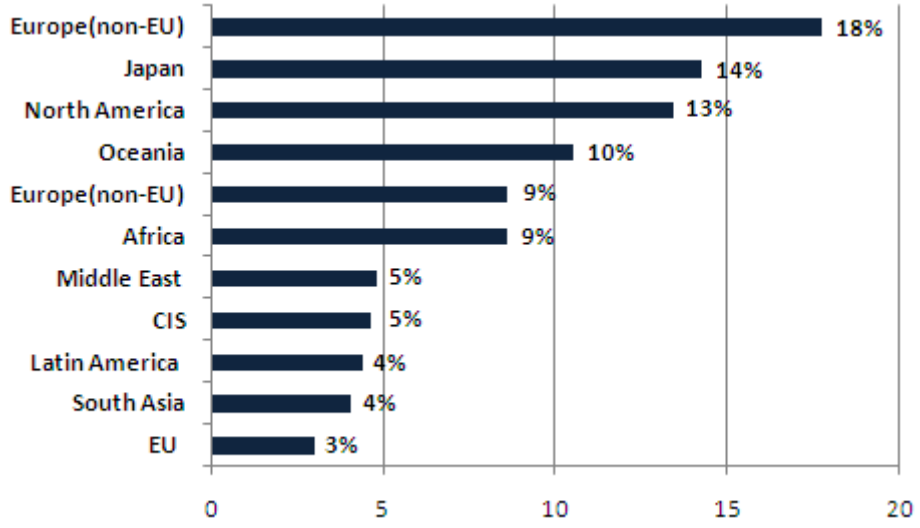

Figure 23 Projected growth of the world pharmaceutical market by region from 2009 to 2014. Source **(Statista, 2018)**.

II.2.5. The largest markets for pharmaceuticals

In 2022, the global drug market will surpass the threshold of $1 trillion in sales, up 6% from 2016. The US market is predicted to remain the most important, far ahead of the main European markets (Germany, France, Italy, United Kingdom, and Spain) **(Statista, 2018)**.

USA: The pharmaceutical market of USA is the world's most important national one. It holds alone over 45% of the global pharmaceutical market. The projected drug expenditure in 2020 is between $560–590 billion and the pharmaceutical sales will arrive to $453 billion. The

annual amount spent per person on prescription drugs in the U.S. averages $1162 in 2017 **(Statista, 2018; IMS, 2018)**.

China is the second largest emerging pharmaceutical market in the world, predicted to increase from $108 billion in 2015 to $167 billion by 2020, with an annual growth rate of 9%. Total public and private healthcare expenditure reached $640 billion in 2015 and are predicted to nearly double to $1.1 trillion by 2020 **(ITA, 2016)**.

Japan: The Japanese pharmaceutical market is the world's third-largest drug market after the U.S. and China, with a share of approximately 10% of the world sales. The projected drug expenditure in 2020 is between $79–89 billion and pharmaceutical sales will arrive to $149 billion according to Business Monitor International.

Germany: The German pharmaceutical market is the largest in Europe; its value augmented from $48.6 billion in 2009 to $67.9 billion in 2016. The German pharmaceutical market is predicted to reach an estimated $65 billion by 2020 **(GlobalData, 2017)**.

III. Medicinal product import rationalization

In the context of medicinal product import rationalization, a ministerial decree published in December 2015 fixed the list of pharmaceuticals for human use and medical devices manufactured in Algeria, which are not allowed to be imported. It comprises approximately 357 drug compounds as tablets, creams and dermal ointments, injectable solutions, suppositories, ophthalmic ointments, and syrup. Also, a list of 11 medical devices manufactured locally was included, the import of which is also prohibited, such as syringes, compresses and gauze bands, and soda for dialysis **(APS, avril 2016)**.

IV. Algerian policy to reduce medicine imports

Algeria produced 25 % of pharmaceutical products in 2008 and reached 70% in 2017, and it aims to produce locally 100% of the needed pharmaceutical products with the collaboration of foreign laboratories by the end of 2020 in order to reduce imports of drugs and hence become a platform of generic products. According to a report on pharmaceuticals of the Algerian Industrial Ministry, the drug market growth rate amounts annually to 10%, and in 2012, the bill of Algerian pharmaceutical imports had increased to $2.23 billion, up 14% from the previous year **(APS, December 2013)**. The investment will allow Algeria to build a national drug industry and reduce its heavy dependence on foreign pharmaceutical companies, which makes the state financially uncomfortable especially in the situation of falling oil

prices. However, the rapid decline in gross oil export revenues is not expected to affect the drug supply **(Djelouat et al., 2018)**.

V. Drug consumption in Algeria

V.1. Leading causes of death in Algeria

In Algeria, the life expectancy at birth is currently 75.7 years. This was a large improvement compared to 52.6 years in the 1970s. As for mortality, the rate has not varied significantly (about 4.5‰) since the beginning of the 70s.

The leading causes of death are shown in Figure 24: cardiovascular disease is the first with a rate of 26%, followed by perinatal conditions (13%), cancer (10%), and trauma (9%). Another factor study **(Gaudry; 2013)** during the period 1970–2007 showed an important evolution in the rate of road accidents, which involves a heavy use of drugs for the treatment of wounded people.

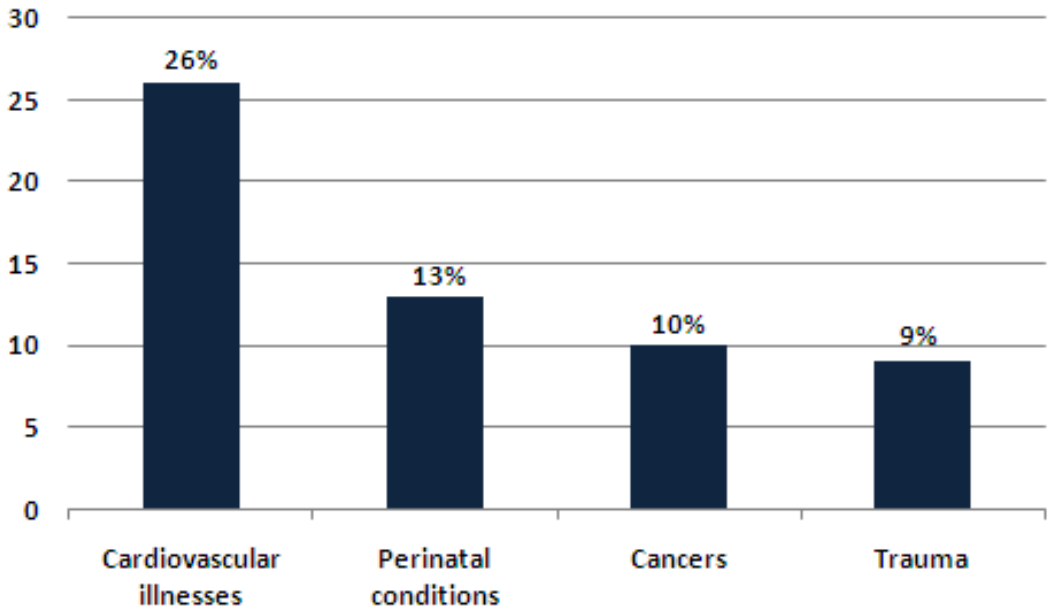

Figure 24 The leading causes of death in Algeria **(Gaudry; 2013)**.

V.2. The leading causes of death in the world

The top ten causes of death account for 51% of all deaths in the world according to statistics of the World Health Organization (WHO) in 2012. The developing world is more prone to certain causes of death because of the lack of education, medical access, and financial resources. Below, presented in the Figure 25, the ten principal causes of death worldwide **(Worldatlas, 2018)**.

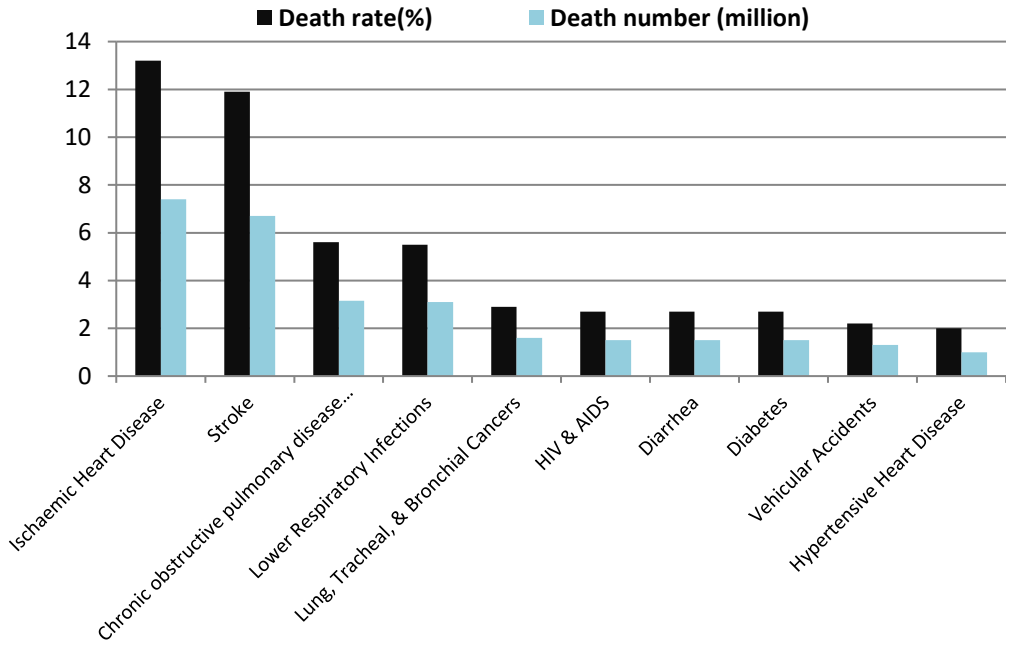

Figure 25 Rate and principal causes of death in the world **(Worldatlas, 2018, WHO, 2018)**.

Figure 25 shows that the leading cause of death in the world is ischemic heart disease with 13% and a death number of 7.4 million, followed by stroke with 12% and 6.7 million; the chronic obstructive pulmonary disease and lower respiratory infection came in the third place with 6% and death number of 3 million; lung, tracheal and bronchial cancers, HIV/AIDS, diarrhea and diabetes have almost the same death rate of 3% corresponding to 1.5 million of deaths, and finally vehicular accidents and hypertensive heart diseases with 2% amount to 1 million of deaths.

V.3. Medical and therapeutic needs

Medical and therapeutic needs are moving towards novel treatments and more expensive, innovative products. However, often the human population in some regions in the world heads toward traditional treatments such as the survey ethnopharmacological plants used for the treatment of diabetes in the south of Algeria **(Telli et al., 2016)**. In 2008, 18% of the consumption of drugs is linked to cardiac disorders, 17% to metabolic and digestive disorders, 15% to anti-infective drugs, and 12% to the central nervous system (Figure 26).

The import bill of drugs increases every year due to enlargement of health coverage and the acquisition of new pharmaceuticals according to the Ministry of Health, Population and Hospital Reform. This rise was also explained by the desire of the state to ensure the availability of different types of cancer drugs, which are expensive, whereas the previous years had been marked through recurring breaks in stock **(APS, January 2015)**.

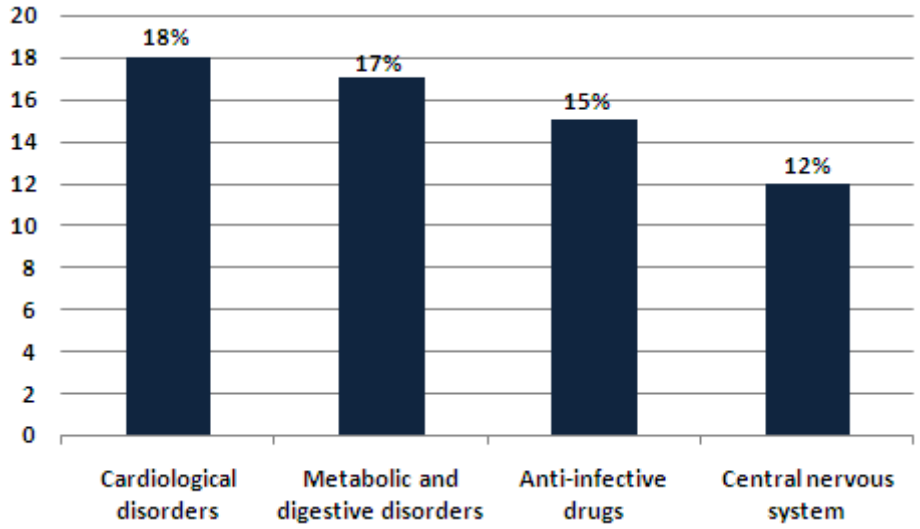

Figure 26 Drug consumption based on the type of disease in 2008 in Algeria **(Semmoud ; 2011)**.

V.4. Consumption per inhabitant

The average consumption per inhabitant of both the drugs purchased and those distributed free of charge between 1990 and 2018 is presented in Figure 27. It was valued at $14 in 1992 and rise to reach $21.4 per inhabitant in 1995. This average reached a high value of $63 in 2000 and decreased again to $13 in 2001. It has been increasing during the period 2001–2008 to reach $59 in 2008. After 2008 the average consumption decreased to $45 in 2009 and started to augment and reached its high value of $100 per inhabitant in 2014 against a global standard of $127 per year per inhabitant **(UNOP)**, and fell back again to $80 in 2017, then to $75 in 2018.

Algeria spends much less than other countries: for example, consumption in Portugal is $413 per year and $668 per year in France. According to UNOP and based on the forecast of the IMS (International Medical Studies), Algeria's pharmaceutical needs will be $5.7 billion in 2018. However, UNOP raises the concern if Algeria will have the financial means to buy pharmaceuticals in the future, due to the falling oil prices (Table 10).

Compared to the total health expenditure, the proportion of expenditures for patented drugs was about 30% in 2006 against 20% in 1995 **(Semmoud, 2001)**. In addition, the average amount per prescription was estimated in 2004 at 8.79US$/year for a total of 45.8 million prescriptions **(list.healthnet.org)**. The pharmaceutical expenditure in Algeria expressed as a share of GDP are compared with selected countries during the period 2015–2016 is presented in Figure 328. The Algerian pharmaceutical expenditure per capita compared with some countries in 2017 is presented in Figure 29.

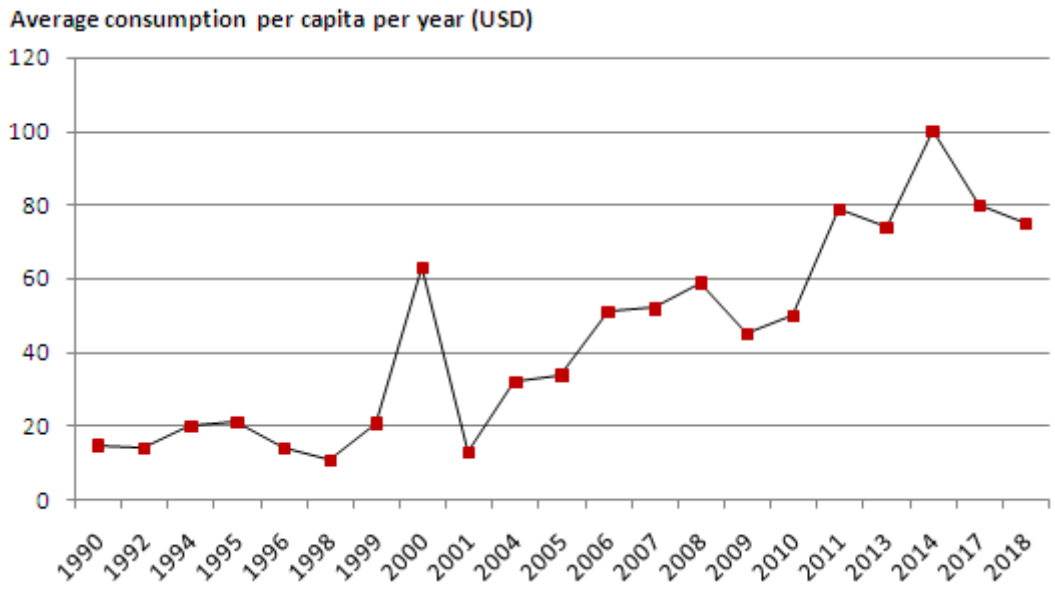

Figure 27 Variation of cost of drugs consumption per capita between 1990 and 2018 in Algeria (**Ziani et al, 2016).**

Table 10 Pharmaceutical expenditure as % of GDP of selected countries ordered by inhabitant (2015–2017). *2015.

Country	Pharmaceutical expenditure as % of GDP2016	Spending per capita (USD)2017	Population(Millions) 2018
USA	2	1162	327
Japan	1.9	803	127
Germany	1.3	766	82
France	1.4	668	65
Italy	1.3	605	59
South Korea	1.3*	320	51
Spain	1.5	572	46
Algeria	2.16	80	42
Canada	1.7*	838	37
Venezuela	-	200	32
Netherland	0.9*	432	17
Belgium	1.2	679	11.5
Greece	1.8	721	11
Hungary	2.2*	559	10
Sweden	1*	519	10
Portugal	1.8	413	10
Austria	1.2*	633	8.7
Switzerland	1.2*	1056	8.5
Lebanon	-	374	6
Finland	1.2*	459	5.5
Ireland	1.1	684	5

Source: **population-2018** (www.Worldometers.info); (Pharmaceutical spending per capita, statista.com, (**Wee, 2015; Akkouche, 2016)**.

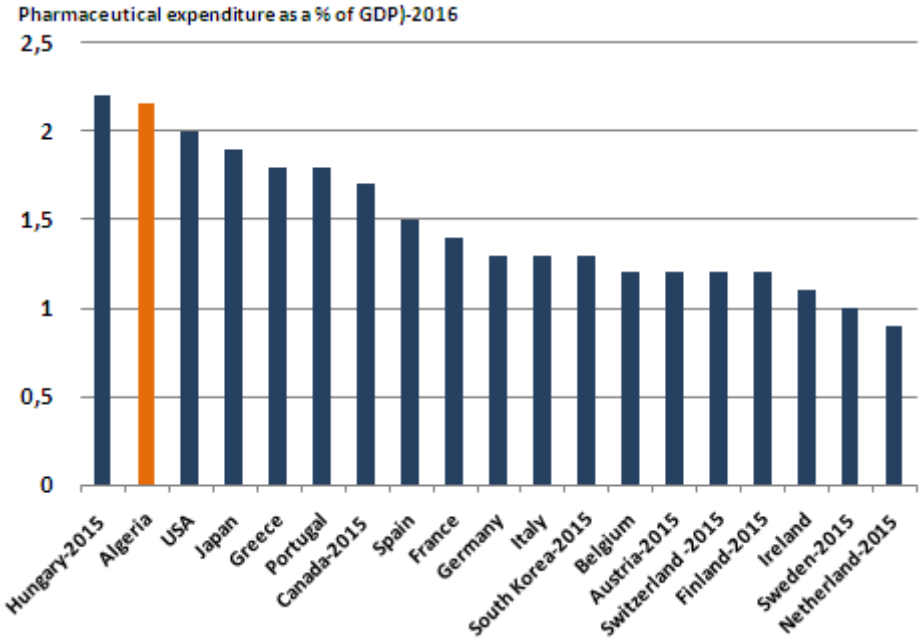

Figure 28 Pharmaceutical expenditure as a share of GDP in Algeria compared with selected countries in 2015–2016.

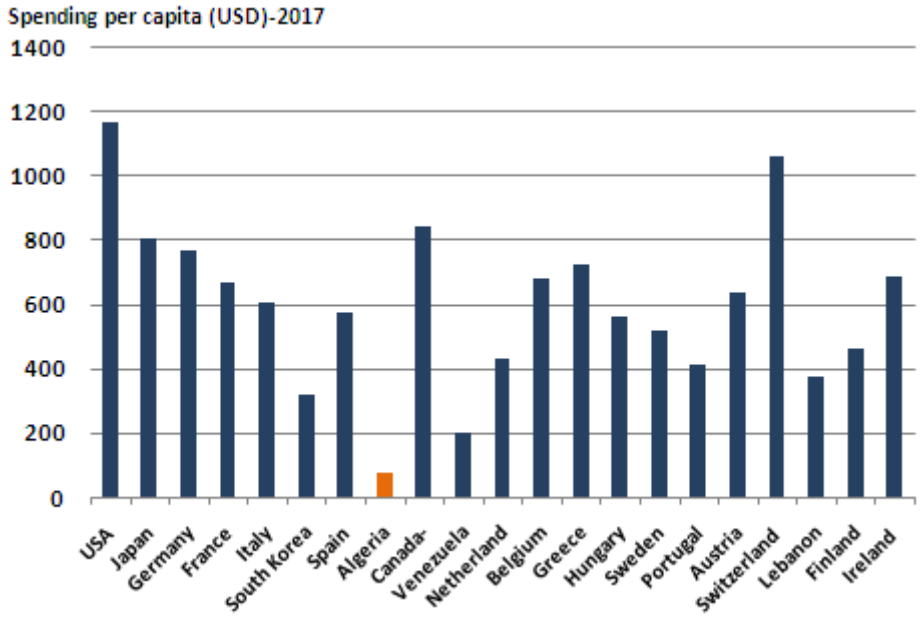

Figure 29 Algerian pharmaceutical expenditure per capita compared with some countries in 2017.

VI. Algerian pharmaceutical industry

The activity of pharmaceutical industry is due to the pharmaceutical and biotechnology companies. This industry includes research activities, manufacturing and marketing of drugs for human or veterinary medicine and it remains an important sector of economy in the world.

Nevertheless, this industry depends very much on patenting of medicines, and it needs national measures of price regulation. Thus, in emerging and developing countries such as Algeria, the pharmaceutical industry could play a major role on the road towards a new economic model **(DGIEEP, 2011)**. The Algerian national pharmaceutical industry has experienced in the recent years a remarkable explosion in investment according to UNOP **(UNOP, February 2015)**.

The pharmaceutical production in Algeria needs a serious and consistent upgrade of a regulatory framework to follow and meet the needs of existing producers and to meet the newcomers' expectations. To reach this goal, officials have focused on two major aspects, specifying that the first is to provide specialized staff and technicians to the pharmaceutical industry. The second is to provide medicines to the market **(UNOP, February 2015)**.

VII. Treatment and disposal

Obsolete pharmaceuticals are typically disposed of in garbage cans, which will eventually end up in landfills, and most of the consumed pharmaceutical products that are released into domestic wastewater end up there via urine or feces, directly threatening the aquatic environment **(Zuccato et al., 2009; Pal et al., 2013)**. So, it is necessary that all pharmaceuticals are safely disposed of, especially controlled drugs. The most usually used methods, throwing drugs into the sink, toilet, garbage, or landfill and inappropriate elimination, have a negative impact on the environment and public safety **(Kadam et al., 2016; Kusturica et al., 2016)**. Incineration may be the ecologically safe method of pharmaceuticals disposal (**Kusturica et al., 2016)**, and it is considered as a solution to overcome this problem in Algeria. The drugs of which the expiry date has passed are disposed of by incineration in some cities, especially expired drugs that have been stored for more than 15 years in pharmacies around the country. Local offices of the Algerian National Syndicate of Pharmacists (SNAPO) ensure to generalize this operation in all cities **(APS, February 2016[1])**.

VIII. Warning against drugs sold informally

The state of Algeria has imposed a lot of measures to reduce the amount of drug sold informally. However, illegally imported pharmaceutical products are sold without label by some pharmacies. Despite the regulation providing severe penalties to perpetrators of such offenses, pharmaceutical products are imported illegally by networks and are distributed in

pharmacies across the country. This level of fraudulent practices threatens the public health **(APS, February 2016)**.

The practices of sale and purchase of pharmaceuticals from outside the formal framework, which the state is fighting against, is considered one of the hazards for the health of the citizens. Therefore, to defeat the illegal drug market in Algeria, the national drug sector has accompanied the evolution of the care system by gradually adapting to changing levels of the national request for pharmaceuticals (**Zerhouni et al., 2015)**.

IX. Concerns about high pharmaceutical consumption

The presence of pharmaceutical compounds in effluents and in the aquatic environment has been detected in the world since the 80s, which has helped to highlight the issue of their presence in our environment **(Garric and Al., 2005)**. The interest in the behavior and impact of these molecules on the environment and human health has thus increased **(Christensen, 1998; Schulman et al., 2002)**.

Currently, Algeria is facing a transition towards environmental protection against these types of substances as it is now proven that pharmaceutical molecules belonging to varied therapeutic classes are present in terrestrial and aquatic environments worldwide, along with other chemicals such as pesticides, plasticizers, and flame retardants **(Daughton and Ternes, 1999; Halling-Sorensen et al., 1998; Ternes, 1998; Buser et al., 1998; Stumpf et al., 1999;. Zuccato et al, 2000)** cited by **(Garric and al, 2005)**.

PART III

EXPERIMENTAL PART

CHAPTER I

PRODUCTS, MATERIAL, METHODS AND CARACTERISATIONS

I. Products, material

I.1. Products

- COFs:TpBD-$(CF_3)_2$, TpBD-Me_2
- Powder Activated Carbon PAC F400
- Methanol, HPLCgrade, 99.9 % (Sigma–Aldrich)
- Acetone, HPLCgrade, 99.9 % (Sigma–Aldrich)
- Ultrapure water (18.2 mΩ cm^{-1} at 25 °C)
- Pure standard Phenobarbital (Sigma–Aldrich) at 99.9%
- Pure standard Ibuprofen (Sigma–Aldrich) at 99.9%
- Pure standard Acetaminophen (Sigma–Aldrich) at 99.9%
- Pure standard Ampicillin (Sigma–Aldrich) at 99.9%
- KCl (Sigma-Aldrich) at 99%
- HCl (Sigma-Aldrich) at 99%
- $Na_2B_4O_7$ (Borax) (Sigma-Aldrich) ≥99%
- NaOH (Sigma-Aldrich) at ≥98%
- Dichloromethane CH_2Cl_2 (Sigma-Aldrich) at ≥99.8%

I.2. Material

- Magnetic stirrers (Fisher bioblock scientific)
- Laboratory glassware
- Qualitative Grade Filter Paper (DR WATTS)
- pH meter (Metrohm)
- 0.22 µm polysulfone syringe filter
- Thermometer (Max 250°C)
- Magnetic bars
- HPLC (WATERS 600 Controller, iodine bar detector: DAP WATERS 2996)
- Column NUCLEOSIL5 C18, L=250 mm, d_i=4.6 mm (OSI)
- Glass syringes Hamilton Microliter série 7000 (0,5 - 5 µl)
- Thermo Scientific ™ NanoDrop ™ 2000/2000c Spectrophotometer
- Centrifuge Hettich Mikro 220r Refrigeree – 2205
- Eppendorf Thermomixer confort, 2 mLBlock
- Ultrasound Bath Elmasonic P70h with Heating
- Oven Air Forced Circul. 64L UT6 HERAEUS

- Micropipette Research® plus Eppendorf
- Micropipette Kit: 4 Pipettors (0.5-10µl; 10-100µl; 100-1000µl; 1000-5000µl)
- Injekt®-F Luer Solo, Size 1 ml
- 2ml 10-425 Screw-Thread Amber HPLC Vial with Matching Cap and Septa
- Fourier Transform Infrared (FTIR) System Vertex 80v
- Powder X-ray diffraction system (PXRD) X PERT PRO MRD
- The Autosorb-iQ Surface Area and Pore Size Analyzer
- HPLC, agilent technologies 1290 infinity
- Column Kinetex® 2.6 µm XB-C18 100 Å, LC Column 75 x 4.6 mm, Ea

II. Experimental protocol

II.1. Adsorbates and chemicals

The pharmaceuticals used in this work are pure standards (99%), and the chemicals are of analytical grade. The pharmaceuticals were purchased from Sigma–Aldrich. Solutions of the pharmaceuticals were prepared in ultrapure water (Millipore Milli-Q Direct 8 Water Purification System). For the adsorption experiments in real water, the pharmaceuticals were prepared in natural waters.

II.2. Preparation of standard solutions

For the purpose of our different studies, stock solutions of the four pharmaceutical products selected were prepared: ibuprofen, phenobarbital, ampicillin and acetaminophen, at a concentration of 1.0 g L^{-1} in methanol to ensure the total solubility of each pharmaceutical. From these mother solutions, diluted solutions were prepared at the desired concentration. All solutions were prepared with ultrapure water at pH = 6–7.

II.3. Real water

In order to study the capacity of COFs to adsorb pharmaceutical products by a test closer to reality, real waters from different regions in Portugal and different types of water such as river, lake, and fountain, have been used to perform the adsorption of pharmaceuticals alone and then mixed on the COFs.

All water samples were collected from natural ecosystems from deferent regions in Portugal on 06-05-2017 (Tables 11, 12). SERA aqua-tests were performed on 01-08-2017. The first one was a freshwater from the Lima River in the Geographical location of Viana do Castelo. The second one was taken from the lake S. Pedro D'Arcos in the Geographical location of Ponte de Lima. The third one was taken from the Fontain of Neiva River in the Geographical location of Baltim- Forjàes. The fourth one was estuary from the Lima River in the Geographical location of Viana do Castelo.

Table 11 Location of the sampling area of the studied real waters.

Sampling	Geographical location	Geographical coordinates
Freshwater from Lima River	Viana do Castelo-Portugal	41041‘17.69“N;8047’23.88“W
Lake S. Pedro D’Arcos	Ponte de Lima-Portugal	41045’52.50“N;8038’13.60“W
Fountain of Neiva River	Baltim- Forjàes-Portugal	41036’10.20“N;8045’14.70“W
Estuary from Lima River	Viana do Castelo-Portugal	41040’58.14“N;8049’35.67“W

Table 12 Properties and chemical characteristics of the real waters.

Sampling	Freshwater from Lima River	Lake S. Pedro D'Arcos	Fontain of Neiva River	Estuary from Lima River
pH	7.661	6.531	4.873	7.793
gH (°dgH)	n/a	8	4	n/a
kH (°dkH)	7	4	4	7
NH_4 (mg L^{-1})	<0.50	<0.50	<0.50	<0.50
NH_3 (mg L^{-1})	0.03	<0.003	<0.003	0.03
NO_2 (mg L^{-1})	0.00	0.00	0.00	1.00
NO_3^- (mg L^{-1})	0.00	0.00	0.00	10.00
PO_4^{3-} (mg L^{-1})	2.00	1.00	2.00	1.00
Fe^{4+} (mg L^{-1})	0.00	0.50	0.00	0.00
Cl^- (mg L^{-1})	0.00	0.00	0.00	0.00

II.4. Adsorbents caracterisations

II.4.1. Activated carbon

Activated carbon PAC (F400) is in the form of a powder with a particle size ≤ 50 μm. Its main physicochemical characteristics are summarized in Table 13 **(Ayele et al., 1998)**. Before each use, the adsorbent is dehydrated in the oven at 105°C for 12 h.

Table 13 PAC F400 characteristics **(Ayele et al., 1998)**.

Origin	Bituminous oil
Activation	High temperature
Specific surface area (m^2 g^{-1})	1050–1200
Iodine number (mg g^{-1})	1050
Acid surface function (mEq g^{-1})	0.23
Porous structure	micro

II.4.2. Covalent Organic Frameworks

The adsorbents used in this work are novel TpBD-$(CF_3)_2$ reported by Salonen and co-workers **(Mellah et al., 2018)**, and TpBD-Me_2 first reported by Banerjee and co-workers (**Chandra et al., 2013).** These COFs are part of Tp-series COFs (Figure 30)**.** The TpBD-$(CF_3)_2$ synthesis was performed by Soraia Fernandes (for details, see in the chapter Adsorption, section: Adsorbents) **(Mellah et al., 2018)**. The both COFs are characterized by their porous structure varied between 22−24 Å, a high chemical stability in water and their

exceptionally stable in aqueous, acidic, and basic media. The Brunauer–Emmett–Teller (BET) surface area was calculated to be 520 and 870 m^2 g^{-1}, with a pore volume of 0.38 and 0.50 cm^3 g^{-1} for TpBD-Me_2 and TpBD-$(CF_3)_2$.

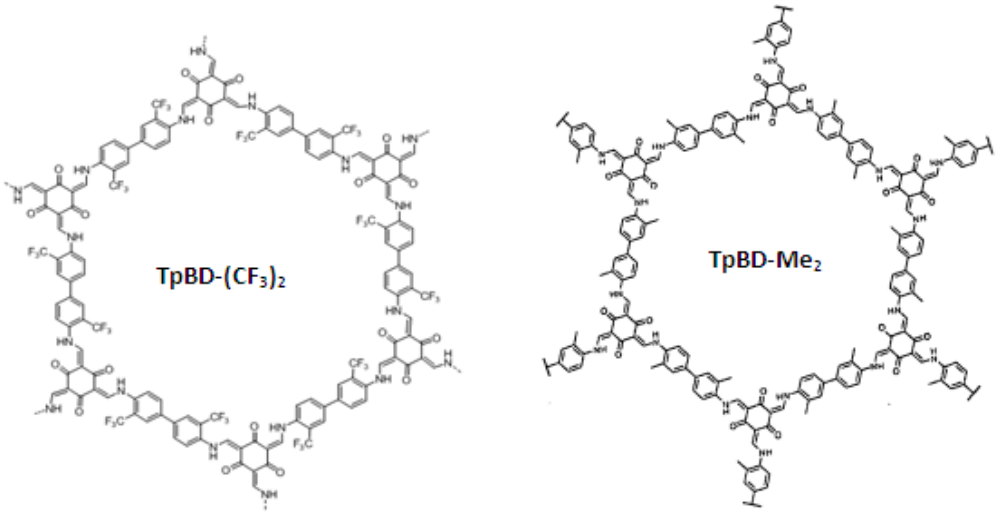

Figure 30 The structure of TpBD-Me_2 (**Chandra et al., 2013)** and TpBD-$(CF_3)_2$ **(Mellah et al., 2018)**.

II.5. Powder X-ray diffraction of TpBD-$(CF_3)_2$

The TpBD-$(CF_3)_2$ was characterized by powder X-ray diffraction (PXRD) illustrated by Figure 31 **(Mellah et al, 2018)**, showing the formation of an ordered porous structure. An evident reflection is seen at 2θ = 3.6°, which is in good agreement with related COFs, holding similar pore dimensions and eclipsed AA COF layer arrangement. Moreover, two broad reflections are seen at about 2θ = 6° and 25°, the latter of which is attributed to the interlayer stacking distance.

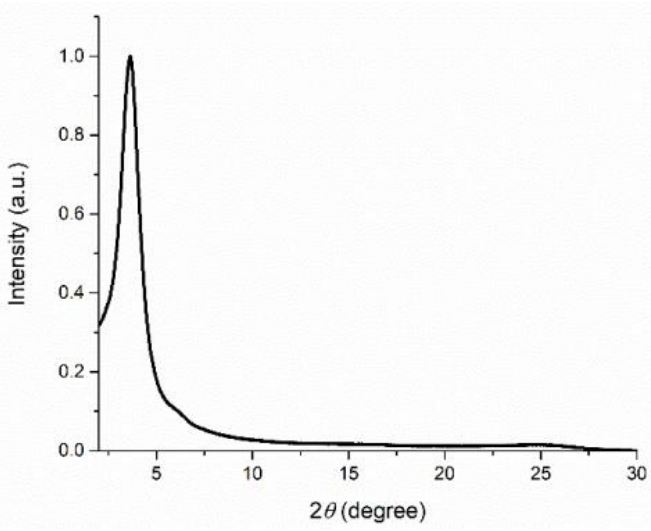

Figure 31 Powder X-ray diffraction pattern of TpBD-$(CF_3)_2$.

II.6. Nitrogen physisorption isotherm

The N_2 sorption measurements of TpBD-$(CF_3)_2$ at 77 K gave a type I isotherm (Figure 32) **(Mellah et al, 2018)**, with a Brunauer–Emmett–Teller (BET) surface area of 870 $m^2\ g^{-1}$ and a pore volume of 0.50 cm^3g^{-1}.

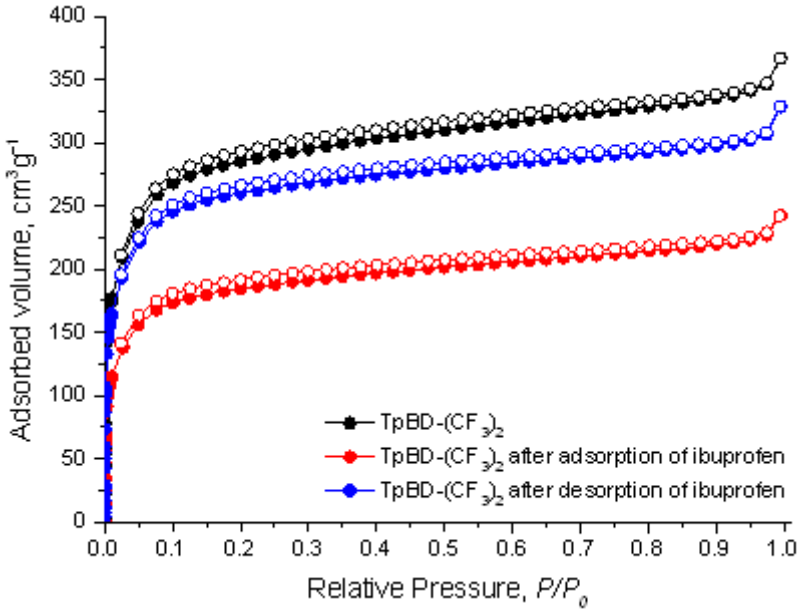

Figure 32 Nitrogen adsorption (filled spheres) and desorption (hollow spheres) isotherm profiles measured at 77 K of TpBD-$(CF_3)_2$ as synthesized (black), after adsorption of ibuprofen (red), and after desorption (blue).

II.7. Adsorption experiments

Adsorption experiments were performed using a batch experimental approach. For the pharmaceuticals, adsorption kinetic experiments were first carried out in order to determine the time necessary to attain equilibrium (t_{eq}). Then, equilibrium experiments were carried out to determine the adsorption isotherms. All experiments were carried out by incubation under constant shaking (maximum speed in the thermomixer of 14000 rpm) a mass of the COF (200µg) in 600 µL of ultrapure water. The initial concentration of the pharmaceuticals in ultrapure water was 50 mg L^{-1}. All experiments were carried out in duplicate and at a constant temperature of 21 ± 2°C using a thermomixer regulated incubator.

II.7.1. Adsorption kinetics

Adsorption experiments were performed using a batch experimental approach with TpBD-$(CF_3)_2$ and TpBD-Me_2 as adsorbents and ibuprofen, ampicillin, and acetaminophen as target compounds. Ultrapure water was used as the solvent at pH 6–7. For COF stock solutions, 4 mg of COF was added to 50 mL of ultrapure water resulting in a final

concentration of 680 mg L^{-1}. For the pharmaceutical stock solutions, 5 mg of ibuprofen was added to 1 mL of methanol with a final concentration of 5000 mg L^{-1}. From the ibuprofen stock solution, 6 µL were withdrawn to a solution of 594 µL of COF stock solution. The mixture was incubated under constant shaking (1400 rpm) at 21 ± 2 °C during a specific time. The supernatant was isolated by centrifugation (15000 rpm, 21°C, 15 min) and analyzed by UV-Vis spectroscopy (λ = 220 nm for ibuprofen, λ = 207 nm for ampicillin, and λ = 243 nm for acetaminophen) to determine the quantity of the pharmaceutical remaining in the solution after adsorption. For the short times of the kinetics (0.5, 5, 10, 20, and 30 minutes), the isolation of the supernatant was performed by filtration (0.22 µm polysulfone syringe filter). The amount of the pharmaceutical adsorbed onto the COF at a specific time, q_t (mg g^{-1}), was calculated as follows:

$$q_t = (C_0 - C_t)\frac{V}{m} \qquad (16)$$

where C_0 and C_t (mg L^{-1}) denote the concentration of the pharmaceutical in the solution initially and at time t (min), V (L) the volume of the solution and m (mg) the mass of the adsorbent.

For the rest of the adsorption experiments, t = 120 min was chosen to reach the equilibrium, as inferred from the kinetics studies. The amount of the pharmaceutical adsorbed onto the COF at equilibrium, q_e (mg g^{-1}), was calculated as follows:

$$q_e = (C_0 - C_e)\frac{V}{m} \qquad (17)$$

where C_e (mg L^{-1}) denotes the concentration of the pharmaceutical in the equilibrium state.

II.7.2. Adsorption isotherms

The adsorption equilibriums were carried out as batch reaction in a microtube containing a specific mass (m) of COF ranging from 25 to 400 µg and a volume of 600 µL of solution at a drug concentration C_0.

When the equilibrium time (determined by the kinetic tests) was reached, each microtube (600µL/microtube) was centrifuged at 15000 rpm; the supernatant was isolated, and the recovered supernatants were analyzed by UV-Vis spectroscopy to determine the residual concentration C_r (mg L^{-1}) of the pharmaceutical products. The adsorbed concentration is:

$$C_{ad} = C_0 - C_r. \qquad (18)$$

II.8. Quantification of drugs using UV-Vis spectroscopy

The quantification of the samples of drugs individually was performed by measuring the absorption of ultraviolet light. For the analysis, a spectrophotometer (Nanodrop) was used at wavelengths of 207 nm for ampicillin, 220 nm for ibuprofen, and 243 nm for acetaminophen (Figures 33–35). The calibration curves are presented in the results and discussion section.

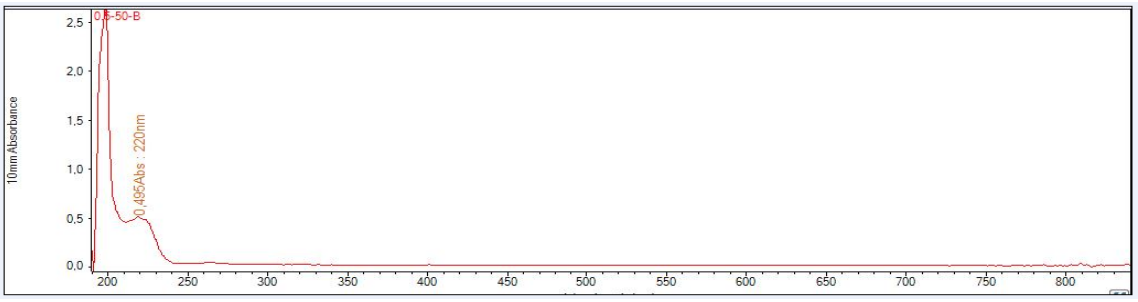

Figure 33 UV spectra of ibuprofen (λ = 220 nm) in ultrapure water.

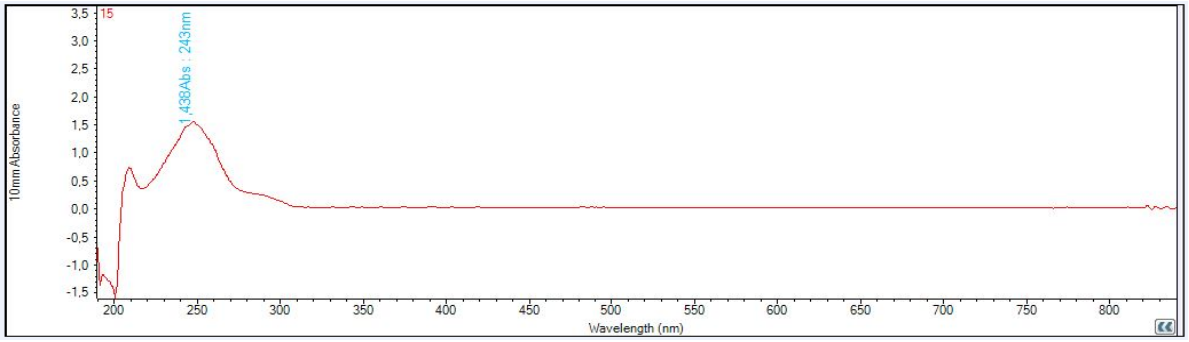

Figure 34 UV spectra of acetaminophen (λ = 243 nm) in ultrapure water.

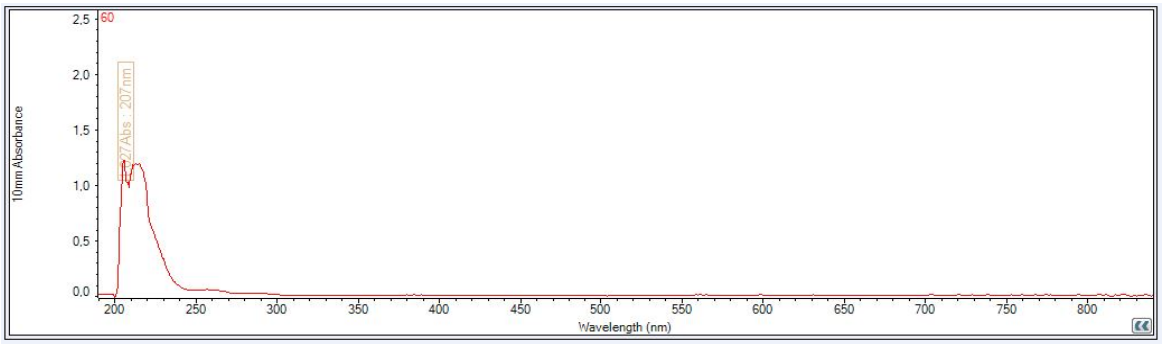

Figure 35 UV spectra of ampicillin (λ = 207 nm) in ultrapure water.

II.9. Quantification of drugs using HPLC

A high-performance liquid chromatographic (HPLC) method for the separation and quantification of the pharmaceuticals using an UV-Vis Abs.-Variable Wave.(UV) @ 254 nm (22°C) detector is used for the determination of residual concentrations of adsorbed products. The developed conditions of analysis allowed for the separation and detection of mixtures that are shown in Table 14 in less than 15 minutes using a column Kinetex® 2.6 µm XB-C18 100 Å, LC Column 75 x 4.6 mm, Ea.

Table 14 Competitive adsorption of the mixture of two pharmaceutical products

150µM(IBU)/50µM(Acet)	100µM(IBU)/100µM(ACE)	50µM(IBU)/150µM(ACE)
150µM(IBU)/50µM(PHEN)	100µM(IBU)/100µM(PHEN)	50µM(IBU)/150µM(PHEN)
150µM(ACE)/50µM(PHEN)	100µM(ACE)/100µM(PHEN)	50µM(acet)/150µM(PHEN)

The gradients used, the methanol, and acetone were grade HPLC (Sigma–Aldrich) (99%). The separation was achieved isocratically, using a ternary mobile phase of water and as a solvent the methanol , acetone as organic modifier (75:25 v/v) were used to separate these three standards reproducibly and easily. The flow rate of the mobile phase was set at 1 mL min^{-1}. The detection takes place in the UV field, the quantification and the qualification of the molecules were carried out at wavelengths corresponding to the maximum absorption in this field, i.e. 210 nm for phenobarbital, 220 nm for ibuprofen, and 243 nm for acetaminophen.

The characteristic retention times of the molecules allow their identification. The surface area of the chromatographic peak was determinated using the software OpenLab for high-throughput HPLC data processing and quantitation. The surface area was used for the quantification of the studied molecules. The chromatograms of solution composed of the mixture (100µM/100µM) of phenobarbital/ibuprofen, phenobarbital/acetaminophen, and ibuprofen /acetaminophen in lake water are presented in Figures 36–38.

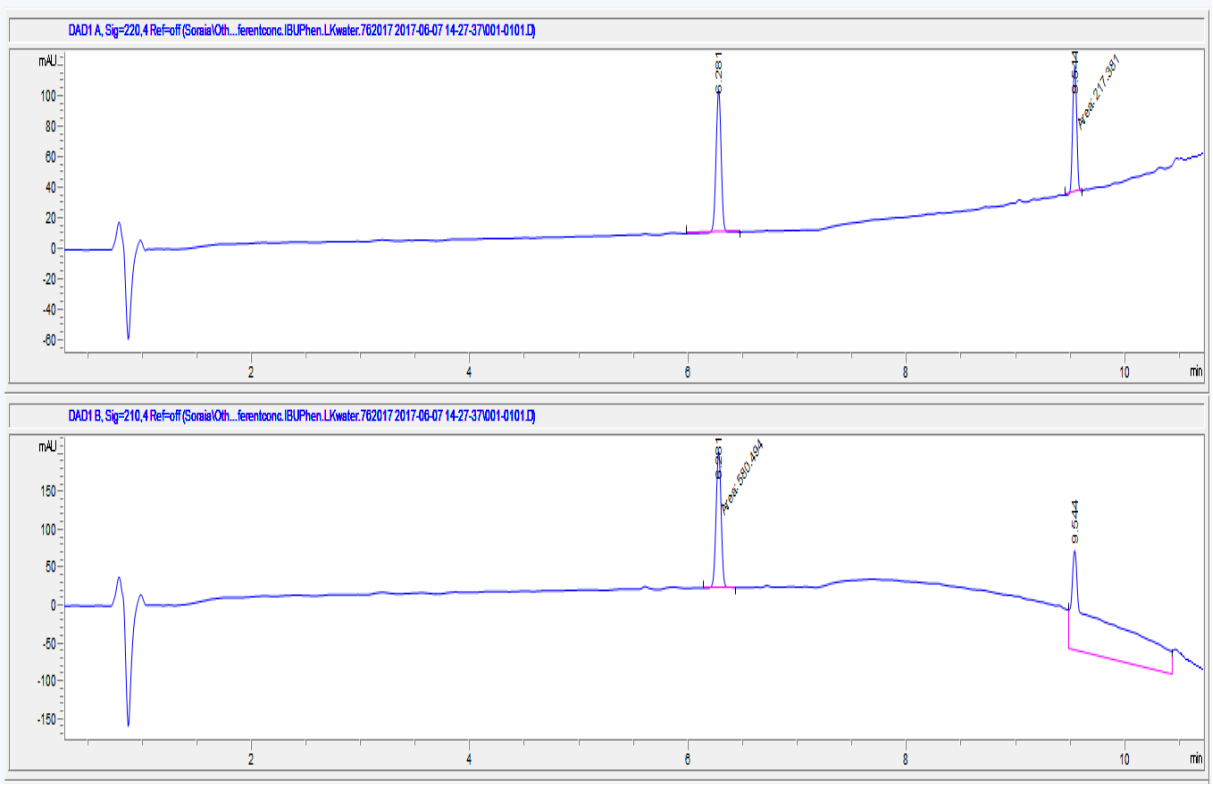

Figure 36 Chromatograms of a solution composed of the mixture (100µM/100µM) of phenobarbital (bottom, λ = 210nm)) and ibuprofen (top, λ = 220 nm)) in lake water.

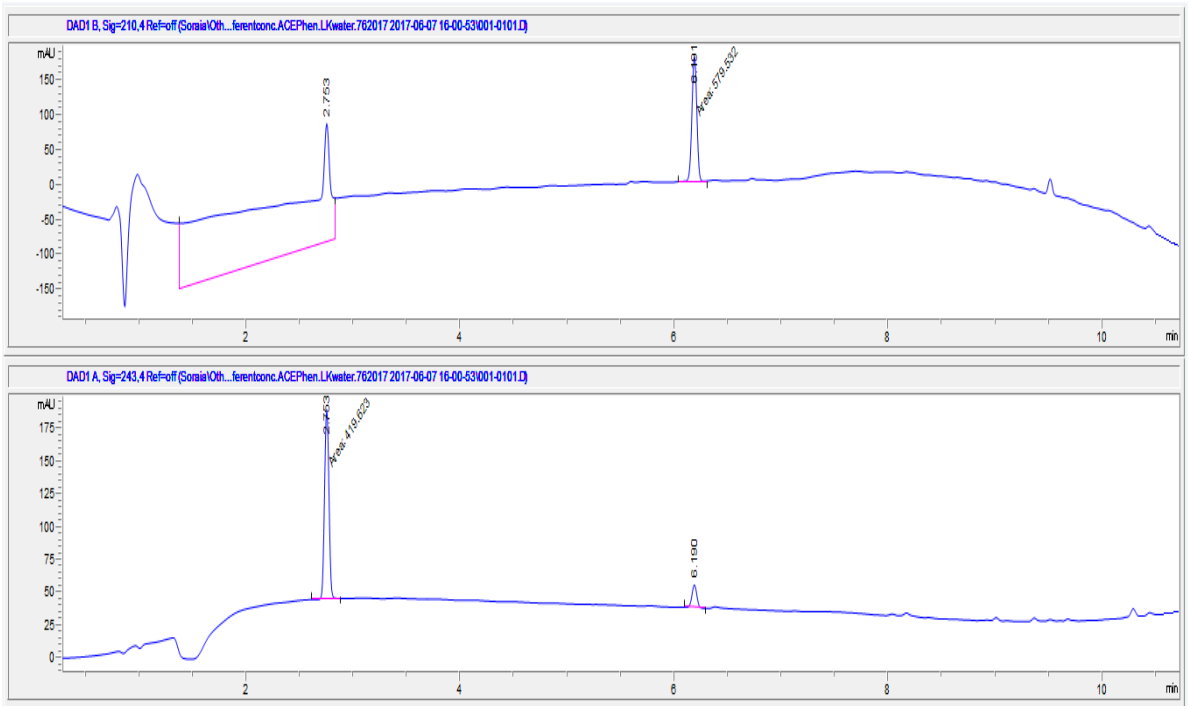

Figure 37 Chromatograms of a solution composed of the mixture (100µM/100µM) of phenobarbital (top, λ = 210 nm) and acetaminophen (bottom, λ = 243 nm) in lake water.

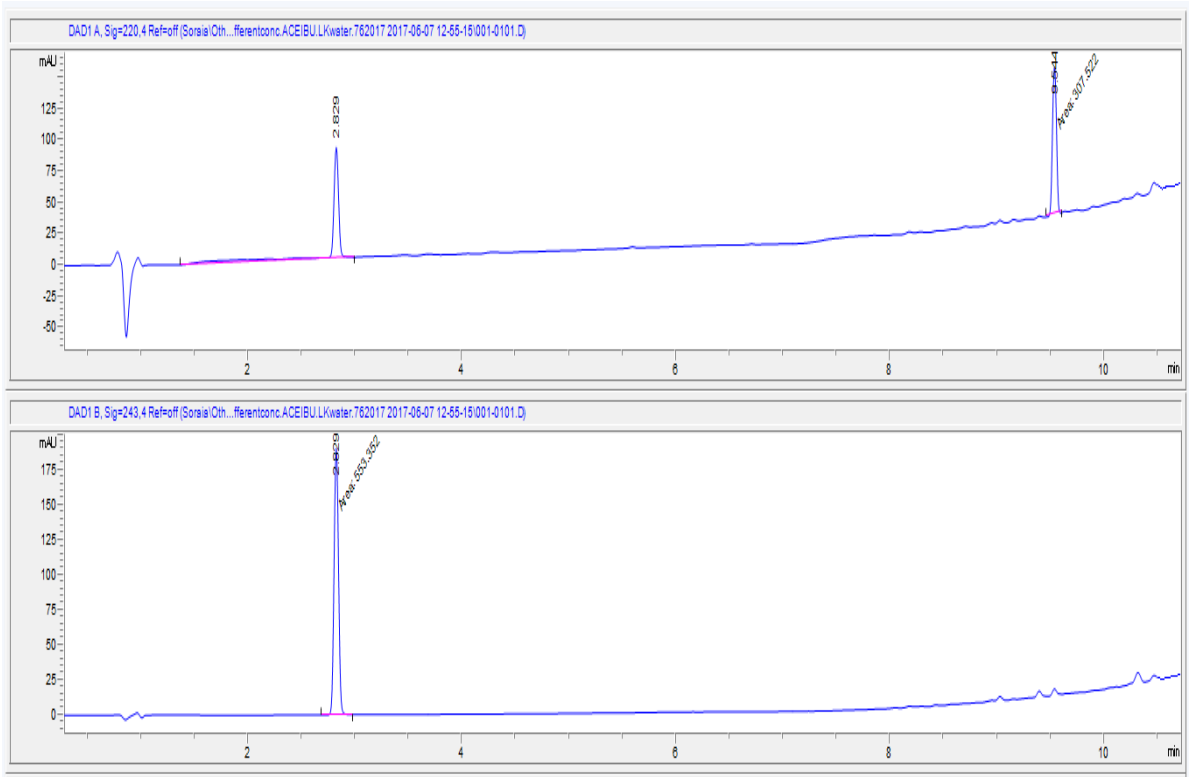

Figure 38 Chromatograms of a solution composed of the mixture (100µM/100µM) of ibuprofen (top, λ = 220 nm) and acetaminophen (bottom, λ = 243 nm) in lake water.

CHAPTER VII

RESULTS AND DISCUSSION OF THE DISPOSAL OF DRUG RESIDUES BY ADSORPTION

I. Results and discussions

With the aim to remove lipophilic pharmaceutical contaminants from water, we chose, the COF, TpBD-$(CF_3)_2$ reported by Salonen and co-workers **(Mellah et al., 2018)** and the COF TpBD-Me_2 reported by Banerjee et al., **(Chandra et al., 2013)** to be tested as adsorbents. These two COFs can be obtained from 3,5-triformylphloroglucinol (Tp) and 3,3'-bis (trifluoromethyl) benzidine (BD-$(CF_3)_2$) or *o*-tolidine (BD-Me_2), respectively. These COFs feature high water-stability, a prerequisite for environmental applications, even under basic or acidic conditions**.** Nitrogen sorption measurements of TpBD-$(CF_3)_2$ provide a type I isotherm, which is characteristic for microporous materials, with Brunauer–Emmett–Teller (BET) surface area of 870 $m^2\ g^{-1}$ and a pore volume of 0.50 cm^3g^{-1}. TpBD-Me_2 exhibits a BET surface area 520 $m^2\ g^{-1}$ and a pore volume of 0.38 cm^3g^{-1} **(Chandra et al., 2013)**. The high stability and surface area of these COFs will make them good candidates to adsorb pharmaceuticals.

Our study is the first report on pharmaceutical removal from water using Covalent Organic Frame Works **(Mellah et al, 2018)**. So, in this study two COFs TpBD-$(CF_3)_2$ and TpBD-Me_2 were used for the removal of pharmaceuticals ibuprofen, acetaminophen, ampicillin and phenobarbital, and compared to PAC F400.

II. Adsorption onto PAC F400

II.1. Linearity limit

The limits of linearity (LOL) for the adsorption of ibuprofen and phenobarbital are presented in the Figure 39.

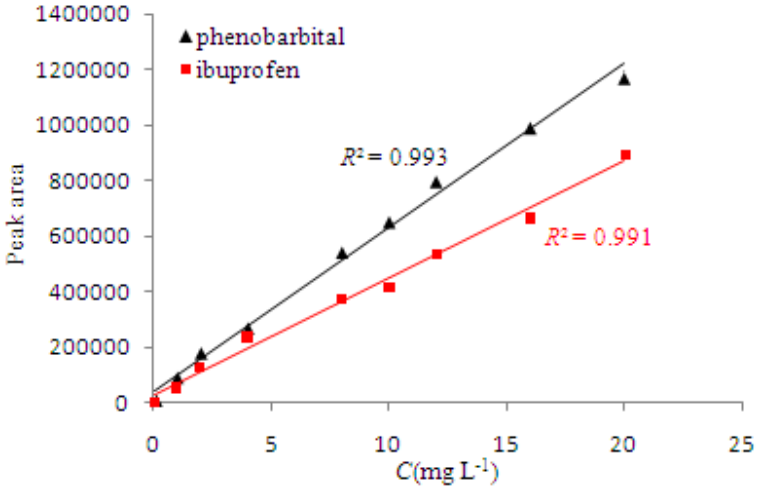

Figure 39 Calibration curves of ibuprofen (λ = 220 nm), and phenobarbital (λ = 210 nm) at 21°C inultrapure water at pH 6–7.

In the present study, ten standard solutions of concentrations between 1 mg L^{-1} and 20 mg L^{-1} were prepared. The results obtained were processed with the Microsoft Excel software. They show that the chosen work domain satisfies the limits relating to the Beer–Lambert law. The correlation coefficient (R^2) is greater than 0.990, which respects the linearity limit criterion.

II.2. Determination of the equilibrium time

The adsorbed quantity q_t (mg g^{-1}) of ibuprofen and phenobarbital per mass of activated carbon PAC in relation to the adsorbent–adsorbate contact time *t*(min) for each of the pharmaceuticals examined at an initial concentration of 8 mg L^{-1} at PAC concentration of 40 mg L^{-1} is presented in Figure 40. The adsorbed quantity of phenobarbital reached 61.0 mg g^{-1} (31%) after 30 min. The slope becomes very small near the equilibrium at 180 min, amounting about 67.5 mg g^{-1} equivalent to 33% of the amount initially present. Similar results were obtained by Cooney using activated carbons Instachar and Liquichar with a surface area of 900 m^2 g^{-1} to adsorb phenobarbital **(Cooney, 1995)**. The quantity of ibuprofen adsorbed after 30 min is higher with 70.9 mg g^{-1} (35%), to reach 53% (106 mg g^{-1}) of the amount initially present after 180 min. According to these results, PAC gave a good affinity towards ibuprofen, which is confirmed by its high adsorption capacity to adsorb ibuprofen compared to phenobarbital. Papciak and co-workers have obtained a good affinity between ibuprofen and activated carbons Norit SA super that exhibit a surface area of 1150 m^2 g^{-1} **(Puszkarewicz et al., 2017)**.

Ibuprofen showed a low adsorption rate at initial times as shown in Figure 40, in which the most quantity of ibuprofen adsorbed took a long time arriving to 150 min. However, a short time is needed for phenobarbital to be near the equilibrium, where its most adsorbed quantity has taken place within 30 min indicating a high adsorption rate. The rate of the initial adsorption process is more rapid for phenobarbital compared to ibuprofen, which may be explained by the influence of solute size and molecular configuration. Indeed, the hydrophobic phenobarbital exhibits a molecular structure a bit larger than ibuprofen, as mentioned in Table 2. This allows it to quickly reach equilibrium and explains its low adsorption capacity than that of ibuprofen.

Weber and Smith (1986), who found a relationship between the adsorption rate and the molar mass during their study of the influence of solute size and the molecular configuration on the adsorption rate on PAC **(Weber et al., 1986)**. El-Mabrouk and co-workers have also highlighted the rapid adsorption of phenobarbital on activated carbon giving low equilibrium

times **(Javaid et al., 1983)**. The adsorption process starts very quickly for both pharmaceuticals, rapidly approaching the maximum of adsorption and then continues much slower to reach the equilibrium in 180 minutes (Figure 40). Similar equilibrium times were obtained by Carvalho and co-workers in their study of adsorption of ibuprofen onto powdered activated carbons prepared from cork waste **(Mestre et al, 2007).** A study of adsorption of ibuprofen into activated carbon cloths reported by Duclaux and co-workers showed an equilibrium time of 600 min more high than obtained with CAP F400 **(Guedidi et al., 2017)**.

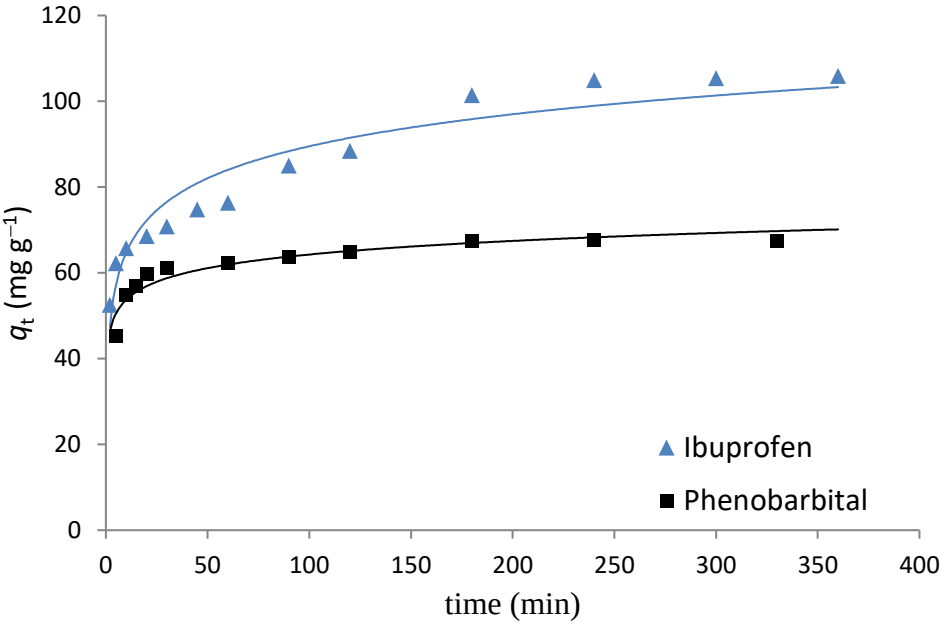

Figure 40 Adsorption kinetics expressed as quantity adsorbed q_t (mg g^{-1}) by PAC (F400) as a function of time t of ibuprofen (λ = 220 nm) and phenobarbital (λ = 210 nm) at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 8 mg L^{-1}; C(PAC) = 40 mg L^{-1}).

II.3. Adsorption kinetics

II.3.1. Pseudo first-order kinetics

The experimental kinetic results were fitted with the pseudo first-order equation **(Lagergren, 1898)**. The graphs obtained by plotting ln (q_e–q_t) as a function of time are presented in Figure 41 for the adsorption of ibuprofen and phenobarbital at an initial concentration of 8 mg L^{-1} on PAC at a concentration of 40 mg L^{-1}. The pseudo first-order kinetic parameters are presented in Table 15. A wide variance can be observed between experience and theory using the Lagergren equation and the correlation coefficient (R^2) values for the pseudo-first-order kinetic model were 0.896 and 0.494 for phenobarbital and ibuprofen, respectively, indicating that the equation does not adequately describe the adsorption process of ibuprofen and phenobarbital onto PAC.

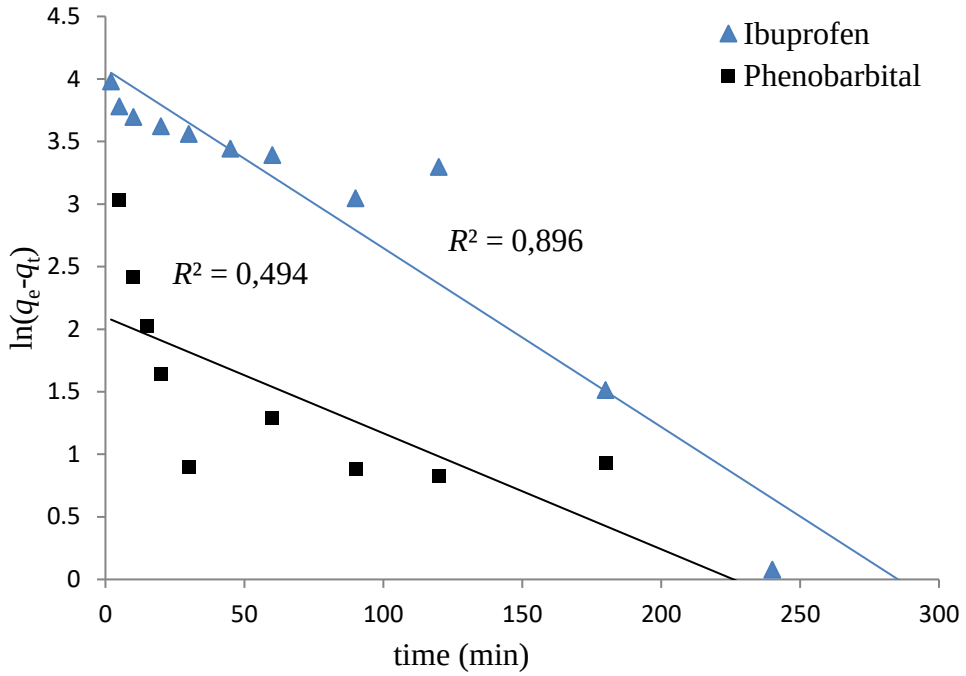

Figure 41 Pseudo-first order kinetic results on the removal of ibuprofen (λ = 220 nm) and phenobarbital (λ = 210 nm) by PAC (F400) at 21°C in ultrapure water at pH 6–7, (C_0(pharmaceutical) = 8 mg L^{-1}; C(PAC) = 40 mg L^{-1}).

Table 15 Pseudo-first order kinetic parameters for ibuprofen and phenobarbital at an initial concentration of 8 mg L^{-1} by PAC (F400) at a concentration of 40 mg L^{-1} at 21°C and pH=6–7.

	k_1(min^{-1})	R^2	$q_{e,exp}$ (mg g^{-1})	$q_{e,calc}$ (mg g^{-1})
Phenobarbital	0.035	0.494	67.45	11.13
Ibuprofen	0.032	0.897	105.9	58.2

II.3.2. Pseudo second-order kinetics

The pseudo second-order equation is suggested by some authors as being more appropriate for describing adsorption kinetics **(Quek et al, 1998)**. The graphs obtained by plotting t/q_t as a function of time for the adsorption of ibuprofen and phenobarbital at an initial concentration of 8 mg L^{-1} by PAC(F400) at a concentration of 40 mg L^{-1} are presented in Figure 42. The k_2 and q_e values determined from the slope and intercepts of the plot of t/q_t vs. t are presented in Table 16 along with the corresponding correlation coefficients.

The correlation coefficient (R^2) values for the pseudo second-order kinetic model are 0.999 and 0.995 for ibuprofen and phenobarbital, respectively, indicating the applicability of the pseudo second-order kinetic model to describe the adsorption process of ibuprofen and phenobarbital by PAC (F400). Many adsorption studies have reported that the pseudo second-

order model is more appropriate for describing adsorption kinetics of both pharmaceuticals onto activated carbons, such as the adsorption of ibuprofen onto activated carbon cloths (**Guedidi et al., 2017)**, CAC, CPAC **(Mestre et al., 2007)**; and by waste-derived activated carbons (**Mestre et al., 2009**). Galardo and co-workers have reported that the pseudo-second order model was the most suitable equation to describe the adsorption of phenobarbital onto activated carbon **(Mafull et al., 2014)**.

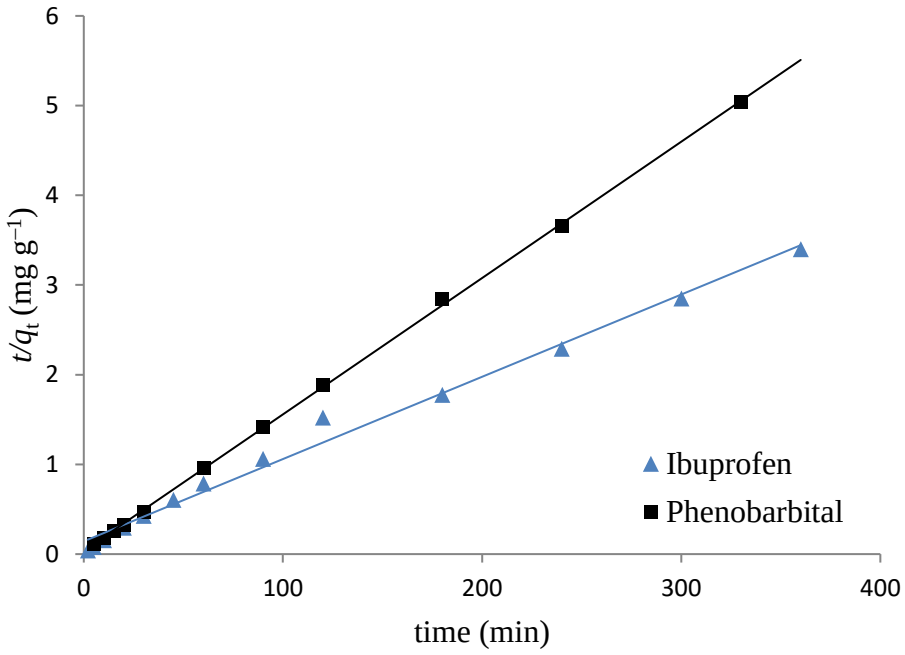

Figure 42 Pseudo-second order kinetics results for the removal of ibuprofen (λ = 220 nm) and phenobarbital (λ = 210 nm), by PAC (F400) at 21°C in ultrapure water at pH 6–7, (C_0(pharmaceutical) = 8 mg L^{-1}; C(PAC) = 40 mg L^{-1}).

The pseudo-second order rate constant k_2 of the adsorption by PAC (F 400) of phenobarbital is 0.0036 g mg^{-1} h^{-1}. It is higher than for ibuprofen that is of 0.0006 g mg^{-1} h^{-1}, which explains the high initial adsorption rate of phenobarbital. This last were confirmed as well by the higher value of the initial adsorption velocity h of phenobarbital compared to ibuprofen as mentioned in Table 16.

The calculated q_e values 71.4 mg g^{-1} and 111 mg g^{-1} of ibuprofen and phenobarbital, respectively, according to the pseudo-second order kinetic model of adsorption by PAC (F400) agreed well with the experimental data, as shown in Table 16. Similar results are obtained by Carvalho and co-workers for the adsorption of ibuprofen onto powdered activated carbons prepared from cork waste that have the same surface area than PAC **(Mestre et al., 2007).**

Table 16 Pseudo-second order kinetic parameters for ibuprofen and phenobarbital at an initial concentration of 8 mg L^{-1} by PAC (F400) at a concentration of 40 mg L^{-1} at 21°C and pH=6–7.

	k_2 (g mg^{-1} h^{-1})	h (mg g^{-1} min^{-1})	R^2	$q_{e,exp}$ (mg g^{-1})	$q_{e,calc}$ (mg g^{-1})
Phenobarbital	0.0036	18.52	0.999	67.5	71.4
Ibuprofen	0.00062	7.69	0.995	106	111

II.3.3. Intra-particle diffusion

The data plotted concerning the intra-particle diffusion model (Figure 43), q_t versus $t^{1/2}$ exhibit multilinear plots, where two steps could be influencing the process. The plots for the adsorption of ibuprofen and phenobarbital at an initial concentration of 8 mg L^{-1} by PAC (F400) at the concentration of 40 mg L^{-1} do not result in a linear relationship passing through the origin, but multimodal graphs with two distinct regions, indicating that intraparticle diffusion is affected by more than one process (**Lopicic et al., 2016).**

The initial curved region corresponds to the external surface adsorption, in which the pharmaceuticals diffuse through the solution to the external surface of adsorbent. The second stage relates to the equilibrium stage, in which the intra-particle diffusion starts to slow down and level out (**Daiffullah et al., 2007; Hamadaoui et al., 2007)**.

The intra-particle velocity constants k_i and the correlation coefficients for their tow parts are presented in Table 17. According to the obtained results, the values of k_{p1} are higher than the values k_{p2} for all pharmaceuticals adsorbed by PAC (F400). It can be deduced that there are two processes that control the rate of pharmaceutical adsorption onto PAC (F400). The first one is probably the diffusion to the exterior surface of the adsorbent, resulting in a faster adsorption rate. The second portion of the plot seems to refer to the diffusion into the PAC (F400) pores (with the lowest slope).

The values of the correlation coefficients R^2 for the intra-particle Weber–Morris diffusion model obtained for the adsorption of ibuprofen and phenobarbital at an initial concentration of 8 mg L^{-1} by PAC (F400) at a concentration of 40 mg L^{-1} are all above 0.911. According to these results, it is probable that the intra-particle scattering model fits the experimental values obtained.

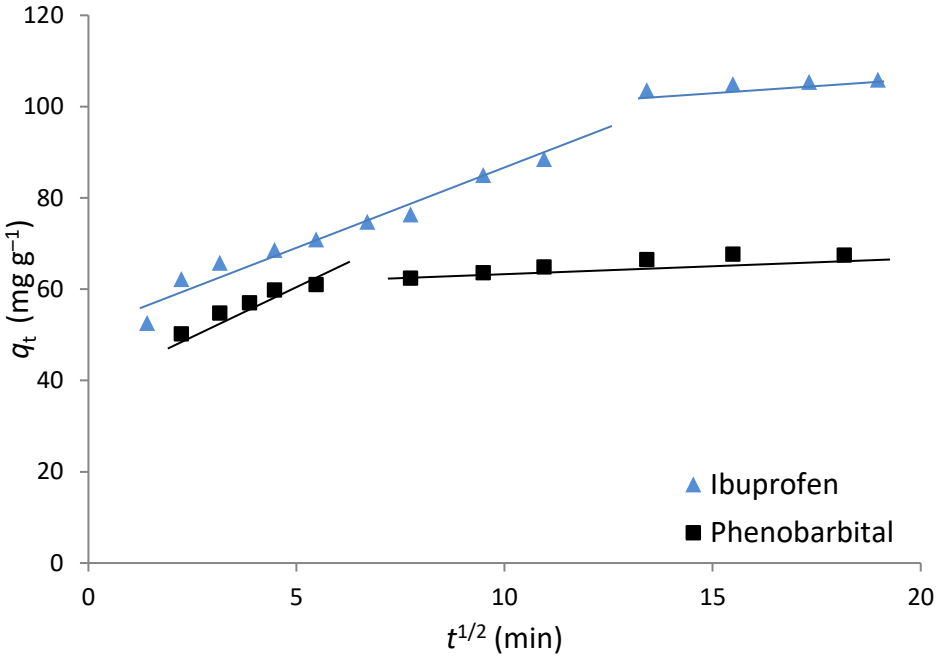

Figure 43 Intra-particle diffusion model for the adsorption kinetics of ibuprofen (λ = 220 nm), phenobarbital (λ = 210 nm) by PAC (F400) at 21°C in ultrapure water at pH 6–7, (C_0(pharmaceutical) = 8 mg L^{-1}; C(PAC(F400)) = 40 mg L^{-1}).

Table 17 Intra-particle diffusion parameters for ibuprofen and phenobarbital at an initial concentration of 8 mg L^{-1} by PAC (F400) at a concentration of 40 mg L^{-1} at 21°C and pH=6–7.

Sample	k_{p1} (mg g^{-1}min$^{-1/2}$)	R^2	k_{p2} (mg g^{-1}min$^{-1/2}$)	R^2
Iburofen	3.3	0.959	0.40	0.952
Phenobarbital	3.4	0.951	0.520	0.911

II.4. Isotherms Models

Equilibrium adsorption isotherms are the data most commonly used to understand the adsorption mechanisms. Many models are available. In this study of adsorption of ibuprofen and phenobarbital on activated carbon PAC (F400), the three most used models in literature were tested: the isotherms of Langmuir (1916), Freundlich (1906), and Temkin (1940).

II.4.1. Langmuir isotherm

The Langmuir isotherm model for the adsorption of ibuprofen and phenobarbital at an initial concentration of 8 mg L^{-1} by PAC (F400) at varying concentrations was tested by fitting the graphs given by C_e/q_e as a function of C_e (Figure 44). The Langmuir isotherm constants b, $1/b$, q_{max} and the correlation coefficients R^2 are presented in Table 18.

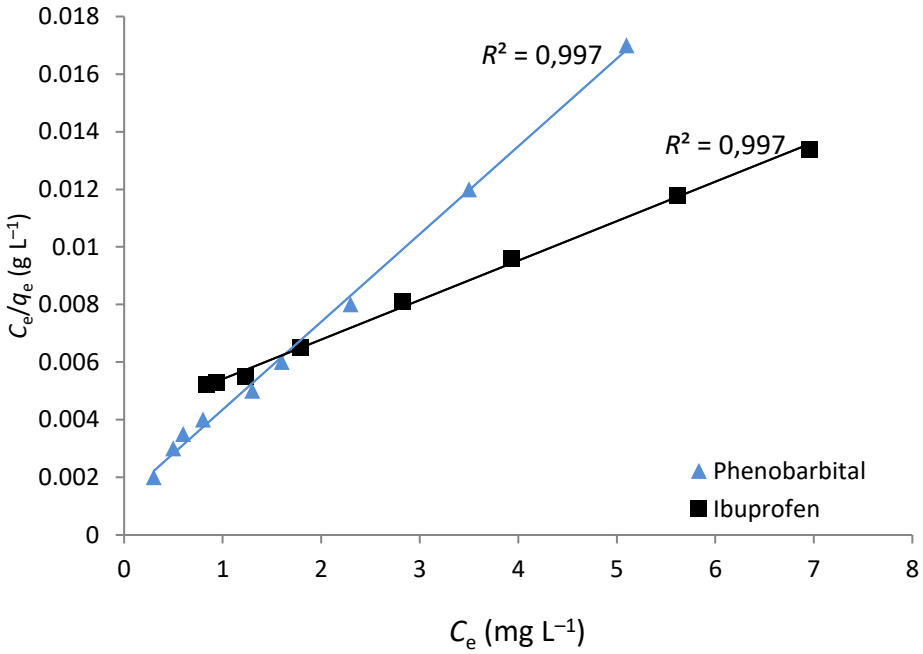

Figure 44 Langmuir isotherm of adsorption of ibuprofen (λ = 220 nm) and phenobarbital (λ = 210 nm) by PAC (F400) at different concentrations C(PAC) = 20–280 mg L^{-1}, at 21°C in ultrapure water at pH 6–7, (C_0(pharmaceutical) = 8 mg L^{-1}).

The Langmuir isotherm model for the adsorption of ibuprofen and phenobarbital onto PAC (F400) fits very well the experimental data (Figure 44) based on the relatively high values of correlation coefficients R^2 of 0.997 (Table 18). The calculated values of maximum adsorption capacities (q_{max}) show that the PAC (F400) exhibits better adsorption capacities for ibuprofen (1000 mg g^{-1}) than phenobarbital (333.3 mg g^{-1}). The b factor relates to the dissociation constant of the adsorbate determined for ibuprofen is 0.25 L mg^{-1} (b<1) shows the good affinity of PAC (F400) towards ibuprofen compared with phenobarbital **(Bembnowska et al., 2003).**

Table 18 Langmuir isotherm parameters for the adsorption of ibuprofen and phenobarbital at an initial concentration of 8 mg L^{-1} by PAC (F400) at different concentrations, at 21°C and pH=6–7.

	b (L mg^{-1})	1/b (mg L^{-1})	q_{max} (mg g^{-1})	R^2
Ibuprofen	0.25	4.00	1000	0.997
Phenobarbital	3.0	0.333	333.3	0.997

II.4.2. Freundlich isotherm

The Freundlich isotherms are presented in Figure 45 by fitting ln(q_e) as a function of ln(C_e) for the adsorption of ibuprofen and phenobarbital at an initial concentration of 8 mg L^{-1}

by PAC (F400) at different concentrations. Straight lines are obtained with the origin at lnK_F and a slope 1/n. The Freundlich isotherm parameters K_F, 1/n, n and the correlation coefficients R^2 are presented in Table 19.

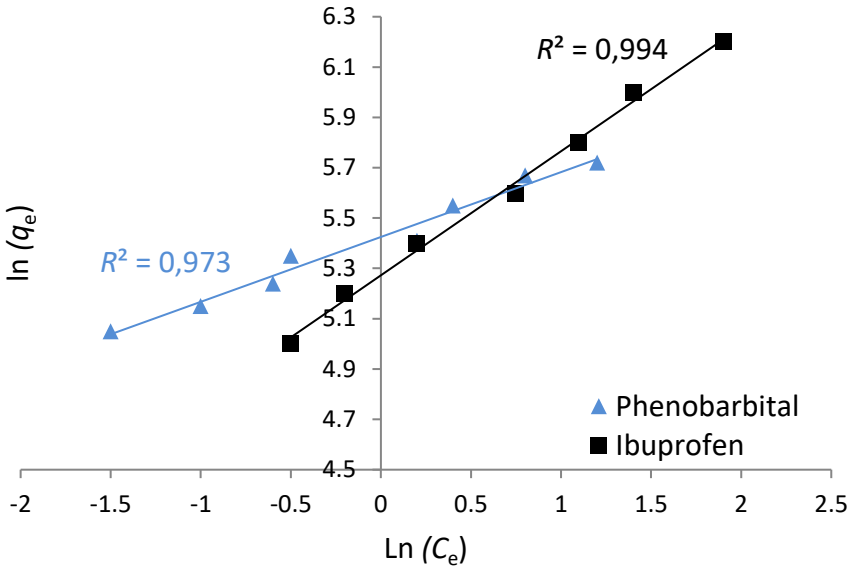

Figure 45 Freundlich isotherm of adsorption of ibuprofen (λ = 220 nm), phenobarbital (λ = 210 nm) by PAC (F400) at different concentrations C(PAC) = 20–280 mg L^{-1}, at 21°C in ultrapure water at pH 6–7, (C_0(pharmaceutical) = 8 mg L^{-1}).

The values of the correlation coefficients R^2 obtained for the Freundlich model for the adsorption of ibuprofen and phenobarbital onto PAC (F400) are 0.973 and 0.994, respectively. According to these results the Freundlich model fits the experimental values obtained. The calculated values of the Freundlich constant 1/n= 0.493 and 0.257 for ibuprofen and phenobarbital, respectively, are less than 1, indicating that the adsorption of the selected drugs is favorable. A high adsorbent capacity is deduced from the K_F values of 194.8 $mg^{0.507}$ g^{-1} $L^{0.493}$, 226.78 $mg^{0.743}$ g^{-1} $L^{0.257}$ for ibuprofen and phenobarbital, respectively.

Table 19 Freundlich isotherm parameters for adsorption of ibuprofen and phenobarbital at an initial concentration of 8 mg L^{-1} by PAC (F400) at different concentrations, at 21°C, and pH=6–7.

	K_F	1/n	n	R^2
Ibuprofen	194.8 $mg^{0.507}$ g^{-1} $L^{0.493}$	0.493	2.03	0.994
Phenobarbital	226.8 $mg^{0.743}$ g^{-1} $L^{0.257}$	0.257	3.89	0.993

II.4.3. Temkin isotherm

The application of the linear equation of the Temkin isotherm model **(Temkin et al., 1940)** is presented in Figure 46 by fitting q_e as a function of ln (C_e) for the adsorption of

ibuprofen and phenobarbital at an initial concentration of 8 mg L^{-1} by PAC (F400) at different concentrations. The adsorption isotherms derived from the experimental data for each of the tested adsorbate and adsorbent are presented in Table 20.

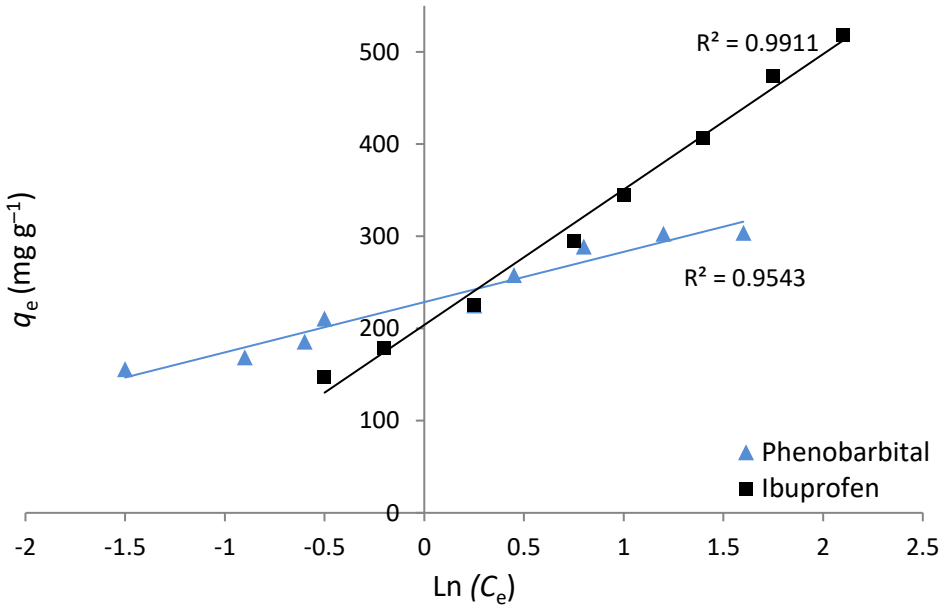

Figure 46 Temkin isotherm of adsorption of ibuprofen (λ = 220 nm) and phenobarbital (λ = 210 nm), by PAC (F400) at different concentrations C(PAC) = 20–280 mg L^{-1} at 21°C in ultrapure water at pH 6–7, (C_0(pharmaceutical) = 8 mg L^{-1}).

The Temkin isotherm model for the adsorption of selected pharmaceuticals by PAC (F400) fits well the experimental data (Figure 46) based on the relatively high values of the correlation coefficients R^2 of 0.991 and 0.954 for ibuprofen and phenobarbital, respectively. The adsorption of ibuprofen and phenobarbital gave values of the adsorption energy variation b_T of 16.65 and 39.76 kJ mol^{-1}, respectively, indicating a physical adsorption **(Dada et al., 2012; Hamdaoui et al., 2007; Aarfane et al.. 2014).** The positive values of the adsorption energy variation b_T (Table 20) indicate an endothermic adsorption process (**Ghogomu et al, 2013)**.

Table 20 Temkin isotherm parameters for adsorption of ibuprofen and phenobarbital at an initial concentration of 8 mg L^{-1} by PAC (F400) at different concentrations at 21°C and pH=6–7.

	b_T (kJ mol^{-1})	A (L g^{-1})	R^2
Ibuprofen	16.65	4.004	0.991
Phenobarbital	39.76	39.69	0.954

Conclusion: the PAC presented a higher adsorbed quantity of ibuprofen, whereas 53 % of the quantity of ibuprofen which present at initial time was adsorbed at equilibrium, however, only 35% of phenobarbital was adsorbed at equilibrium. Some reported works confirm the low adsorption of phenobarbital onto activated carbon, such as the works mentioned above, of Cooney using the activated carbons Instachar and Liquichar to adsorb phenobarbital **(Cooney; 1995)**, and the reported work of Papciak and co-workers about adsorption of ibuprofen onto Norit SA super and Carbopol MB5 (**Puszkarewicz et al., 2017)**.

The obtained results for the correlation coefficient (R^2) values indicate the applicability of the pseudo second-order kinetic model to describe the adsorption process of ibuprofen and phenobarbital by PAC (F400). These results were confirmed by some other works reported in this field, indicating the appropriate pseudo-second order model to describe the adsorption of ibuprofen and phenobarbital onto activated carbons (**Guedidi et al., 2017; Mafull et al., 2014; Mestre et al., 2007; Mestre et al., 2009)**.

The obtained adsorption results have been described by Freundlich, Langmuir, and Temkin equations. The investigation results are best described by the Langmuir equation (R^2 = 0.997) for both ibuprofen and phenobarbital, followed, in decreasing order, by the Temkin and Freundlich equations. Morley and co-workers had presented same results in which they confirmed that freundlish and Langmuir fit well their results about adsorption of ibuprofen onto activated carbon F400 **(Delgado et al., 2015)**. Carvalho and co-workers had as well reported that Langmuir model fits best the results of adsorption onto activated carbons CAC and CPAC than the Freundlich model **(Mestre et al., 2007)**. Papciak and co-workers have furthermore reported that Freundlich and Langmuir fit well the results of adsorption of ibuprofen onto Norit and Carbopol with preference of the Freundlich model **(Puszkarewicz et al., 2017)**. The application of the isotherms models for the adsorption of ibuprofen onto activated carbons F300 by Ociepa–Kubicka and co-workers showed that the Freundlich model fit the best the results followed by Temkin and Langmuir models **(Lach et al., 2018**). Some works have indicated that the Langmuir isotherm fits very well the results of phenobarbital adsorption onto activated carbons such us the adsorption onto activated charcoal reported by El-Mabrouk and co-workers **(Javaid et al., 1982)**, and onto activated carbons like SuperChar, Darco KB-B, Norit B Supra, Norit USP XX by Wurster and co-workers **(VanDer Camp et al., 2004)**. Langmuir fits best the results of adsorption of phenobarbital onto activated carbon Norit USP XX, Ch3J, and MI that presented a high value R^2 of 0.99,

followed by Temkin and then the Freundlich model according to Gallardo and co-workers **(Mafull et al., 2014)**.

III. Adsorption onto Covalent Organic Frameworks (COFs)

All measurements in the sections adsorption kinetics and adsorption of pharmaceuticals by COFs in real water were performed by duplicate. Three measurements were performed by duplicate for the section adsorption isotherms. Error bars correspond to the standard deviation of the mean.

III.1. Linearity limit

The limits of linearity (LOL) and detection (LOD) are established for the reliability of the analytical procedure for accurately assaying drug concentrations in water. Multiple analyses of analytes over an extended range of concentrations provide a measure of the ability of the analytical procedure to correctly identify known quantities in the water.

The linearity range is the concentration range of the standards between the detection limit (LOD) and the linearity limit (LL), which is the highest reliable level of measurement and can be used for quantification (limits of Beer–Lambert law). To meet the LL criterion, the correlation coefficient (R^2) must be greater than 0.990.

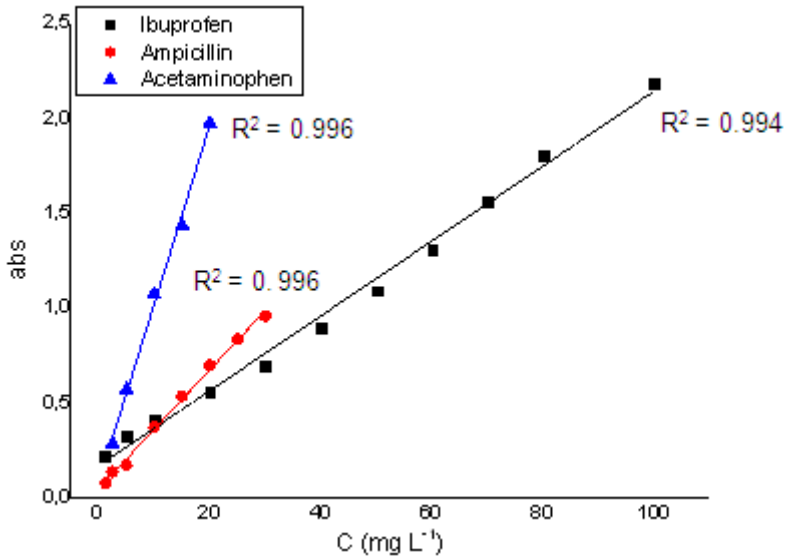

Figure 47 Calibration curves of ibuprofen (λ = 220 nm), ampicillin (λ = 207 nm) and acetaminophen (λ = 243 nm) at 21°C in ultrapure water at pH 6–7.

In the present study, 14 standard solutions were prepared with concentrations between 0 and 200 mg L^{-1}. The samples were analyzed by UV-Vis spectroscopy (λ = 220 nm for ibuprofen,λ = 207 nm for ampicillin, and λ = 243 nm for acetaminophen) and the absorptions vs concentrations were plotted (Figure 47). The obtained results have been processed using

the OriginLab software. They show that the chosen work domain satisfies the limits related to the Beer–Lambert law.

II.2. Adsorption kinetics

III.2.1. Determination of the equilibrium time

The procedure to determine the kinetics of adsorption is identical to that of determining equilibrium **(Baccar et al., 2012)**. The adsorbed quantity q_t of each pharmaceutical per mass of the adsorbate used (mg g^{-1}) in relation to the adsorbent–adsorbate contact time t(min) for each of the pharmaceuticals examined is presented in Figures 48, 49.

After 10 min, 45 min, and 1 h of contact between the TpBD-Me_2 COF adsorbent and the adsorbates ibuprofen, ampicillin and acetaminophen, respectively, the change of the liquid-phase concentration C_e of the adsorbate becomes insignificant and it can therefore be assumed that equilibrium has been reached. These time periods needed for reaching equilibrium are very short, and the quantity adsorbed (115 mg g^{-1}) is larger than what has been reported for the adsorption of ibuprofen on two types of activated carbons by Carvalho et al., where the quantities adsorbed for initial concentrations of 20, 40, 60 mg L^{-1} were 30, 60, and 90 mg g^{-1}, respectively, and the equilibrium time was about 2h30 min **(Mestre et al., 2007)**, and on metal–organic frameworks by Jhung et al., where the equilibrium time for all MOFs used was 4h and the quantity adsorbed varied between 50 and 82 mg g^{-1} for an initial concentration of 50 mg L^{-1} **(Seo et al, 2016)**. A short equilibrium time and a high adsorption capacity per unit weight of COF are very important for their possible application in commercial plants to adsorb pharmaceutical pollutants from contaminated water.

The dynamics of the adsorption of ibuprofen, acetaminophen, and ampicillin at an initial concentration of 50 mg L^{-1} on TpBD-Me_2 COF at a concentration of 333 mg L^{-1} are presented in Figure 48, where it is observed that about 70% of the total amount of ibuprofen and ampicillin are adsorbed during the first 20 min, and about 40% of the total amount of acetaminophen is adsorbed in the first 10 min. The quantity of pharmaceuticals adsorbed is larger with 100–115 mg g^{-1} for ibuprofen and ampicillin compared to 60 mg g^{-1} of acetaminophen. The initial adsorption process takes place very quickly; however, short times are needed to reach equilibrium of adsorption of the three pharmaceuticals, with 10, 45, and 60 min for ibuprofen, ampicillin, and acetaminophen, respectively.

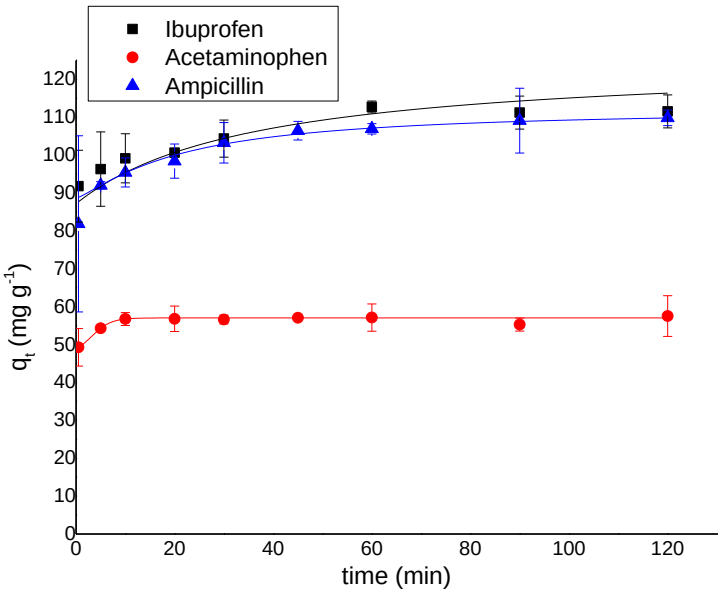

Figure 48 Adsorption kinetics expressed as quantity adsorbed q_t (mg g^{-1}) by TpBD-Me$_2$ as a function of time t of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (207nm) at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}; C(COF) = 333 mg L^{-1}).

The amount q_t (mg g^{-1}) of pharmaceuticals adsorbed at time t for each pharmaceutical on the TpBD-(CF$_3$)$_2$ COF is presented in Figure 49. The curves show that equilibrium is reached for all pharmaceuticals after 10 min, much faster than with TpBD-Me$_2$.

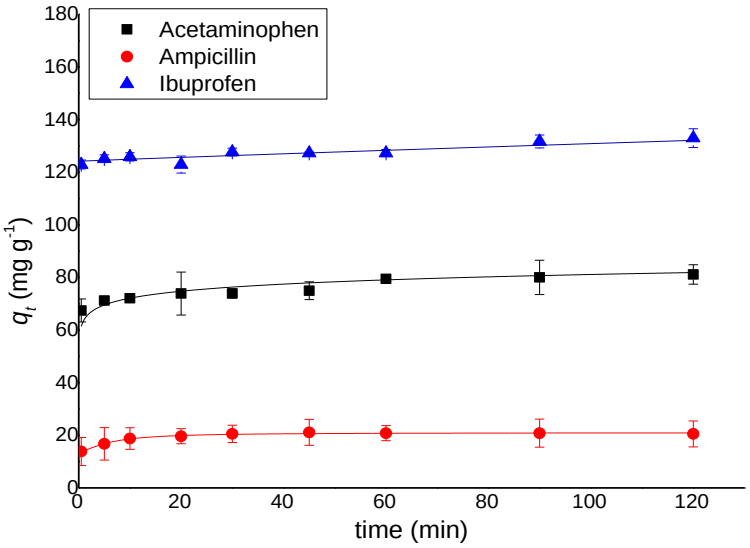

Figure 49 Adsorption kinetics expressed as quantity adsorbed q_t (mg g^{-1}) by TpBD-(CF$_3$)$_2$ as a function of time t of ibuprofen (λ = 220 nm), acetamenophen (λ = 243 nm), and ampicillin (λ = 207 nm) at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}; C(COF) = 333 mg L^{-1}).

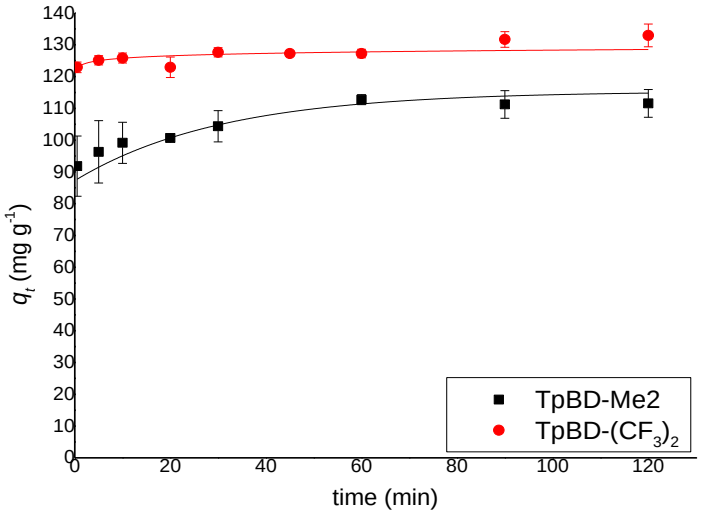

Figure 50 Ibuprofen adsorption kinetics expressed as the quantity adsorbed q_t (mg g^{-1}) by TpBD-$(CF_3)_2$ and TpBD-Me_2 at 21°C in ultrapure water at pH 6–7 (C_0(ibuprofen) = 50 mg L^{-1}; λ(ibuprofen) = 220 nm;C(COF) = 333 mg L^{-1}).

The dynamics of the adsorption of ibuprofen, acetaminophen, and ampicillin at initial concentration of 50 mg L^{-1} by TpBD-$(CF_3)_2$ COF at a concentration of 333 mg L^{-1} are presented in Figure 50. It is observed that about 85% of the total amount of ibuprofen is adsorbed in the first 10 min, reaching 90% at equilibrium with a maximum adsorbed quantity of 133 mg g^{-1}, higher to what was observed with TpBD-Me_2 (113 mg g^{-1}).

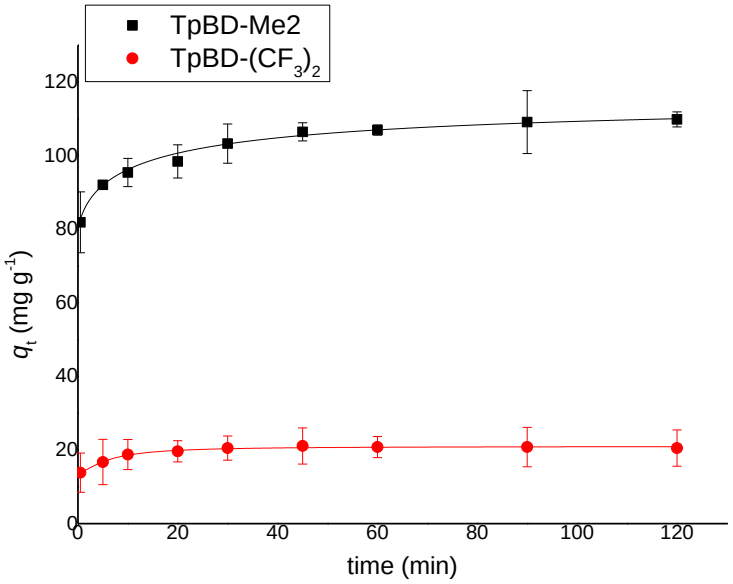

Figure 51 Ampicillin adsorption kinetics expressed as quantity adsorbed q_t (mg g^{-1}) by TpBD-$(CF_3)_2$ and TpBD-Me_2 at 21°C in ultrapure water at pH 6–7 (C_0(ampicillin) = 50 mg L^{-1}; λ(ampicillin) = 207 nm;C(COF) = 333 mg L^{-1}).

For ampicillin, about 12% of the total amount is adsorbed during the first 10 min, reaching only 14% at equilibrium with a maximum adsorbed quantity of 21 mg g^{-1} at an initial concentration of ampicillin of 50 mg L^{-1} and a concentration of TpBD-$(CF_3)_2$ of 333 mg L^{-1}. This amount is much smaller than that adsorbed on TpBD-Me_2 (110 mg g^{-1}; Figure 51).

For an initial concentration of acetaminophen of 50 mg L^{-1} and a concentration of TpBD-$(CF_3)_2$ and TpBD-Me_2 of 333 mg L^{-1}, about 48% of the total amount is adsorbed in the first 10 min and equilibrium is reached very quickly. The adsorption of acetaminophen is more important on TpBD-$(CF_3)_2$ with maximal quantity adsorbed of 80 mg g^{-1} compared with 57 mg g^{-1} on TpBD-Me_2 (Figure 52).

According to Figure 51 and Figure 52, TpBD-$(CF_3)_2$ adsorbs ibuprofen and acetaminophen well compared with TpBD-Me_2, in contrary to ampicillin, which is adsorbed better by TpBD-Me_2. This can be explained by the mixed hydrophilic/lipophilic character of TpBD-Me_2. TpBD-$(CF_3)_2$ is much more lipophilic, and does not adsorb well hydrophilic ampicillin (20 mg g^{-1} adsorbed at equilibrium). Other factors such as the size of the ampicillin molecule can also contribute.

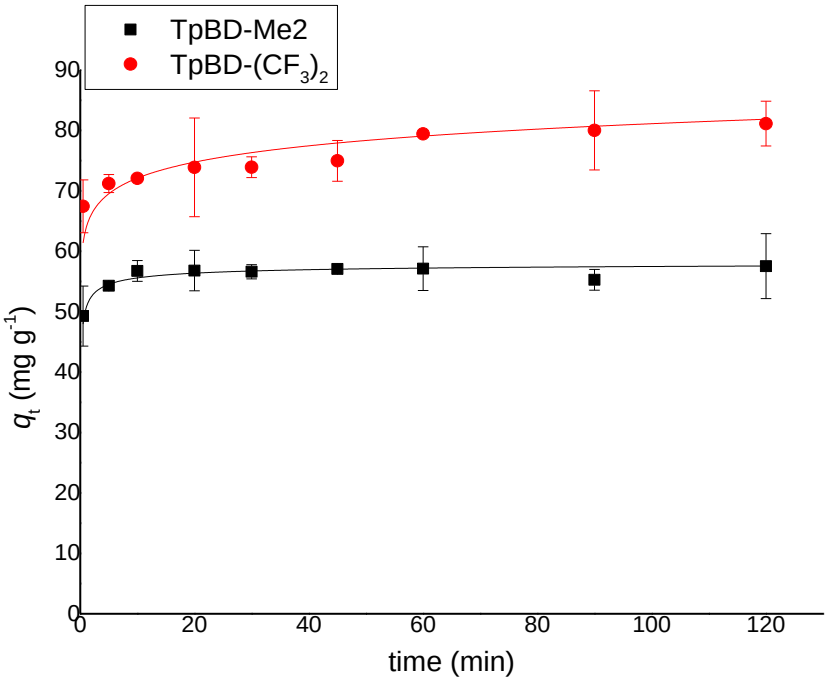

Figure 52 Acetaminophen adsorption kinetics expressed as the quantity adsorbed q_t (mg g^{-1}) by TpBD-$(CF_3)_2$ and TpBD-Me_2 at 21°C in ultrapure water at pH 6–7 (C_0(acetaminophen) = 50 mg L^{-1}; λ(acetaminophen) = 243 nm; C(COF) = 333 mg L^{-1}).

The difference between adsorbed quantities of ibuprofen, ampicillin, and acetaminophen at an initial concentration of 50 mg L^{-1} by the COFs TpBD-Me_2 and TpBD-$(CF_3)_2$ at the concentration of 333 mg L^{-1} is due to the lipophilicity of the drugs, which plays a larger role in the adsorption. The structure of the COFs is as well influencing the adsorption by the size of its particles. Indeed, the smaller size, the larger contact surface, which will increase the retention capacity. In addition, this surface increases because of the porous character of the COFs (**Ala, 2009)**. Also, the size of the pharmaceutical molecules can greatly influence the process of adsorption by their arrangement on the surface of the COFs, as it has been shown by the vertical fixation of acid and alcohol molecules by the carboxylic group (COOH) and by the hydroxyl (OH), respectively, in the case of high concentration of adsorbate **(Bekouche, 2003)**.

III.2.2. Effect of the pharmaceutical products concentration on the adsorption

The study of the adsorption equilibrium allows evaluating the capacities of the material to adsorb various molecules. The thermodynamic equilibrium is achieved with a rate depending not only on the rate at which the constituents of the mixture to be separated diffuse in the adsorbent and in the fluid, but also on the adsorbent–adsorbate interaction. This equilibrium is also closely related to the concentration of the adsorbate. It is therefore important to determine the optimum required for the adsorption study (Figures 53, 54).

The initial pharmaceutical product concentration is an important factor that affects the quantity of ibuprofen adsorbed, which can also give important informations on the driving force to transport the adsorbate to the adsorbent surface. The driving force increases with increasing concentration of ibuprofen in the solution and the higher probability of collision between the adsorbate and the adsorbent surface (**Khalir et al., 2011)**. In order to study the effect of adsorbate dosage on the quantity of ibuprofen adsorbed, a serie of adsorption experiments was carried out with different ibuprofen concentrations, varying from 50 to 400 mg L^{-1} and a constant concentration of COF at 333 mg L^{-1}.

As shown in Figures 53, 54, the quantity of ibuprofen adsorbed by the COFs increases with the increase in the initial concentration of ibuprofen, which can be explained by the active sites available on the COF surface to adsorb a higher amount of ibuprofen, confirming that the initial adsorbate concentration is important in the relative adsorption of the pharmaceuticals on the COFs. Similar results of adsorption have been reported on activated carbon (**Mukoko et al., 2015)**, alumina nanoparticles (**Banerjee et al., 2017; Pekel et al., 2002),** and wheat bran (**Ata et al., 2013).**

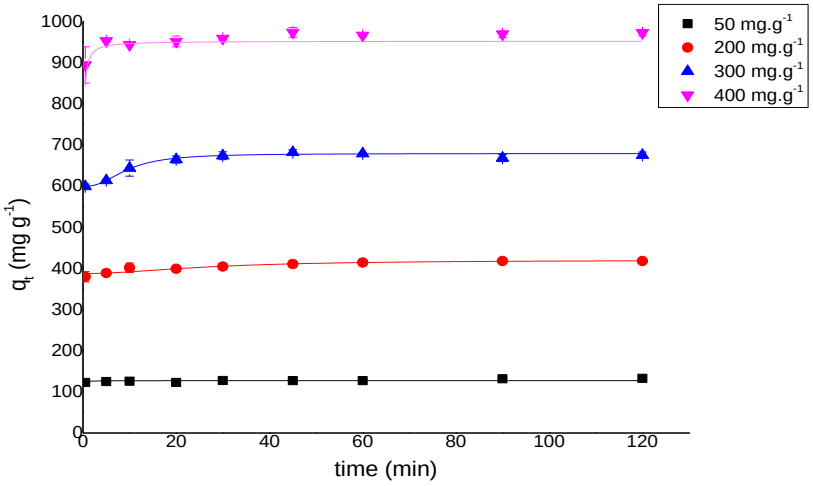

Figure 53 Concentration effect of ibuprofen (λ = 220 nm) on the quantity adsorbed q_t (mg g^{-1}) by TpBD-$(CF_3)_2$ at 21°C in ultrapure water at pH 6–7, (C_0(ibuprofen)= 50, 200,300,400 mg L^{-1}; C(COF)=333 mg L^{-1}).

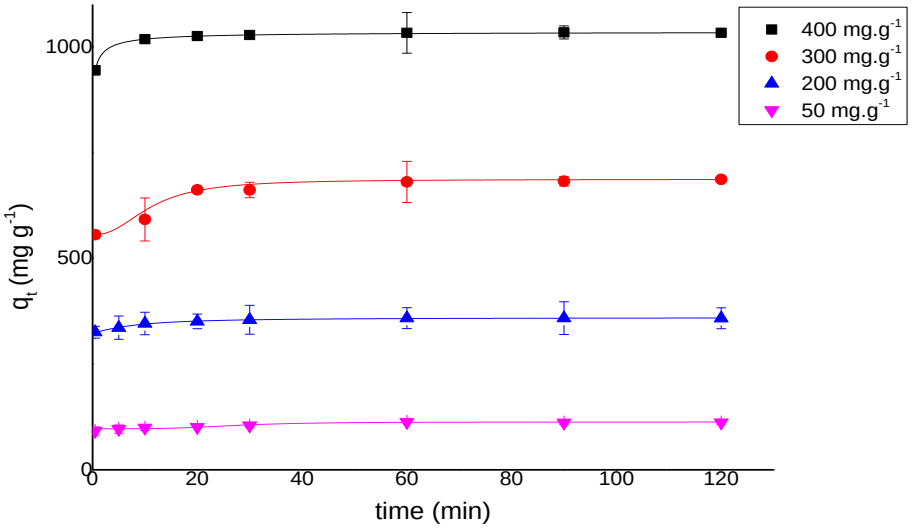

Figure 54 Concentration effect of ibuprofen (λ = 220 nm) on the quantity adsorbed qt (mg g^{-1}) by TpBD-Me_2 at 21°C in ultrapure water at pH 6–7 (C_0(ibuprofen)= 50, 200,300,400 mg L^{-1}; C(COF)=333 mg L^{-1}).

As shown in Figure 53, the amount of ibuprofen adsorbed by TpBD-$(CF_3)_2$ increased from 127 to 414, 675, and 967 mg g^{-1} as the ibuprofen concentration was increased from 50 to 200, 300 and 400 mg L^{-1}, respectively. As shown in Figure 54, the amount of ibuprofen adsorbed by TpBD-Me_2 increased from 112 to 358, 680, and 1032 mg g^{-1} as the ibuprofen concentration was increased from 50 to 200, 300, and 400 mg L^{-1}, respectively. These results showed that the COFs adsorbed ibuprofen well and hold a good affinity to attract it even

when the initial concentration is higher and reached 400 mg L^{-1}, with a slight preference of TpBD-$(CF_3)_2$, due probably to the influence of the higher surface area of TpBD-$(CF_3)_2$ (870 m^2 g^{-1}) as compared to TpBD-Me_2 (520 m^2 g^{-1}), confirming also the effect of the type of adsorbent on the adsorption **(Jorgensen, 1979)**. These results show that COFs are good candidates to purify water contaminated by pharmaceutical pollutants.

III.2.3. Modeling of adsorption results

III.2.3.1. Pseudo first-order kenitic

The experimental kinetic results were fitted with the pseudo first-order equation **(Lagergren, 1898)**:

$$q_t = q_e\left(1 - e^{-k_1 t}\right) \qquad (6)$$

where k_1(min^{-1}) is the pseudo-first order rate constant.

The plots given by ln(q_e–q_t) as a function of time are presented in Figure 55 and Figure 56, relative to the pseudo-first-order kinetics, for the adsorption of ibuprofen, ampicillin and acetaminophen at an initial concentration of 50 mg L^{-1} by TpBD-Me_2 and TpBD-$(CF_3)_2$ at a concentration of 333 mg L^{-1}.

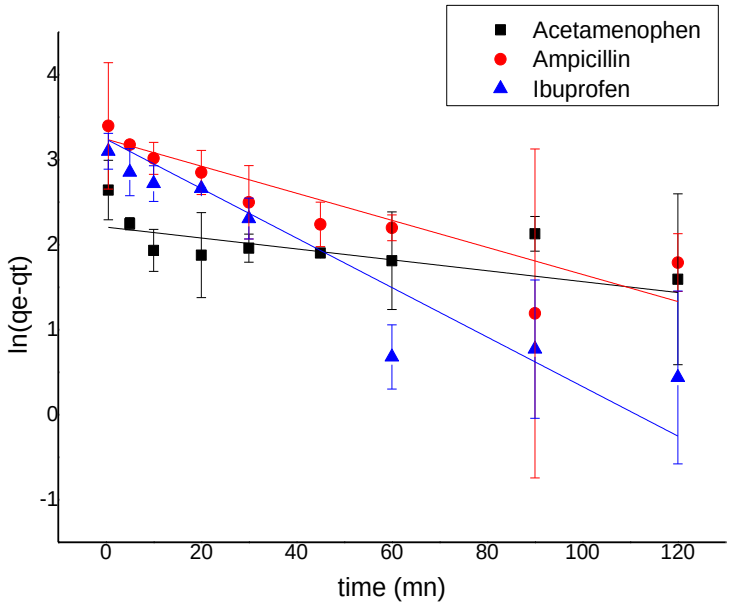

Figure 55 Pseudo-first-order kinetic results on the removal of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (λ = 207 nm) by TpBD-Me_2 at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}; C(COF) = 333 mg L^{-1}).

A large difference can be observed between experiment and theory using the Lagergren equation and all theoretical results were found smaller than the experimental values for the adsorption of ibuprofen, ampicillin and acetaminophen onto TpBD-Me_2 and TpBD-$(CF_3)_2$.

The correlation coefficients (R^2) for the pseudo-first-order kinetic model were < 0.896 for all pharmaceuticals, indicating that the pseudo first-order kinetic model does not describe adequately the adsorption process (Tables 21, 22).

Table 21 Pseudo-first-order kinetic parameters for ibuprofen, acetaminophen, and ampicillin at an initial concentration of 50 mg L^{-1} by TpBD-Me_2 at a concentration of 333 mg L^{-1} at 21°C and pH= 6–7.

Sample	k_1(min^{-1})	R^2	$q_{e,calc}$ (mg g^{-1})	$q_{e,exp}$(mg g^{-1})
Iburofen	0.0553	0.896	19	113
Acetaminophen	0.0069	0.155	9	58
Ampicillin	0.0553	0.697	33	109

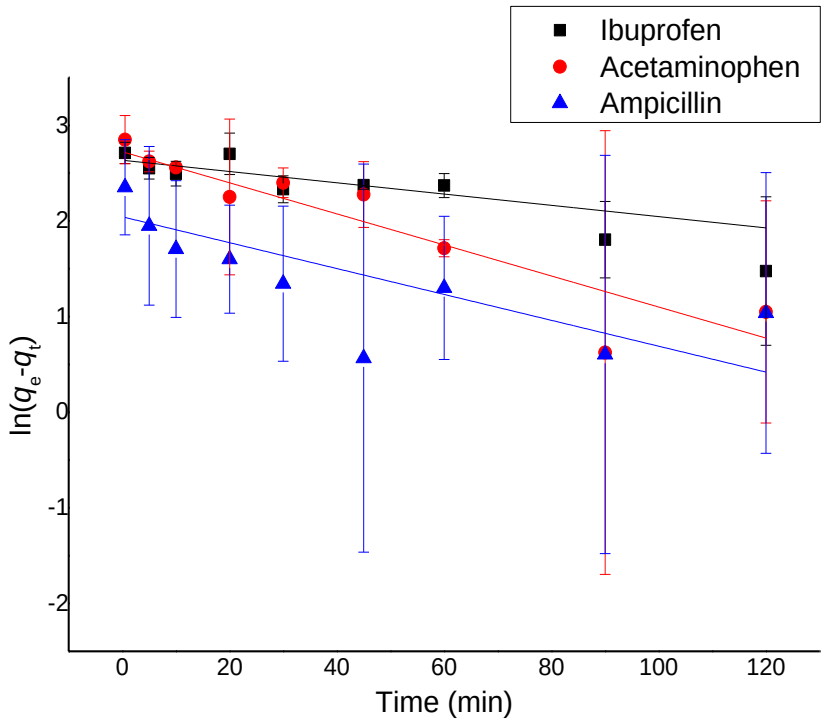

Figure 56 Pseudo-first-order kinetic results on the removal of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (λ = 207 nm) by TpBD-$(CF_3)_2$ at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}; C(COF) = 333 mg L^{-1}).

Table 22 Pseudo-first order kinetic parameters for ibuprofen, acetaminophen, and ampicillin at an initial concentration of 50 mg $L^{-1}$by TpBD-$(CF_3)_2$ at a concentration of 333 mg L^{-1} at 21°C and pH=6–7.

Sample	k_1 (min^{-1})	R^2	$q_{e,calc}$ (mg g^{-1})	$q_{e,exp}$(mg g^{-1})
Iburofen	0.0207	0.896	15	138
Acetaminophen	0.0392	0.864	16	85
Ampicillin	0.023	0.548	6	25

III.2.3.2. Pseudo-second-order kinetics

The experimental kinetic results were fitted with the pseudo-second-order equation **(Ho and McKay, 1999)**:

$$q_t = 1 + \frac{q_e^2 k_2 t}{1 + q_e k_2 t}$$

The initial rate of adsorption h is given by equation:$h = k_2 q_e^2$, where k_2 (g mg^{-1} min^{-1}) is the pseudo-second-order rate constant.

The plots given by t/q_t as a function of time are presented in Figure 57 and Figure 58, relative to the pseudo-second-order kinetics, for the adsorption of ibuprofen, ampicillin and acetaminophen at an initial concentration of 50 mg L^{-1} by TpBD-Me_2 and TpBD-$(CF_3)_2$ at a concentration 333 mg L^{-1}.

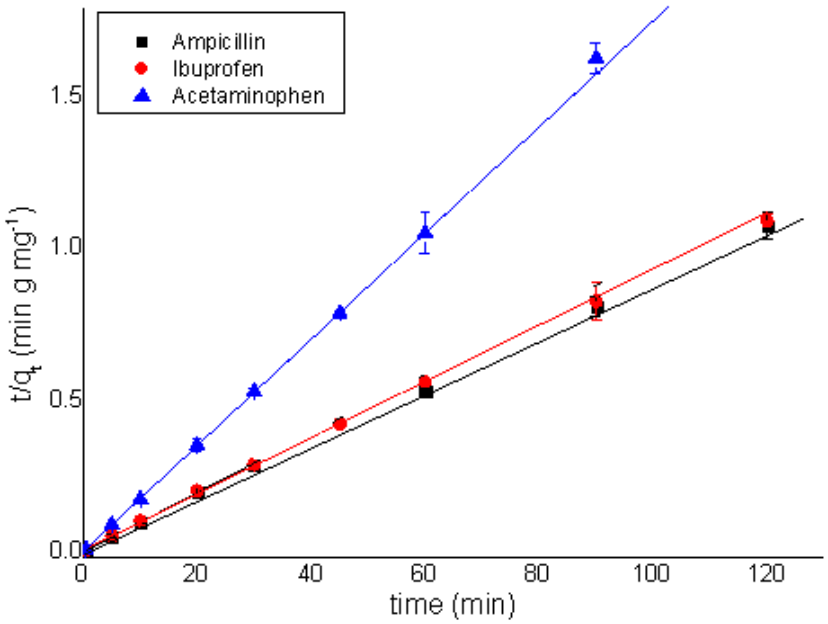

Figure 57 Pseudo-second-order kinetic results on the removal of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (λ = 207 nm) by TpBD-Me_2 at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}; C(COF) = 333 mg L^{-1}).

The k_2 and q_e values determined from the slope and intercept of the plot t/q_t vs. t are presented in Table 23 and Table 24 along with the corresponding correlation coefficients. The correlation coefficient (R^2) values for the pseudo-second-order kinetic model are 0.999 for all pharmaceuticals, indicating the applicability of the model to describe the adsorption process.

Table 23 Pseudo-second-order kinetic parameters for ibuprofen, acetaminophen, and ampicillin at an initial concentration of 50 mg L^{-1} by TpBD-Me_2 at a concentration of 333 mg L^{-1} at 21°C and pH=6–7.

Sample	k_2 (g mg^{-1} h^{-1})	R^2	h (mg g^{-1} h^{-1})	$q_{e,calc}$ (mg g^{-1})	$q_{e,exp}$ (mg g^{-1})
Iburofen	0.0064	0.999	100	125	113
Acetaminophen	0.289	0.999	1000	59	58
Ampicillin	0.0062	0.999	77	111	109

The pseudo-second-order rate constant k_2 of adsorption by TpBD-Me_2 at a concentration of 333 mg L^{-1} of acetaminophen is 0.289 g mg^{-1} h^{-1}, which is higher than for ibuprofen (0.0064 g mg^{-1} h^{-1}) and ampicillin (0.0062 g mg^{-1} h^{-1}) at an initial concentration of pharmaceuticals of 50 mg L^{-1}. The pseudo-second-order rate constant k_2 of adsorption by TpBD-$(CF_3)_2$ at a concentration of 333 mg L^{-1} of ampicillin is 0.133 g mg^{-1} h^{-1}, which is higher than for acetaminophen (0.007 g mg^{-1} h^{-1}) and ibuprofen (0.0072 g mg^{-1} h^{-1}) at an initial concentration of pharmaceuticals of 50 mg L^{-1}. The calculated q_e value according to the pseudo-second-order kinetic model of adsorption of ibuprofen, ampicillin, and acetaminophen by TpBD-Me_2 and TpBD-$(CF_3)_2$ agreed well with the experimental data, as shown in Table 23 and Table 24, respectively. The similar high adsorbed quantities presented by ibuprofen and ampicillin compared to acetaminophen confirm their high affinity towards TpBD-Me_2 as shown in Figure 48, which can probably due to their high lipophilic characters compared to acetaminophen.

The initial rate of adsorption h for acetaminophen is 1000 mg g^{-1} h^{-1}, which is higher than for ibuprofen (100 mg g^{-1} h^{-1}) and ampicillin (76.92 mg g^{-1} h^{-1}), allowing to confirm the high affinity and binding capacity of TpBD-Me_2 for acetaminophen which can be explained also by its insolubility in pure water **(Lechat et al., 1982)**. TpBD-Me_2 probably has a high attraction towards hydrophobic products **(Beausse et al., 2004)**.

For the adsorption by TpBD-$(CF_3)_2$, the initial rate is similar for acetaminophen and ampicillin (50 mg g^{-1} h^{-1} and 56 mg g^{-1} h^{-1}, respectively), but higher for ibuprofen with 143 mg g^{-1} h^{-1}, indicating the high affinity and binding capacity of TpBD-$(CF_3)_2$ toward ibuprofen. To summarize, the adsorption of ibuprofen, ampicillin, and acetaminophen at a

concentration of 50 mg L^{-1} by TpBD-Me_2 and TpBD-$(CF_3)_2$ at a concentration of 333 mg L^{-1} was better described by the pseudo-second-order kinetic model than with the pseudo-first-order kinetic model.

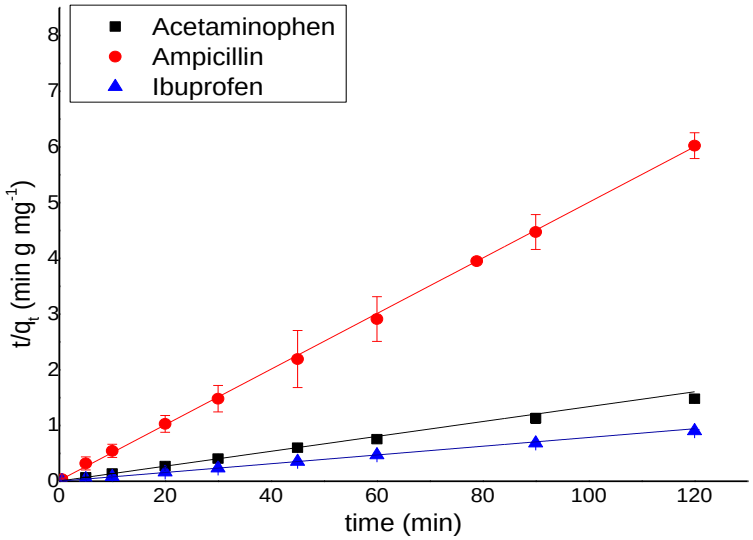

Figure 58 Pseudo-second-order kinetic results on the removal of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (λ = 207 nm) by TpBD-$(CF_3)_2$ at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}; C(COF) = 333 mg L^{-1}).

Table 24 Pseudo-second order kinetic parameters for ibuprofen, acetaminophen, and ampicillin at an initial concentration of 50 mg L^{-1} by TpBD-$(CF_3)_2$ at a concentration of 333 mg L^{-1} at 21°C and pH=6–7.

Sample	k_2 (g mg^{-1} h^{-1})	R^2	h (mg g^{-1} h^{-1})	$q_{e,calc}$ (mg g^{-1})	$q_{e,exp}$ (mg g^{-1})
Iburofen	0.007	0.999	143	143	138
Acetaminophen	0.007	0.999	50	83	85
Ampicillin	0.133	0.999	56	20	25

III.2.3.3. Intra-particle diffusion

Since the pseudo-first-order and pseudo-second-order kinetic models do not reveal the adsorption diffusion mechanism, the intraparticle diffusion model (**Weber, 1963**) was further used to define the rate-controlling step(s). As shown by the model, if the rate-limiting step of the adsorption process is intraparticle diffusion, the plots of q_t versus $t^{1/2}$ will be a straight line, which will pass through origin **(Wenjie, 2017)**. Figure 59 and 60 show this plot for each COF.

According to the model, if the data exhibit multilinear plots, then two or more steps influence the process. The plots q_t versus $t^{1/2}$ for the adsorption of ibuprofen, acetaminophen, and ampicillin at an initial concentration of 50 mg L^{-1} by TpBD-Me_2 and TpBD-$(CF_3)_2$ at the concentration 333 mg L^{-1} do not show a linear relationship passing by the origin, but rather a multimodal one with three distinct regions (Figure 59, 60), indicating that intraparticle diffusion is not the sole rate-limiting step and that adsorption is affected by more than one process (**Lopicic et al., 2016)**, but only one is the rate limiting in a particular time range **(Lopicic et al., 2016; Cheung et al., 2007)**.

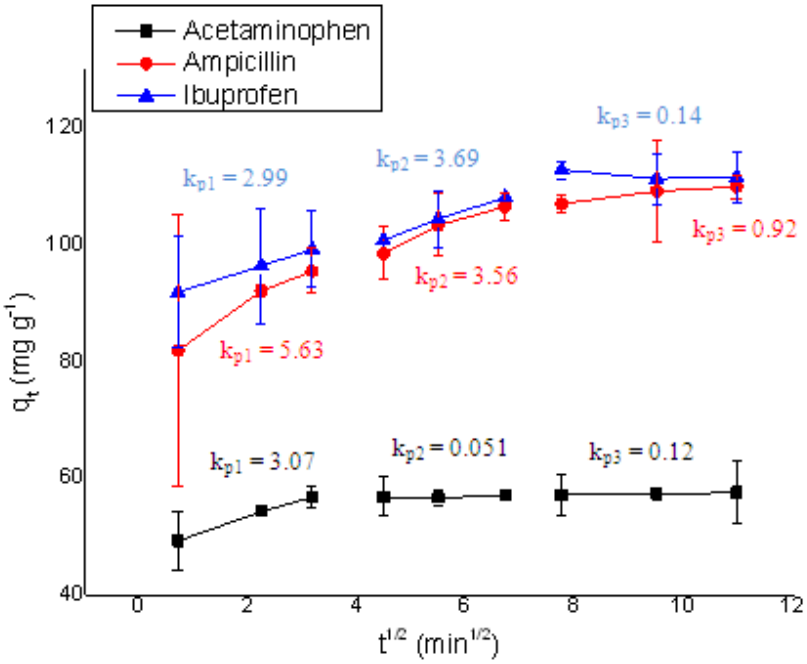

Figure 59 Intra–particle diffusion model for the adsorption kinetics of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (λ = 207 nm) by TpBD-Me_2 at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}; C(COF) = 333 mg L^{-1}).

The initial curved region corresponds to the external surface adsorption, in which the drugs diffuse through the solution to the external surface of the adsorbent. The second stage relates to the gradual adsorption reflecting intra-particle diffusion as the rate-controlling step. The final plateau region points out the surface adsorption and the equilibrium stage, in which the intra-particle diffusion starts to slow down and level out (**Daiffullah et al., 2007; Hamadaoui et al., 2007; Saha, 2012**, **Chowdhury, 2010**). Based on the literature **(Deniz, 2013)**, the present results (Figure 59, 60 and Table 25, 26) reflect that intra-particle diffusion is involved in the adsorption process, but it is not the only rate-limiting step and the other step(s) might also be involved.

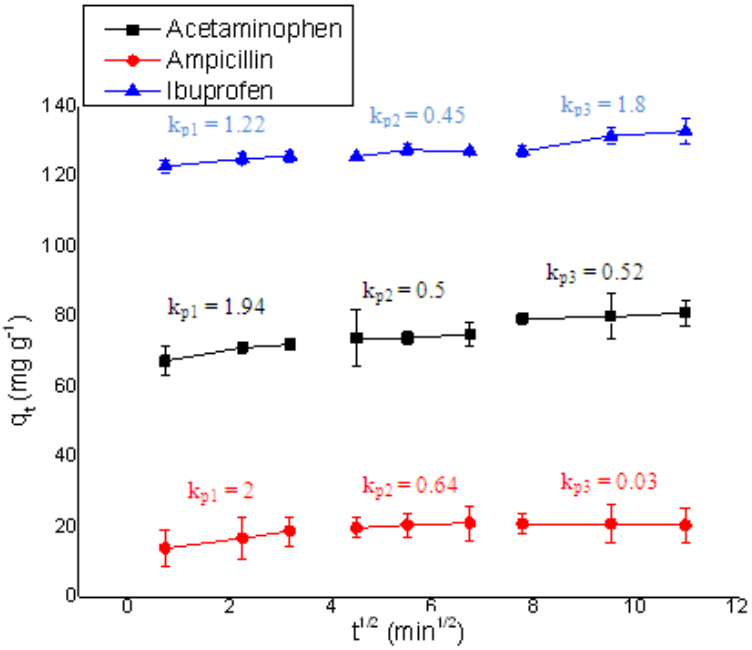

Figure 60 Intra-particle diffusion model for the adsorption kinetics of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (λ = 207 nm) by TpBD-$(CF_3)_2$ at 21°C in ultrapure water at pH 6–7(C_0(pharmaceutical) = 50 mg L^{-1}; C(COF) = 333 mg L^{-1}).

The multilinearity of the intra-particle scattering curves is described in the literature for many adsorbate–adsorbent pairs: metal–natural material cations **(Gherbi, 2008),** diuron and metribuzin–activated carbon **(Boucif, 2009),** biosorption kinetics of Cu(II) onto Prunus persica stones (PSs) by Kijevcanin et al., and Ofomaja in biosorption of Pb(II) onto mansonia wood sawdust **(Lopicic et al., 2016 ; Ofomaja, 2010)**. The slope of the linear part indicates the rate of adsorption; the lowest slope corresponds to the slowest adsorption process. The factors k_p, which relate to the three parts, are presented in Tables 25, 26. Note that in coadsorption, the less soluble compounds are adsorbed more easily **(Gendrault, 2004)**. The intra-particle velocity constants k_i and the correlation coefficients for these three parts, in each case, are presented in Table 25 and Table 26. According to the obtained results, the values of k_{p1} are relatively close to the values of k_{p2} for ibuprofen and ampicillin, and k_{p2} is relatively close to k_{p3} for acetaminophen. The k_{p3} values are very low compared to k_{p1} and k_{p2} for ibuprofen and ampicillin, and k_{p3} is higher than $k_{p1}$and k_{p2} for acetaminophen (Figure 59). The values of k_{p2} are close to values of k_{p3} in the case of the adsorption of pharmaceuticals onto TpBD-$(CF_3)_2$ and they are lower compared with the k_{p1} values except k_{p3} of ibuprofen, which is at 1.8 mg g^{-1} min$^{-1/2}$ higher than the k_{p3} of acetaminophen and ampicillin (Figure 60). It can be deduced that there are two processes that control the rate of pharmaceutical adsorption onto COFs. The first one is probably the diffusion to the exterior surface of the adsorbent,

resulting in the fastest adsorption rate. The second portion of the plot seems to refer to the diffusion into the COF pores (with the lowest slope).

Table 25 Intra-particle diffusion parameters for ibuprofen, acetaminophen and ampicillin at an initial concentration of 50 mg L^{-1} by TpBD-Me_2 at a concentration of 333 mg L^{-1} at 21°C and pH=6–7.

Sample	k_{p1} (mg $g^{-1}min^{-1/2}$)	R^2	k_{p2} (mg $g^{-1}min^{-1/2}$)	R^2	k_{p3} (mg g^{-1} $min^{-1/2}$)	R^2
Iburofen	2.99	0.999	3.69	1	0.14	0.92
Acetaminophen	3.07	0.997	0.05	0.998	0.12	0.991
Ampicillin	5.63	0.98	3.56	0.969	0.92	0.95

The values of the correlation coefficients R^2 for the intra-particle Weber–Morris diffusion model obtained for the adsorption of ibuprofen, acetaminophen and ampicillin at an initial concentration of 50 mg L^{-1} by TpBD-Me_2 and TpBD-$(CF_3)_2$ at a concentration of 333 mg L^{-1} are >0.920, except in the case of TpBD-$(CF_3)_2$, where the values of the correlation coefficients were 0.72 and 0.819 for ibuprofen and acetaminophen, respectively, in step 2, and 0.709 for ampicillin in step 3. According to these results, it is probable that the intra-particle scattering model fits the experimental values obtained.

Table 26 Intra-particle diffusion parameters for ibuprofen, acetaminophen, and ampicillin at an an initial concentration of 50 mg L^{-1} by TpBD-$(CF_3)_2$ at a concentration of 333 mg L^{-1} at 21°C and pH=6–7.

Sample	k_{p1} (mg g^{-1} $min^{-1/2}$)	R^2	k_{p2} (mg g^{-1} $min^{-1/2}$)	R^2	k_{p3} (mg g^{-1} $min^{-1/2}$)	R^2
Iburofen	1.22	0.978	0.45	0.72	1.8	0.933
Acetaminophen	1.94	0.957	0.50	0.819	0.52	0.947
Ampicillin	2.00	0.998	0.64	0.97	0.03	0.709

III.2.3.4. Reichenberg model

The Reichenberg equation **(Reichenberg, 1953)** was applied to investigate if the sorption proceeds via an external diffusion or an intraparticle diffusion mechanism **(Ahmad, 2005**). The Reichenberg equation can be expressed in the following form:

$$B_t = -0{,}4977 - \log(1 - F).$$

where the fractional attainment of equilibrium F is calculated by the equation : $F = \frac{q_t}{q_e}$

The plots B_t versus t for the adsorption of ibuprofen, acetaminophen and ampicillin at an initial concentration 50 mg L^{-1} by TpBD-Me_2 and TpBD-$(CF_3)_2$ at the concentration of 333 mg L^{-1} are shown in Figures 61, 62. The values of the correlation coefficients R^2 for the Reichenberg model are shown in Table 27

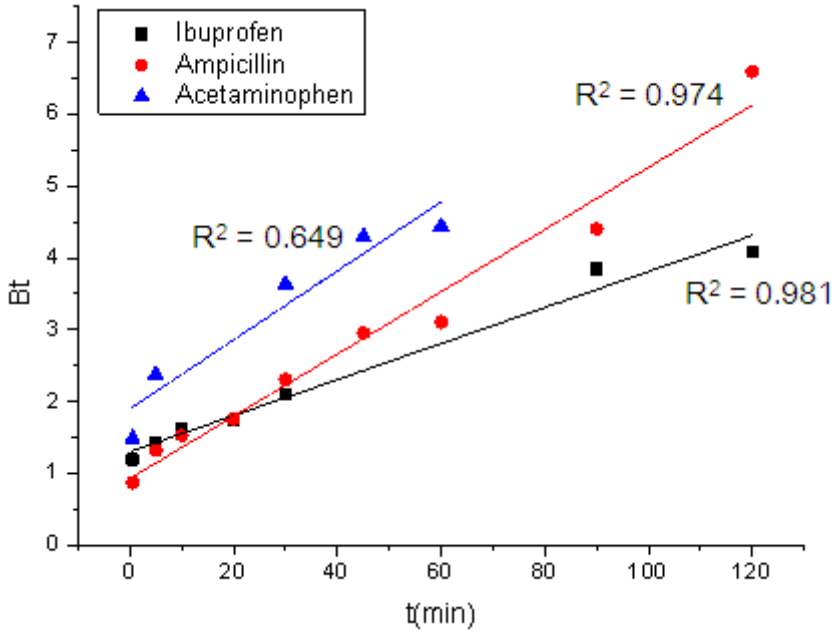

Figure 61 Reichenberg model for the adsorption kinetics of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (λ = 207 nm) by TpBD-Me_2 at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}; C(COF) = 333 mg L^{-1}).

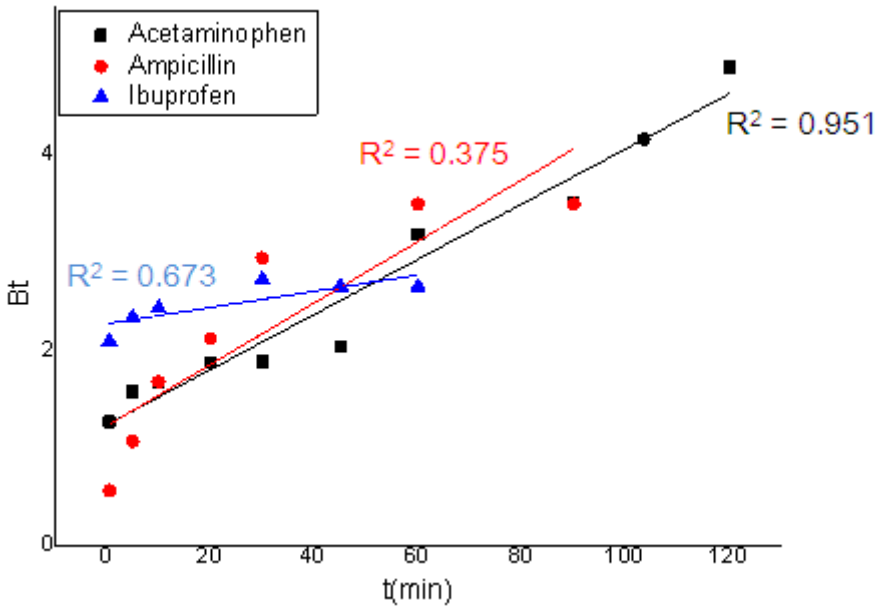

Figure 62 Reichenberg model for the adsorption kinetics of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (λ = 207 nm) by TpBD-$(CF_3)_2$ at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}; C(COF) = 333 mg L^{-1}).

Table 27 Correlation coefficient R^2 parameters of the Reichenberg model for ibuprofen, acetaminophen, and ampicillin at an initial concentration of 50 mg L^{-1} by TpBD-Me_2 and TpBD-$(CF_3)_2$ at a concentration of 333 mg L^{-1} at 21°C and pH=6–7.

		Ibuprofen	Acetaminophen	Ampicillin
R^2	TpBD-Me_2	0.981	0.649	0.974
	TpBD-$(CF_3)_2$	0.673	0.951	0.375

They indicate that the model of Reichenberg does not seem adequate for the adsorption process of the ibuprofen, ampicillin, and acetaminophen by TpBD-Me_2 and TpBD-$(CF_3)_2$.

III.2.3.5. Elovich equation

When the adsorbate ions and the surface sites of the adsorbent interact chemically through a second-order mechanism, the application of the Elovich equation may be appropriate **(Ho et al., 1998)**. The Elovich equation describes predominantly chemical adsorption on highly heterogeneous adsorbents, but the equation does not propose any definite mechanism for adsorbate–adsorbent interaction. The coefficients depend significantly on the amount of adsorbent **(Ho et al., 1998**). Figures 63, 64 show a plot of q_t versus ln*t* for the Elovich equation of different drugs at the concentration of 50 mg L^{-1}.

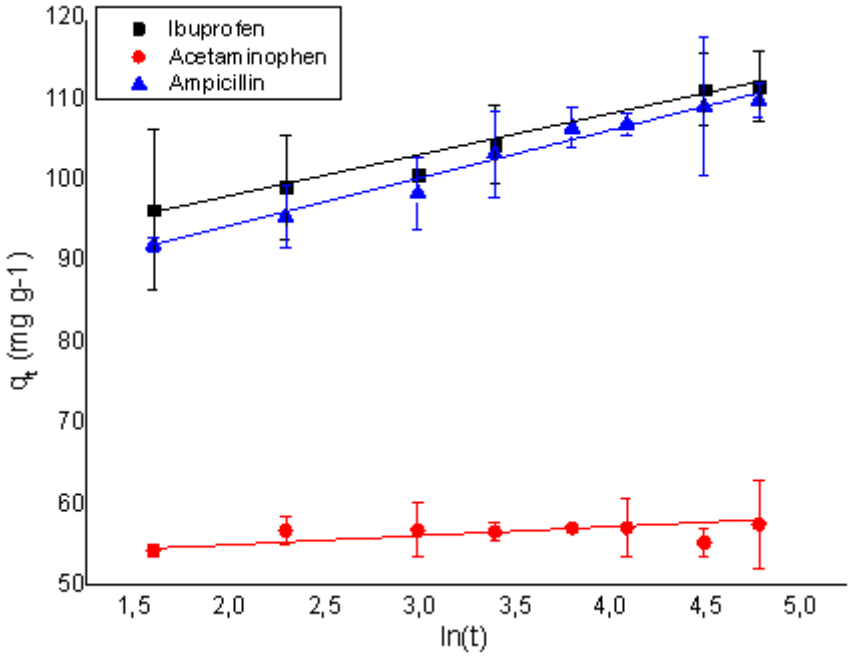

Figure 63 Elovich model for the adsorption kinetics of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (λ = 207 nm) by TpBD-Me_2 at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}; C(COF) = 333 mg L^{-1}).

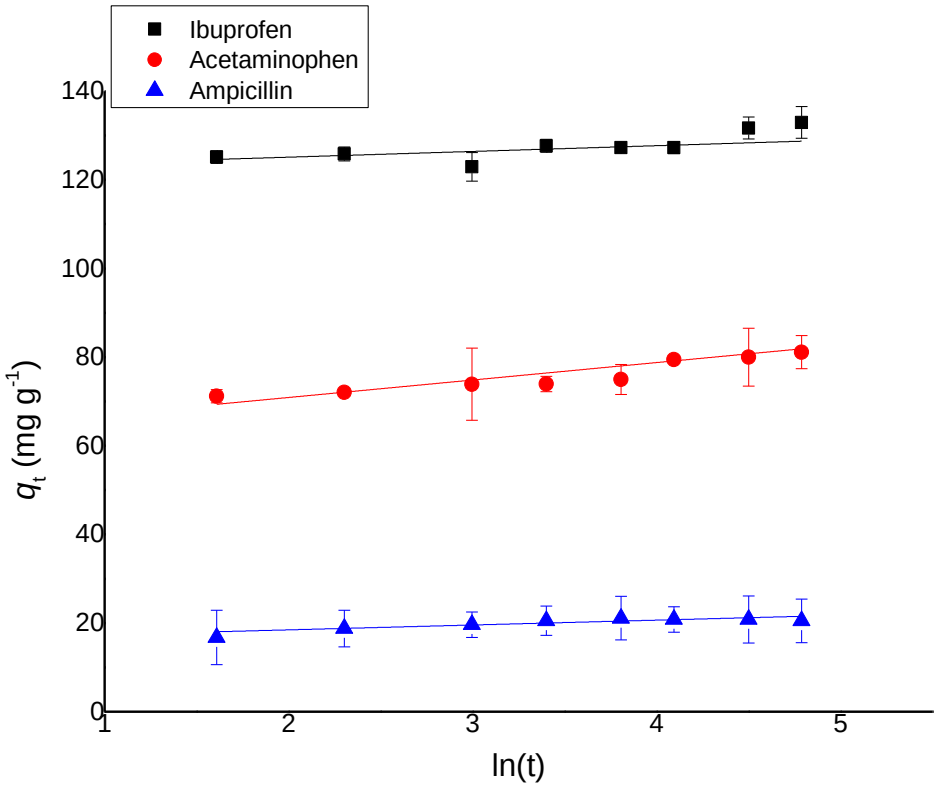

Figure 64 Elovich model for the adsorption kinetics of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (λ = 207 nm) by TpBD-$(CF_3)_2$ at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}; C(COF) = 333 mg L^{-1}).

The Elovich parameters for the adsorption of pharmaceuticals onto TpBD-Me_2 and TpBD-$(CF_3)_2$, such as the initial adsorption rate α (mg g^{-1} min^{-1}), the parameter $1/\beta$ (mg g^{-1}) that is linked to the number of sites available for adsorption, and the values of the correlation coefficients R^2, are shown in Table 28 and Table 29, respectively.

The results of the regression, shown in Table 28, show that the Elovich model does not seems applicable in the case of the adsorption process of ibuprofen, ampicillin and acetaminophen by TpBD-$(CF_3)_2$. The R^2 represented in Table 29 indicate that the Elovich model fits the experimental values obtained of the adsorption process of ibuprofen, ampicillin and acetaminophen by TpBD-Me_2 and TpBD-$(CF_3)_2$. The initial adsorption rate α of acetaminophen is much higher than what is obtained for the adsorption of ibuprofen and ampicillin onto TpBD-Me_2 as shown in Table 28, as well as, for its adsorption onto TpBD-$(CF_3)_2$ followed by ibuprofen and than ampicillin (Table 29). TpBD-$(CF_3)_2$ presented more available sites for acetaminophen compared to TpBD-Me_2, and its adsorption according to the

parameter β, 0.306 g mg^{-1} and 3.049 g mg^{-1} of both COFs as shown in Table 28, 29, contrary to what was obtained for the adsorption of ibuprofen and ampicillin, where TpBD-Me_2 presented more available sites for those both pharmaceutical than TpBD-$(CF_3)_2$.

Table 28 Elovich model parameters for ibuprofen, acetaminophen, and ampicillin at an initial concentration of 50 mg L^{-1} by TpBD-Me_2 at a concentration of 333 mg L^{-1} at 21°C and pH=6–7.

Sample	α (mg g^{-1} min^{-1})	β (g mg^{-1})	R^2
Ibuprofen	1.372x10^8	0.182	0.916
Acetaminophen	2.58309E+73	3.049	0.910
Ampicillin	0.049 x10^8	0.166	0.977

Table 29 Elovitch model parameters for ibuprofen, acetaminophen and ampicillin at an initial concentration of 50 mg L^{-1} by TpBD-$(CF_3)_2$ at a concentration of 333 mg L^{-1} at 21°C and pH=6–7.

Sample	α (mg g^{-1} min^{-1})	β (g mg^{-1})	R^2
Ibuprofen	1.79636E+22	0.422	0.612
Acetaminophen	1.86007E+92	0,306	0.873
Ampicillin	6.33 x 10^5	0.836	0.787

III.3. Adsorption isotherms

Adsorption isotherms are used for the characterization of porous solids and design of industrial adsorption processes **(Keller et al., 2005)**. Plotting the adsorption isotherms of a given system is a mean to characterize all the thermodynamic properties of the 2D layer on the surface **(Guesmi, 2005)**, which describes the phenomenom of retention of the substance from the aquatic environment to a solid phase and the interaction between adsorbate and adsorbent at constant pH and temperature.

In addition, isotherms help to find out the relationship between quantity of target compound adsorbed and the remaining concentration in liquid at the time of equilibrium **(Saruchi et al; 2016).**There are a wide variety of equilibrium isotherm models, such as Langmuir, Freundlich, Redlich–Peterson, Dubinin–Radushkevich, Temkin, Sips, and Flory–Huggins (two/three-parameter isotherm model).

In this study, the Langmuir, Freundlich, and Temkin models are used to describe the interdependence between the amount of adsorbed ibuprofen, acetaminophen, and ampicillin at an initial concentration of 50 mg L^{-1} by TpBD-Me_2 and TpBD-$(CF_3)_2$ at different

concentrations and at equilibrium concentration.

The Langmuir and Freundlich models are chosen to describe the adsorption process because they are the most frequently used isotherms due to their importance for explaining characteristics of adsorption **(Ji et al., 2012; Hameed et al., 2007)**. The Langmuir model describes in a simple way the formation of a monolayer of an adsorbate on a surface. Although the Langmuir model is very simple, it is widely used to represent the adsorption phenomenon in a large number of applications such as catalyst characterization and capture of pollutants by the adsorption process (**De Sá et al., 2017)**. The Freundlich model can be applied for non-ideal sorption on heterogeneous surfaces as well as multilayers sorption. The Freundlich model, however, accounts for the adsorption when there are more complex phenomena such as the presence of several adsorption sites on the surface, interaction between the adsorbate molecules in the liquid phase and the cooperative adsorption on the surface (**Liu et al, 2008)**. The Temkin model is used in the adsorption process of the liquid phase. It is linearizable and allows the determination of two parameters: the adsorbate–adsorbent equilibrium constant and the adsorption energy **(Ferrandon et al., 1995)**. The Temkin model is more particularly used for the determination of the adsorbent adsorption energy variation **(Kavitha et al., 2007)**.

III.3.1. Type of isotherm

The isotherms obtained following the protocol described in the Materials and Methods section are shown in Figure 65– 67. The data were obtained by varying the amounts of adsorbent for a fixed concentration of the pharmaceutical product and stirring times equal to the equilibrium time determined from the adsorption kinetics, which are 10 min, 45 min, and 1 h for ibuprofen, ampicillin, and acetaminophen, respectively, adsorbed by TpBD-Me_2, and10 min for all pharmaceuticals adsorbed by TpBD-$(CF_3)_2$.

Referring to the Giles classification **(Giles et al., 1960)**, the adsorption isotherms of pharmaceuticals on TpBD-Me_2 and TpBD-$(CF_3)_2$ (Figures 65, 66) are of type H (high affinity) for both ibuprofen and ampicillin. Step isotherms (type H) are observed with porous materials (**Butt et al., 2003)**. At low pressure, a single layer of molecules adsorbs to the surface as in the Langmuir adsorption. At intermediate pressure, multilayers start to form and the pores are filled. The saturation at high pressure is caused by the reduction of the effective surface area once the pores have been filled **(Butt et Al., 2003)**.

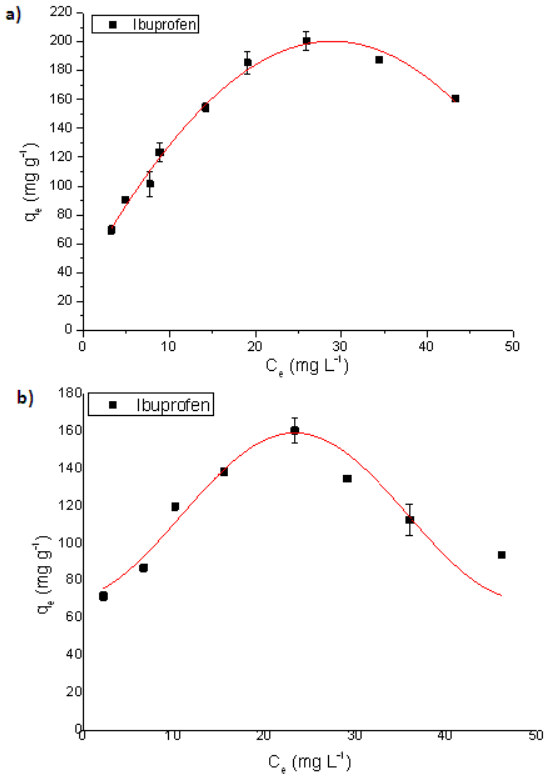

Figure 65 Adsorption isotherms of ibuprofen (λ = 220 nm) by (a) TpBD-Me_2 and (b) TpBD-$(CF_3)_2$ at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}).

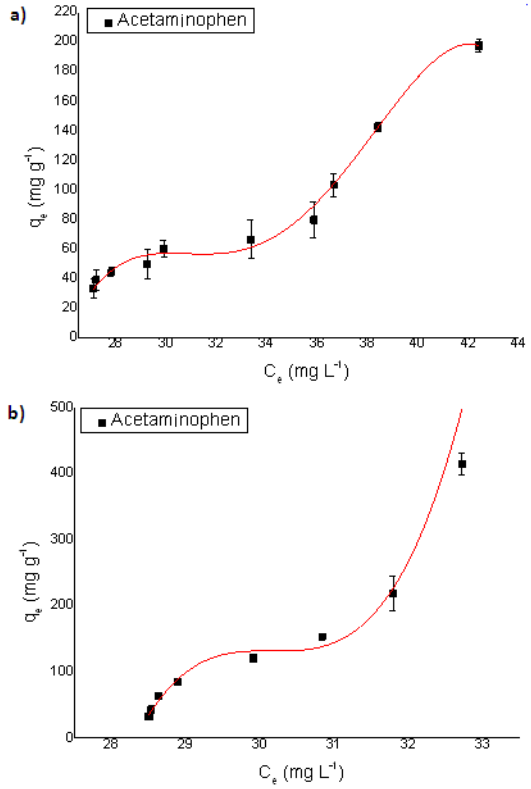

Figure 66 Adsorption isotherms of acetaminophen (λ = 243 nm) by (a) TpBD-Me_2 and (b) TpBD-$(CF_3)_2$ at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}).

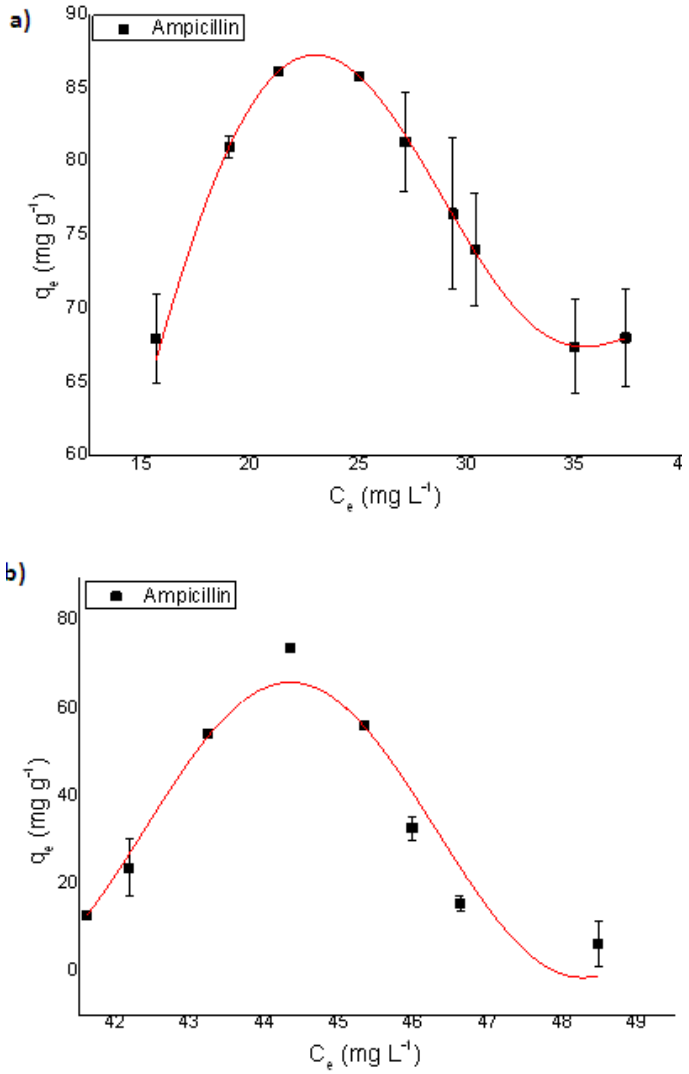

Figure 67 Adsorption isotherms of ampicillin (λ = 207 nm) by (a) TpBD-Me_2 and (b) TpBD-$(CF_3)_2$ at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}).

The type of isotherm for the adsorption of acetaminophen onto TpBD-Me_2 and TpBD-$(CF_3)_2$ is type L, under groups 3. Class L isotherms exhibit at low concentrations of the solution a downward concavity, which reflects a decrease in free sites as the adsorption of acetaminophen on the COFs progresses **(Belmouden, 2008)**.

This behavior is found in the case where the attractive forces between the adsorbed molecules are low **(Belmouden, 2008)**, and when the molecules are not oriented vertically but rather flat, which minimizes their lateral attraction **(Belmouden, 2008; Butt, 2003)**, so it is probable that the acetaminophen molecules cling flat onto the COF. An isotherm type L can also appear when the molecules are adsorbed vertically and when the adsorption competition between the solvent and the solute is weak **(Belmouden, 2008)**.

III.3.2. Isotherms Models

Three isotherm models related to adsorption equilibrium have been considered in the present study, i.e., Langmuir, Freundlich and Temkin. An adsorption isotherm is the presentation of the amount of solute adsorbed per unit weight of adsorbent as a function of the equilibrium concentration in the bulk solution at a constant temperature in a liquid–solid system. Langmuir, Freundlich, and Temkin adsorption isotherms were used for the description of adsorption data of ibuprofen, acetaminophen, and ampicillin at an initial concentration of 50 mg L^{-1} from liquid phase to solid, TpBD-Me_2 and TpBD-$(CF_3)_2$, at different concentrations between 25 µg/600 µL and 400 µg/600 µL at 21°C in ultrapure water at pH 6–7. The isotherms fit well the adsorption of pharmaceuticals onto COFs according to the literature such as the adsorption of pharmaceuticals onto pyrolyzed pulp mill sludge by Otero et al. **(Coimbra et al., 2015)**, onto pyrolyzed pulp mill sludge by Barlas et al. **(Vergili et al., 2009)**, and onto carbon materials by Rodríguez et al.**(Sotelo et al., 2012)**.

The different equation parameters and the underlying thermodynamic hypotheses of these isotherm models often give insight into both the adsorption mechanism and the surface properties and affinity of the adsorbents (**Crini et al., 2008)**.

III.3.3. Langmuir isotherm

The adsorption isotherms derived from the experimental data for each of the tested adsorbates and adsorbents are presented in Table 30 and Table 31.

The plots given by C_e/q_e as a function of C_e according to the Langmuir isotherm model for the adsorption of ibuprofen, ampicillin and acetaminophen at an initial concentration of 50 mg L^{-1} by TpBD-Me_2 and TpBD-$(CF_3)_2$ at different concentration are presented in Figure 68 and Figure 69.

The Langmuir isotherm model for the adsorption by TpBD-Me_2 fit better the experimental data for ibuprofen and ampicillin (Figure 68) based on the relatively high values of the correlation coefficient R^2 of 0.997 and 0.994, respectively, as opposed to the data of acetaminophen, with R^2 of 0.889 that does not fit the Langmuir model. The maximum adsorption capacity q_{max} derived for ibuprofen is 250 mg g^{-1}, which is higher than for ampicillin (q_{max}= 53 mg g^{-1}). The values of the maximum adsorption capacities show that TpBD-Me_2 exhibits good adsorption capacities of ibuprofen. Carvalho et al. obtained a maximum adsorption capacity q_{max} of 145 mg g^{-1} for ibuprofen adsorbed onto activated carbon **(Mestre et al., 2007)**, showing a lower value compared with the maximum adsorption

capacity in this study.The q_{max} obtained by Bychkovsky et al. for the adsorption of ampicillin onto cellulose oxide was 139 mg g^{-1} (**Zimnitsky et al., 2004)**, higher than the q_{max} of ampicillin adsorbed onto TpBD-Me_2.

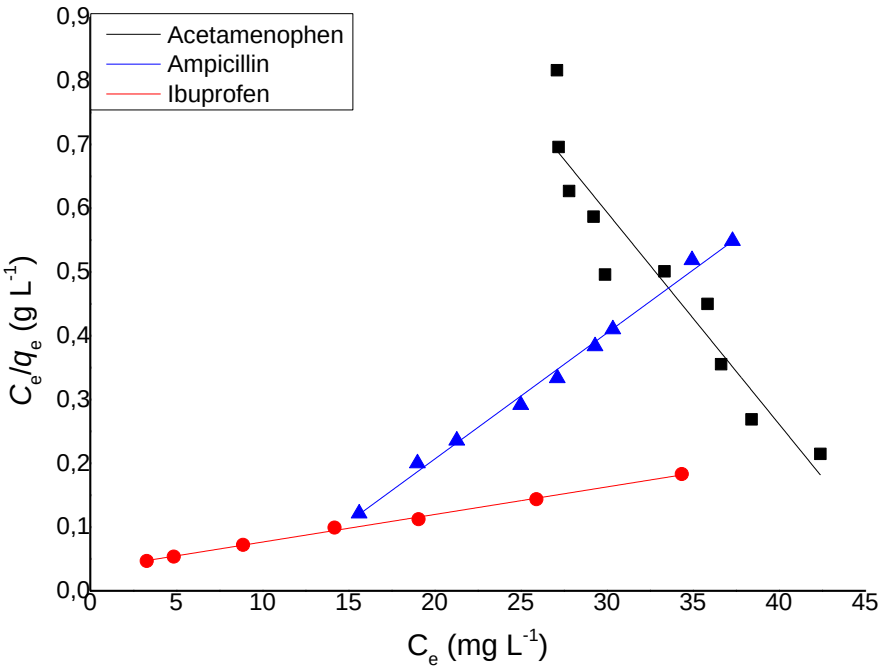

Figure 68 Langmuir isotherm of adsorption of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (λ = 207 nm) by TpBD-Me_2 at different concentrations at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}).

Table 30 Langmuir isotherm parameters for adsorption of ibuprofen, acetaminophen, and ampicillin at an initial concentration of 50 mg L^{-1} by TpBD-Me_2 at different concentrations at 21°C and pH 6–7.

	b (L mg^{-1})	1/b (mg L^{-1})	q_{max} (mg g^{-1})	R^2
Ibuprofen	0.12	8	250	0.997
Acetaminophen	0.02	482	303	0.889
Ampicillin	0.1	10	53	0.994

The b factor values related to the dissociation constant of the adsorbate or Langmuir constant K_d (1/b) are all less than unit (b<1), showing the good affinity of TpBD-Me_2 for ibuprofen compared with acetaminophen and ampicillin.

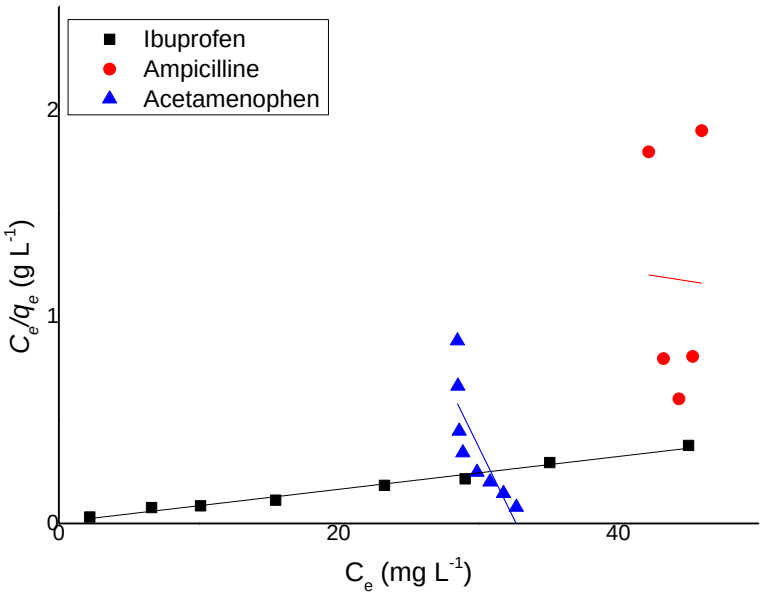

Figure 69 Langmuir isotherm of adsorption of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (λ = 207 nm) by TpBD-$(CF_3)_2$ at different concentrations at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}).

Table 31 Langmuir isotherm parameters for adsorption of ibuprofen, acetaminophen and ampicillin at an initial concentration of 50 mg L^{-1} by TpBD-$(CF_3)_2$ at different concentrations at 21°C and pH 6–7.

	b (L mg^{-1})	1/b (mg L^{-1})	q_{max} (mg g^{-1})	R^2
Ibuprofen	0.17	0.86	142.86	0.985
Acetaminophen	0.031	32.73	7.25	0.669
Ampicillin	0.024	40.86	1.30	0.395

The Langmuir isotherm model (Figure 69) for the adsorption by TpBD-$(CF_3)_2$ fits best the experimental data for ibuprofen, based on its relatively high values of the correlation coefficient R^2 of 0.985. The values of the maximum adsorption capacities (q_{max}) show that the TpBD-$(CF_3)_2$ exhibits good adsorption capacities with respect to ibuprofen. According to values of the correlation coefficient R^2 of acetaminophen (0.669) and ampicillin (0.395), the experimental data do not fit the Langmuir model. Ibuprofen presents a high q_{max} of 143 mg g^{-1}.

The *b* factors determined are less than the unit (b<1), showing the good affinity of TpBD-$(CF_3)_2$ COF for ibuprofen compared with acetaminophen and ampicillin.

III.3.4. Freundlich isotherm

The Freundlich equation is useful in its logarithmic form **(Freundlich, 1906):**

$$\ln(q_e) = \log k_f + \frac{1}{n}\ln(C_e)$$

where k_f (mg g^{-1}) and $1/n$ are the characteristic constants of the system.

The $\ln(q_e)$ plot as a function of $\ln(C_e)$ for the adsorption of ibuprofen, ampicillin, and acetaminophen at an initial concentration of 50 mg L^{-1} by TpBD-Me_2 and TpBD-$(CF_3)_2$ at different concentrations are presented in Figures 70, 71, which show a straight line with the origin at $\ln K_f$ and the slope $1/n$. The adsorption isotherms that are derived from the experimental data for each of the tested adsorbate and adsorbent are presented in Table 32 and Table 33.

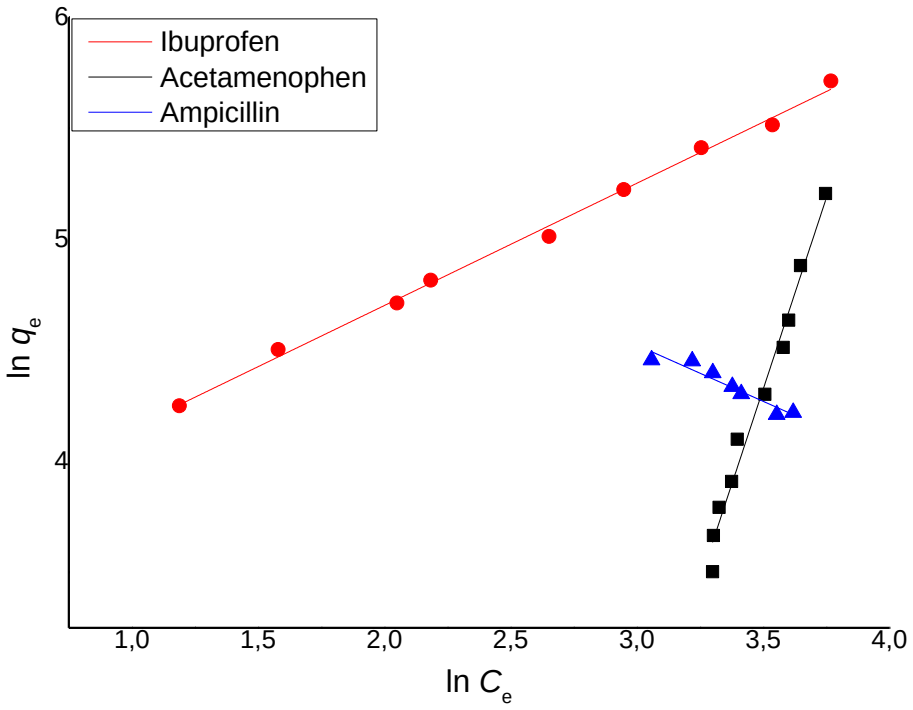

Figure 70 Freundlich isotherm of adsorption of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (λ = 207 nm) by TpBD-Me_2 at different concentrations at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}).

The values of the correlation coefficients R^2 for the Freundlich model obtained for the adsorption of ibuprofen, acetaminophen and ampicillin are all above 0.991. According to these results, the Freundlich model fits the experimental values obtained.

The Freundlich constant 1/*n* calculated is less than the unit (1/*n*<1) for ibuprofen, indicating that the adsorption of the selected drug onto both COFs is favorable. The values 1/*n* 3.521 and 12.51 presented in Tables 32, 33 for the adsorption of acetaminophen ontoTpBD-Me_2 and TpBD-$(CF_3)_2$, respectively, could indicate a cooperative sorption, the same for ampicillin adsorbed onto TpBD-$(CF_3)_2$ where the value of 1/*n* is 28.2 **(Mohan and Karthikeyan, 1997; Atkins, 1970)** cited by **(Voudrias et al; 2002)**.

Freundlich constants K_f are 38 mg g^{-1} and 53 mg g^{-1} for ibuprofen adsorbed onto TpBD-Me_2 and TpBD-$(CF_3)_2$, respectively, which are much higher than K_f of adsorption of acetaminophen and ampicillin.

Table 32 Freundlich isotherm parameters for the adsorption of ibuprofen, acetaminophen and ampicillin at an initial concentration of 50 mg L^{-1} by TpBD-Me_2 at different concentrations at 21°C and pH=6–7.

	K_F (mg g^{-1})	1/*n*	*n*	R^2
Ibuprofen	38.21	0.534	1.87	0.991
Acetaminophen	0.0003	3.521	0.280	0.991
Ampicillin	420.31	0.51	1.96	0.991

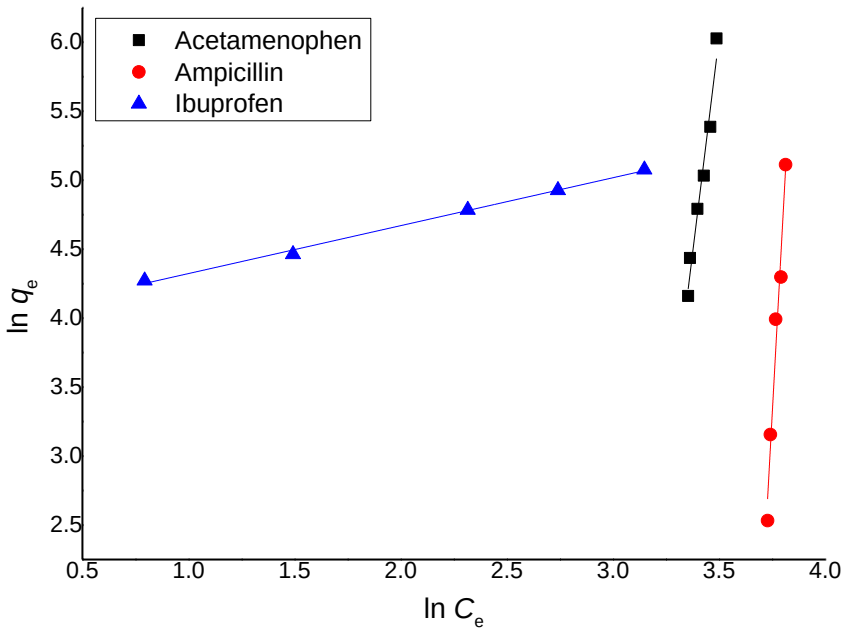

Figure 71 Freundlich isotherm of adsorption of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (λ = 207 nm) by TpBD-$(CF_3)_2$ at different concentrations at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}).

Table 33 Freundlich isotherm parameters for the adsorption of ibuprofen, acetaminophen, and ampicillin at an initial concentration of 50 mg L^{-1} by TpBD-$(CF_3)_2$ at different concentrations at 21°C and pH 6–7.

	K_F (mg g^{-1})	1/*n*	*n*	R^2
Ibuprofen	53.25	0.347	2.88	0.996
Acetaminophen	4,0307E-17	12.51	0.08	0.970
Ampicillin	3,3748E-45	28.2	0.035	0.970

III.3.5. Temkin isotherm

The linear equation of the Temkin isotherm model **(Temkin et al., 1940)** is given by the equation:

$$q_e = \left(\frac{RT}{b_T}\right) logA + \left(\frac{RT}{b_T}\right) logC_e$$

Where b_T is the Temkin constant related to the heat of sorption (J mol^{-1}) and *A* is the Temkin isotherm constant (L g^{-1}).

The q_e plot as a function of lnC_e for the adsorption of ibuprofen, ampicillin and acetaminophen at an initial concentration of 50 mg L^{-1} by TpBD-Me_2 andTpBD-$(CF_3)_2$ at different concentration are presented in Figures 72, 73. The adsorption isotherms derived from the experimental data for each of the tested adsorbates and adsorbents are presented in Tables 34, 35.

The Temkin isotherm model for the adsorption of selected pharmaceuticals by the two COFs fits well the experimental data (Figures 72, 73) based on the relatively high values of the correlation coefficient R^2, 0.979, 0989, 0989 for ibuprofen, acetaminophen, and ampicillin, respectively, adsorbed by TpBD-Me_2, and 0.992, 0.974, 0.988, respectively, adsorbed by TpBD-$(CF_3)_2$.

The positive values of the adsorption energy variation b_T (Tables 34, 35) indicate an endothermic adsorption process (**Ghogomu et al, 2013)**. The negative value of b_T of −30.99 kJ mol^{-1} for ampicillin adsorbed onto TpBD-Me_2 (Table 34) indicates an exothermic reaction and a spontaneous process during the adsorption.The adsorption of acetaminophen onto TpBD-$(CF_3)_2$ and TpBD-Me_2 gives a b_T value of 3.07 and 1.69 kJ mol^{-1}, respectively, and the adsorption of ampicillin onto TpBD-$(CF_3)_2$ 2.66 kJ mol^{-1}.Values < 40 kJ mol^{-1} indicate a physical adsorption **(Dada et al., 2012; Hamdaoui et al., 2007; Aarfane et al.. 2014)**.

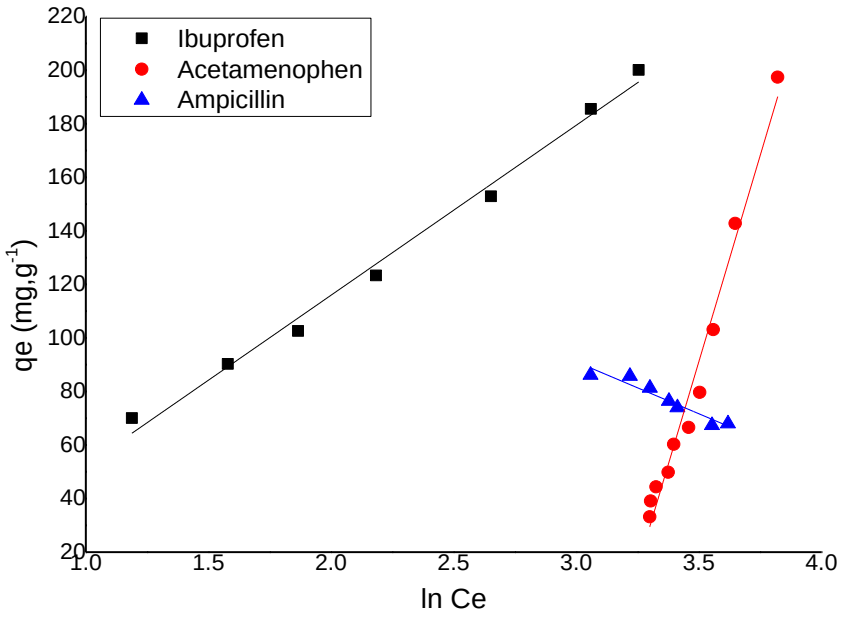

Figure 72 Temkin isotherm of adsorption of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (λ = 207 nm) by TpBD-Me_2 at different concentrations at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}).

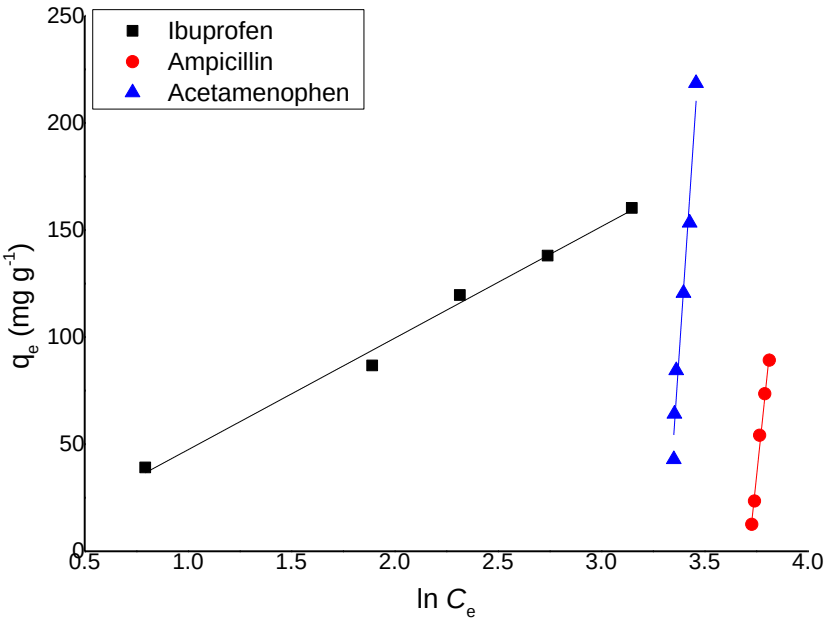

Figure 73 Temkin isotherm of adsorption of ibuprofen (λ = 220 nm), acetaminophen (λ = 243 nm), and ampicillin (λ = 207 nm) by TpBD-$(CF_3)_2$at different concentrations at 21°C in ultrapure water at pH 6–7 (C_0(pharmaceutical) = 50 mg L^{-1}).

Table 34 Temkin isotherm parameters for the adsorption of ibuprofen, acetaminophen, and ampicillin at an initial concentration of 50 mg L^{-1} by TpBD-Me_2 at different concentrations at 21°C and pH 6–7.

	b_T (kJ mol^{-1})	A (L g^{-1})	R^2
Ibuprofen	64.54	1.57	0.979
Acetaminophen	3.07	0.04	0.989
Ampicillin	–30.99	0.016	0.989

Table 35 Temkin isotherm parameters for the adsorption of ibuprofen, acetaminophen and ampicillin at an initial concentration of 50 mg L^{-1} by TpBD-$(CF_3)_2$ at different concentrations, at 21°C and pH=6–7.

	b_T (kJ mol^{-1})	A (L g^{-1})	R^2
Ibuprofen	46.96	0.913	0.992
Acetaminophen	1.69	0.04	0.974
Ampicillin	2.66	0.024	0.988

IV. Influence of pH on the adsorption

The adsorption capacity at different pH values was determined and compared for the lipophilic ibuprofen and both hydrophilic pharmaceuticals acetaminophen and ampicillin, in which the adsorption is measured at the low pH of 2 and at the high pH of 10 (Figure 74) **(Mellah et al, 2018)**. Acetaminophen is of a very similar size than ibuprofen, whereas ampicillin is slightly larger. A large quantity of ibuprofen, featuring a carboxylic acid moiety, was captured at pH 2, which may be explained by enhanced interactions with the COF adsorbent due to protonation at a lower pH. Moreover, this preferal adsorption of ibuprofen is enhanced in lipophilic environment because of its high distribution coefficient log*D* at pH 2 to ~3.5 **(Hansen et al., 2015)**.

A dramatic decrease in adsorption capacity is detected at a high pH 10, which probably due to repulsions between the negatively charged ibuprofen and the COF surface. Similar results have been reported with activated carbon **(Mestre et al., 2007)** and graphene oxide **(Cai et al., 2004)**. In comparison, acetaminophen and ampicillin that have a high polarity compared to ibuprofen according to their log*D* values of 0.51 and –1.13 **(La Rotonda et al., 1983)**, respectively, the adsorption capacity at pH 2 is much smaller compared to ibuprofen. At pH 6 the quantity adsorbed for acetaminophen increases slightly, indicating that hydrophobic interactions play a role in the pharmaceutical adsorption. Additionally, the influence of the large differences in the electrostatic potential surfaces may affect the adsorption as well (**Nielsen et al., 2016)**.

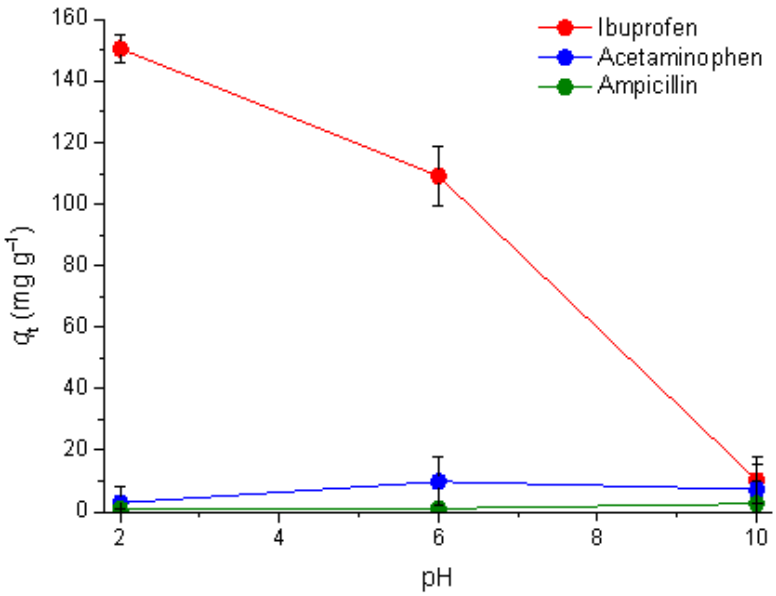

Figure 74 The adsorbed quantities of the pharmaceuticals as a function of pH (pH 6 denotes ultrapure water, C_0(pharmaceutical) = 20 mg L^{-1}, C(COF) = 100 mg L^{-1}, t = 120 min) with the studied COFs. Results are expressed as the mean of two separate experiments with measurements performed by duplicate. Error bars correspond to the standard deviation of the mean.

V. Adsorption of pharmaceuticals by COFs in real water

Competitive adsorption is the usual adsorption phenomenon in real applications, and it is of critical importance in determining the overall performance of an adsorbent. However, as the pharmaceuticals are generally encountered in combination, it is of importance to study the competitive adsorption. Therefore, the purpose of the present study is to analyze the adsorptive behavior of the COFs when the pharmaceuticals exist in a multi-component solution, which is a preferable exemplification of what happens during water treatment. Thus, it will study the competitive adsorption characteristics of all the combinations of binary mixtures of three pharmaceutical compounds, including ibuprofen, acetaminophen, and phenobarbital, were evaluated on two COFs TpBD-$(CF_3)_2$ and TpBD-Me_2 in four real water samples, that is, Lima river, Estuary, lake and fountain of Forjães. The adsorption tests were carried out by COFs at a concentration of 333 mg L^{-1} to identify the adsorption capacity of four pharmaceuticals. The concentrations of pharmaceuticals were 50 µM, 100 µM, and 150 µM.

First, the adsorption is studied for each pharmaceutical separately in each water sample, and than as a mixture of two pharmaceuticals at different proportional concentrations 100/100 µM, 50/150 µM, and 150/50 µM.

V.1. Limit of detection

Ibuprofen, phenobarbital, and acetaminophen concentrations were measured using an UV detector. The calibration curves to determine each pharmaceutical are presented in Figure 75.

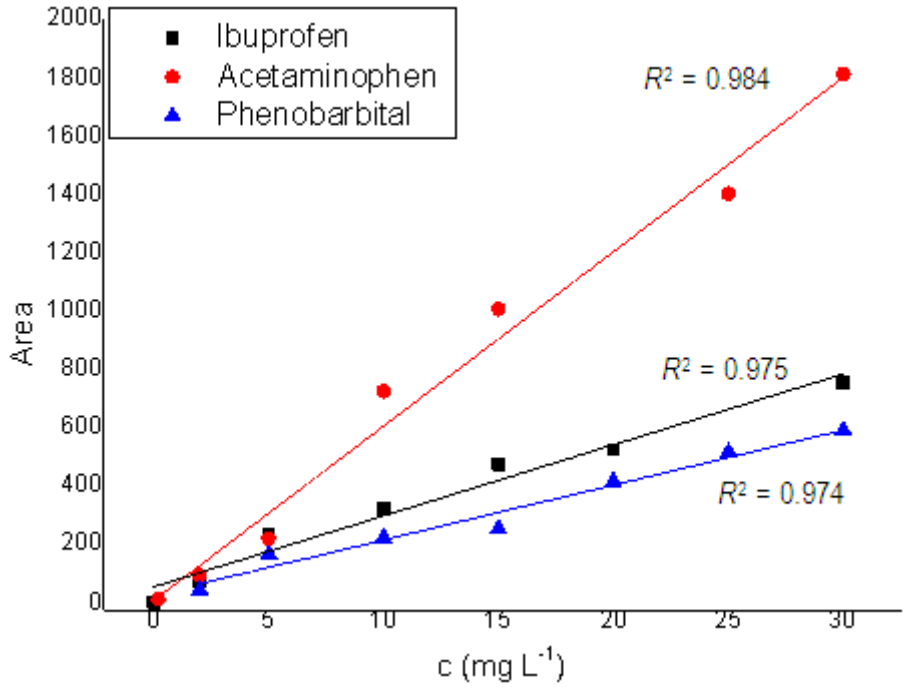

Figure 75 Calibration curves of ibuprofen (λ = 220 nm), phenobarbital (λ = 210 nm), and acetaminophen (λ = 243 nm) at 21°C inultrapure water at pH 6–7.

V.2. Adsorption of pharmaceuticals individually on TpBD-$(CF_3)_2$ and TpBD-Me_2

The adsorption results of ibuprofen, acetaminophen, and phenobarbital individually taken in samples from the Lima river, estuary, lake, and Fonte de Forjães at concentrations of 50 µM, 100 µM, and 150 µM, by TpBD-$(CF_3)_2$ and TpBD-Me_2 at concentration of 333 mg L^{-1} expressed as quantity adsorbed q_t (mg g^{-1}) at equilibrium are presented in Figures 76, 77.

The adsorbed quantity q_t of pharmaceuticals by both COFs increases with the increase of initial pharmaceutical concentration. This may be explained by the effects of the initial concentration on the adsorbed quantity of pharmaceutical products (**Khalir et al; 2011)**.

As seen in Figures 76, 77, ibuprofen was adsorbed well on both TpBD-$(CF_3)_2$ and TpBD-Me_2 in different real water samples compared to phenobarbital and ibuprofen at different initial concentrations. These results are according to the results of the adsorption of ibuprofen in ultrapure water. Ibuprofen shows some preference for the adsorption onto TpBD-$(CF_3)_2$ in lake water, and onto TpBD-Me_2 in Fonte de Forjães. Relatively similar quantities are observed for its adsorption onto both COFs in estuary and Lima Rivers at different concentrations as shown in Table 36.

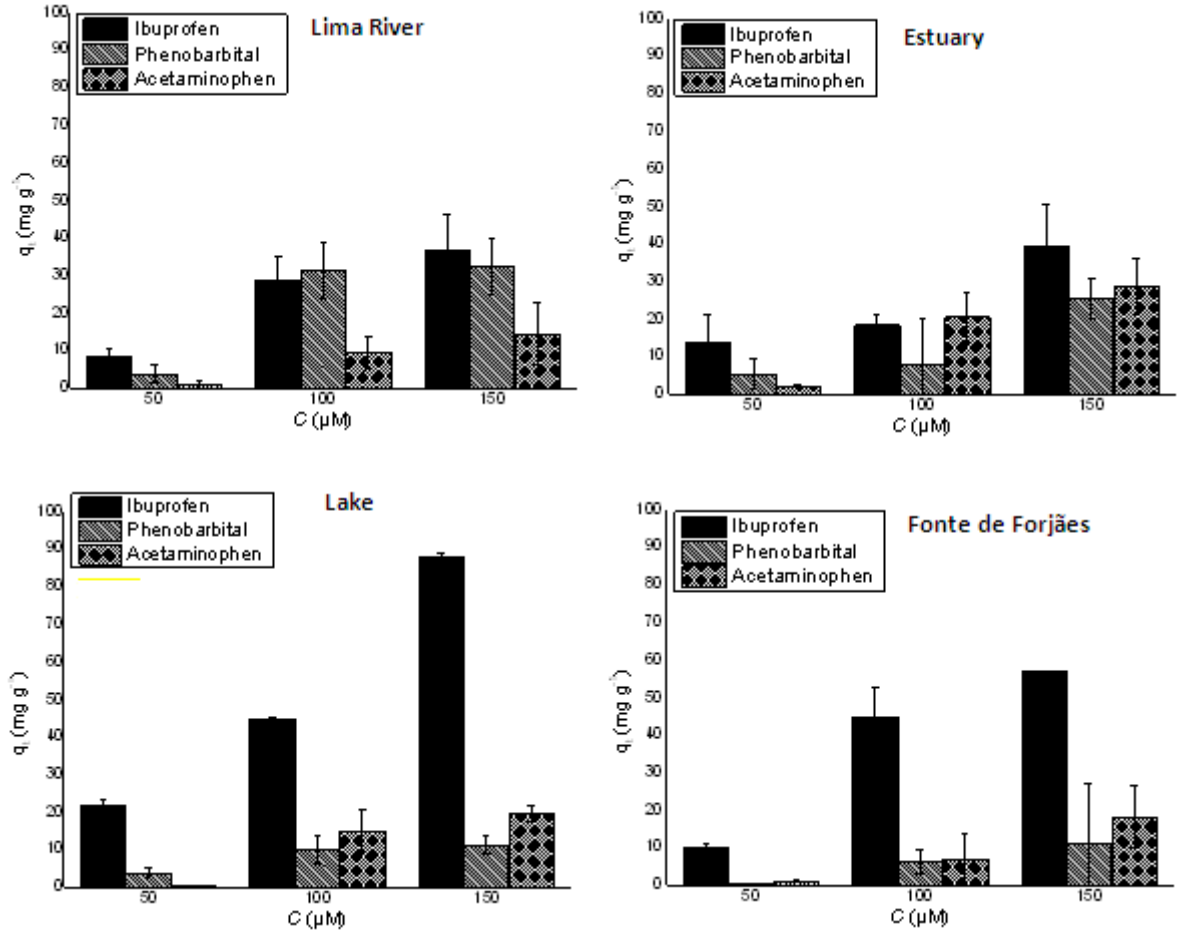

Figure 76 Adsorption of ibuprofen, acetaminophen, and phenobarbital individual by TpBD-$(CF_3)_2$ expressed as the quantity adsorbed q_t (mg g^{-1}) at 21°C in real waters at (C_0(pharmaceutical) = 50, 100, 150 µM; C(COF) = 333 mg L^{-1}).

The adsorption efficiency of phenobarbital is nearly zero on TpBD-Me_2. On the other hand, the adsorption of phenobarbital in Lima river water is similar to that found for ibuprofen with TpBD-$(CF_3)_2$ at different concentrations. The highest adsorbed quantity of phenobarbital registered was 32 mg g^{-1} and 25 mg g^{-1} in Lima River and estuary, respectively, at a concentration of 150 µM.

The adsorption capacity of acetaminophen on both COFs in different real water samples did not give an important difference between the water samples. The highest adsorbed quantities of acetaminophen registred were 29 mg g^{-1} onto TpBD-$(CF_3)_2$ and 26 mg g^{-1} onto TpBD-Me_2 in Fonte de Forjães at 150 µM. The adsorption of acetaminophen and phenobarbital in different water samples did not present a significant difference expect in some cases (Table 36). This lower affinity of acetaminophen towards the COFs was already seen in the studies with ultrapure water.

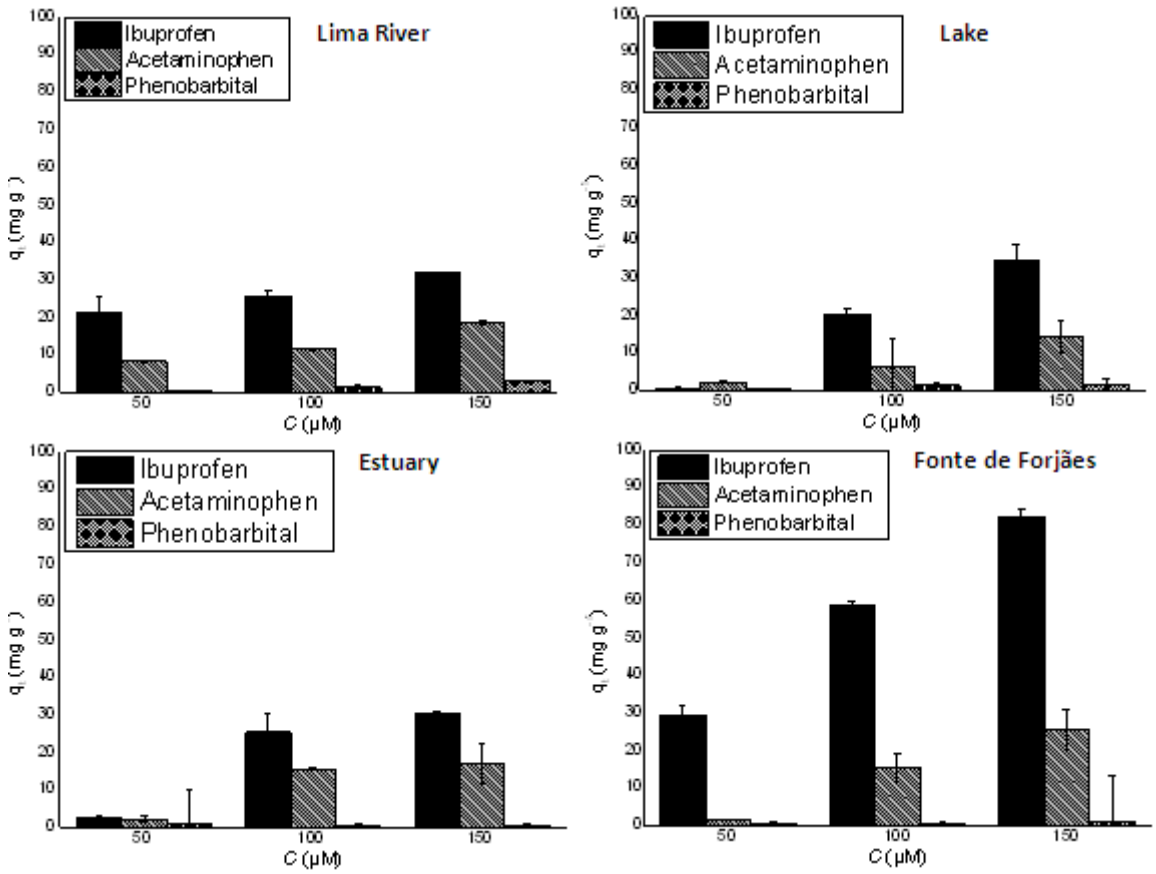

Figure 77 Adsorption of ibuprofen, acetaminophen, and phenobarbital individual by TpBD-Me_2 expressed as the quantity adsorbed q_t (mg g^{-1}) at 21°C in real waters at (C_0(pharmaceutical) = 50, 100, 150 µM; C(COF) = 333 mg L^{-1}).

Table 36 Adsorption of ibuprofen (IBU), phenobarbital (PHE), and acetaminophen (ACE), at different concentrations in different real water onto TpBD-$(CF_3)_2$ and TpBD-Me_2

			q_t (mg g^{-1})			
			Lima River	Lake	Fonte de Forjães	Estuary
TpBD-$(CF_3)_2$	50	IBU	8	22	10	14
		PHE	4	4	0,28	5
		ACE	1	0.33	1,1	2
	100	IBU	29	45	44	18
		PHE	31	10	6	8
		ACE	10	15	7	20
	150	IBU	37	88	57	39
		PHE	32	12	11	25
		ACE	14	20	18	29
TpBD-Me_2	50	IBU	21	0,3	29	2
		PHE	0,46	0,45	0,55	0,72
		ACE	8	2	1,50	2
	100	IBU	25	20	58	25
		PHE	1	1	0,64	0,19
		ACE	11	6	15	16
	150	IBU	32	35	82	30
		PHE	3	2	0,82	0,58
		ACE	19	14	26	17

All three products have interesting adsorptions on both COFs in real water samples, especially in Lima River and the estuary waters, validating the selection of these adsorbents to test the competitive adsorption of pharmaceutical pollutants. The differences in the natural water samples may be due to differences in the characteristics of the water (pH, compounds present etc etc) **(Mansouri et al, 2015)**.

V.3. Binary adsorption of pharmaceuticals by TpBD-$(CF_3)_2$ and TpBD-Me_2

The results of the competitive adsorption experiments between IBU/ACE, IBU/PHEN, and ACE/PHEN at proportional initial concentrations of 150 µM/50 µM, 100 µM/100 µM, and 50 µM/150 µM onto TpBD-$(CF_3)_2$ and TpBD-Me_2 at a concentration of 333 mg L^{-1} are presented in Figures 78–79. Overall, the adsorbed quantity q_t of a pharmaceutical in competitive adsorption in both COFs is increased with increasing initial pharmaceutical concentration.

V.3.1. Adsorption of different binary mixtures by TpBD-$(CF_3)_2$ in real water

Overall, the amounts adsorbed on TpBD-$(CF_3)_2$ in the different real waters increase proportionally with the concentration of the pharmaceutical product.

V.3.1.1. In Lima river water

Figure 78 shows the adsorption on TpBD-$(CF_3)_2$ in Lima River water of each of the products of the different binary mixtures IBU/PHEN; IBU/ACE and ACE/PHEN in three different ratios of concentrations, 50/150; 100/100 and 150/50 µM. The results are collated in Table 37.

The best adsorbed quantities are given by the IBU/PHEN pair. The adsorbed quantities being much greater than those of the other two mixtures IBU/ACE and ACE/PHEN which give values of the same order of quantities for the same ratios of concentrations.

The adsorption of the binary mixture IBU/PHEN shows a much higher adsorbed quantity for ibuprofen compared to phenobarbital at an initial concentration of ratio 3/1 (Figure 78). Phenobarbital starts to compete with ibuprofen adsorption at equal initial concentrations, where the adsorbed quantities were 44 mg g^{-1} and 32 mg g^{-1} for ibuprofen and phenobarbital respectively.

When the initial concentration ratio IBU/PHEN is reversed (1/3), a preferential adsorption of phenobarbital is seen with 40 mg g^{-1} while the adsorbed quantity of ibuprofen is 28 mg g^{-1} (Table 37, Figure 78).

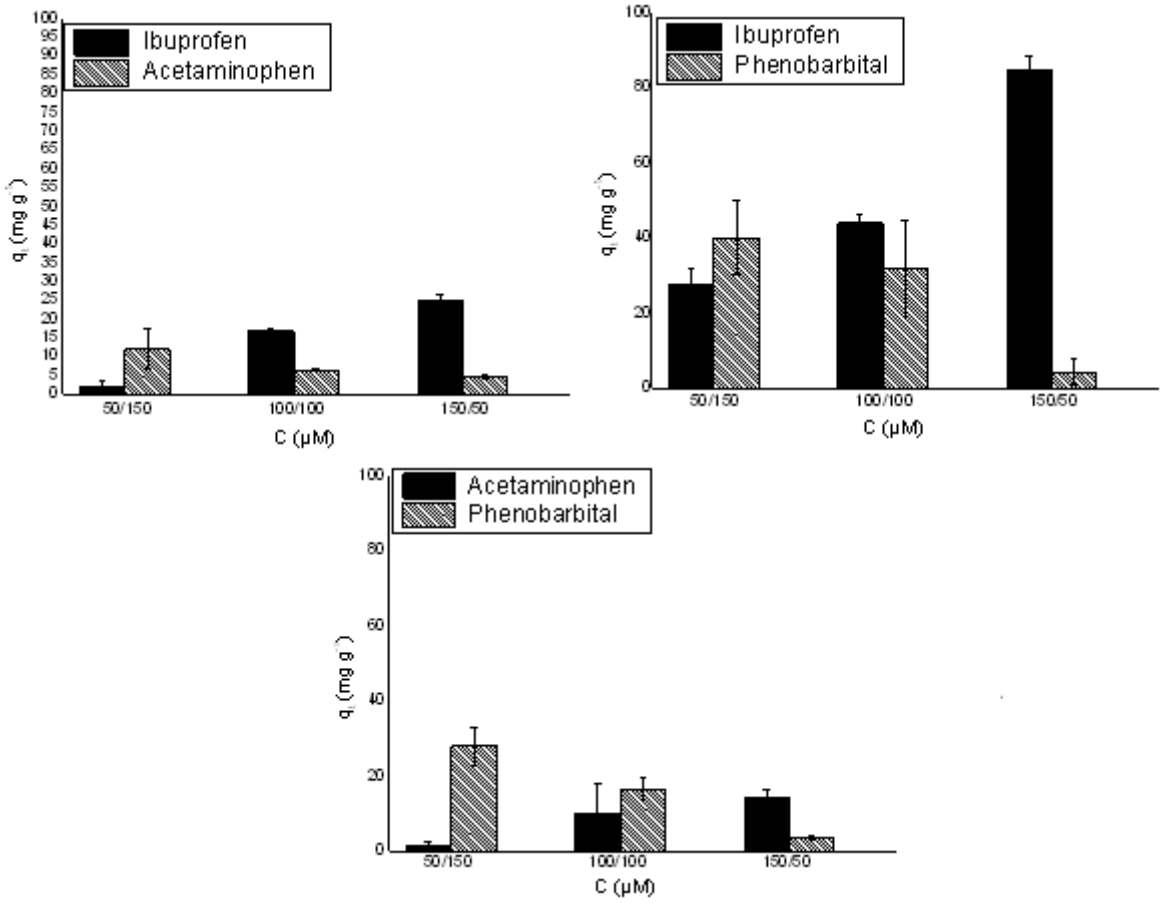

Figure 78 Adsorption of mixed ibuprofen/acetaminophen, ibuprofen/phenobarbital, and acetaminophen/phenobarbital by TpBD-$(CF_3)_2$ expressed as the quantity adsorbed q_t (mg g^{-1}) at 21°C in Lima river water at proportional concentrations (C_0(pharmaceutical) = 50/150, 100/100, 150/50 µM; C(COF) = 333 mg L^{-1}).

The amounts adsorbed of ibuprofen alone are lower than those given by its mixture with phenobarbital, which allows us to deduce that the affinity of TpBD-$(CF_3)_2$ towards ibuprofen is improved by the presence of phenobarbital.

For both binary mixtures of IBU/ACE and ACE/PHEN, the adsorbed amounts are much lower compared to those given by the IBU/PHEN pair. Preferential adsorption of acetaminophen compared to phenobarbital is observed for the ratio 1/3 and reverses as soon as the amount of ibuprofen is the same or three times higher than that of acetaminophen (Table 37).

This phenomenon is reversed for the ACE/PHEN pair, where acetaminophen is preferentially adsorbed as soon as the mixture is equimolar (Table 37). Thus, TpBD-$(CF_3)_2$ has a higher affinity for acetaminophen in the presence of phenobarbital but not in the presence of ibuprofen which is also preferentially adsorbed in the presence of phenobarbital.

Table 37 Adsorption of mixed IBU/ACE, IBU/PHEN, and ACE/PHEN at different proportional concentrations by TpBD-$(CF_3)_2$ in Lima river water at 21°C expressed as the quantity adsorbed q_t (mg g^{-1}).

q_t (mg g^{-1}) / Lima River water / TpBD- $(CF_3)_2$			
C(µM)	IBU/PHEN	IBU/ACE	ACE/PHEN
50/150	28 / 40	2 / 12	4 / 14
100/100	44 / 32	17 / 7	17 / 10
150/50	85 / 4	25 / 5	28 / 2
	IBU	PHEN	ACE
50 µM (10 mg L^{-1})	8	4	1
100 µM (21 mg L^{-1})	29	31	10
150 µM (31 mg L^{-1}),	37	32	14
q_t (mg g^{-1}) / ultra pure water			
50 mg L^{-1}	133		80

Comparing the adsorbed amounts on TpBD- $(CF_3)_2$, ibuprofen alone in ultrapure water (133 mg g-1), Lima River water and when it is mixed with phenobarbital or Acetaminophen, it is noticed that ibuprofen has a very good adsorption in ultra pure water compared to a lower adsorption in Lima river water. This adsorption appears to improve in the presence of phenobarbital and approach its initial values in the presence of acetaminophen. This allows us to say that ibuprofen adsorbs preferentially on TpBD- $(CF_3)_2$ in the water of the Lima River.

V.3.1.2. In Fonte de Forjães water

In Fonte de Forjães water samples, ibuprofen mixed with phenobarbital onto TpBD-$(CF_3)_2$ is better adsorbed whatever the ratio of its concentrations as shown in Figure 79 and Table 38.

Ibuprofen is preferentially adsorbed on TpBD-$(CF_3)_2$ in Fonte de Forjães water when it is mixed with acetaminophen especially at the concentration ratio 3/1. It reaches a value of 78 mg g^{-1} compared to 1 mg g^{-1} of acetaminophen (Figure 79), while it gives alone only 57 mg g^{-1} on TpBD-$(CF_3)_2$ in the same water (Table 38).

Phenobarbital is poorly adsorbed either in the presence of ibuprofen or acetaminophen; it gives a zero adsorption value when the ratio is 3/1 with acetaminophen.

The adsorption of ibuprofen in ultrapure water at an initial concentration of 50 mg L^{-1} onto TpBD-$(CF_3)_2$ was 133 mg g^{-1}, being much higher than its adsorbed quantity in Fonte de Forjães at a close concentration. Apart from the amount of ibuprofen recorded in the presence of acetaminophen (78 mg g^{-1}), all others are low. This phenomenon is even more marked with the other two molecules, which allows us to conclude that in the water of the Fonte de Forjães, the adsorbent TpBD- $(CF_3)_2$ does not have a great affinity for the pharmaceuticals studied.

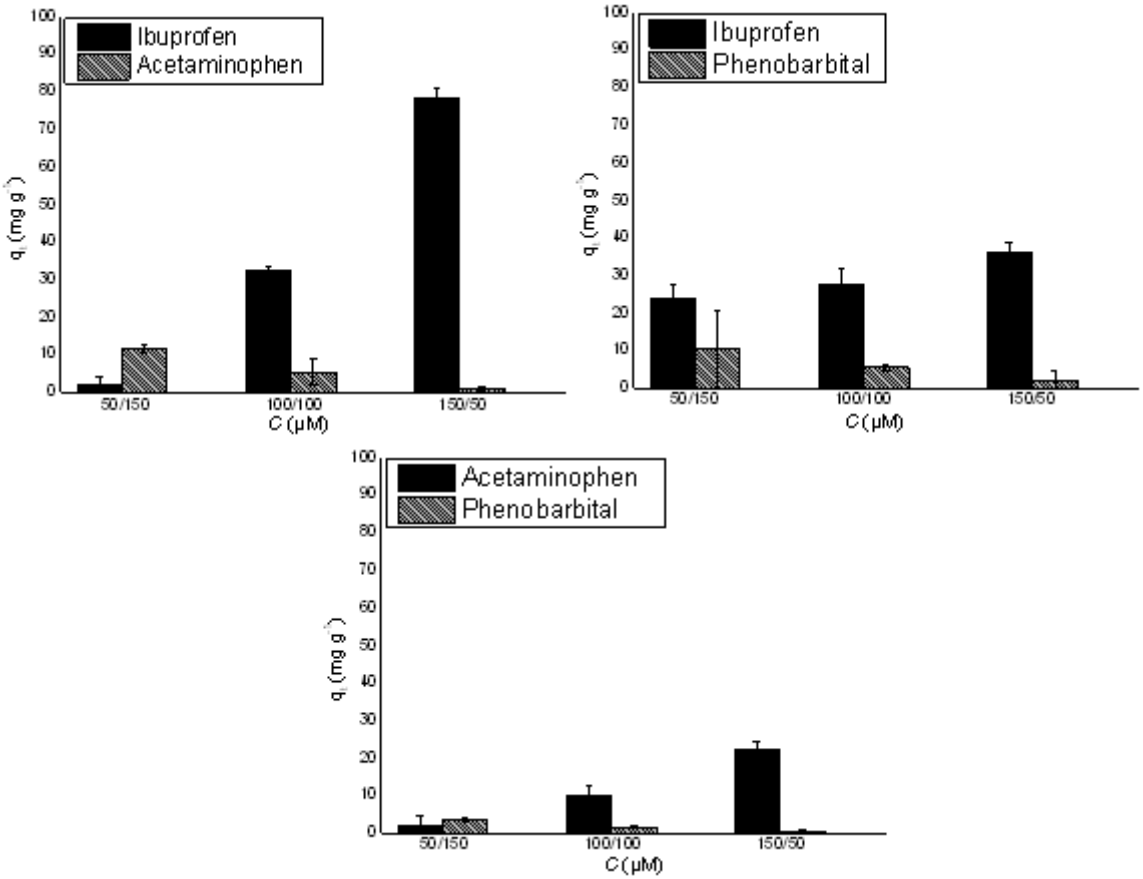

Figure 79 Adsorption of mixed ibuprofen/acetaminophen, ibuprofen/phenobarbital, and acetaminophen/phenobarbital by TpBD-$(CF_3)_2$ expressed as the quantity adsorbed q_t (mg g^{-1}) at 21°C in Fonte de Forjães water at proportional concentrations (C_0(pharmaceutical) = 50/150, 100/100, 150/50 µM; C(COF) = 333 mg L^{-1}).

Table 38 Adsorption of mixed IBU/ACE, IBU/PHEN, and ACE/PHEN at different proportional concentrations by TpBD-$(CF_3)_2$ in Fonte de Forjães water at 21°C expressed as the quantity adsorbed q_t (mg g^{-1}).

	q_t (mg g^{-1})/ fonte de Forjães water		
***C*(µM)**	IBU/PHEN	IBU/ACE	ACE/PHEN
50/150	24 / 11	2 / 12	2 / 4
100/100	28 / 6	32 / 5	10 / 2
150/50	36 / 2	78 / 1	22 / 0
	IBU	PHEN	ACE
50 µM (10 mg L^{-1})	10	0	1
100 µM (21 mg L^{-1})	44	6	7
150 µM (31 mg L^{-1}),	57	11	18
q_t (mg g^{-1}) / ultra pure water			
50 mg L^{-1}	133		80

V.3.1.3. In lake water

In lake water, the study of the adsorption of ibuprofen mixed with phenobarbital and acetaminophen onto TpBD-$(CF_3)_2$ at different initial concentrations ratios (Figure 80), A high quantity of ibuprofen is adsorbed compared to others pharmaceutical products whatever the initial ratio. It is preferably adsorbed either in the presence of phenobarbital or acetaminophen.

The adsorption of ibuprofen in ultrapure water at an initial concentration of 50 mg L^{-1} onto TpBD-$(CF_3)_2$ was 133 mg g^{-1}, much higher than its quantity adsorbed in lake water either alone or in binary mixture (Table 39) at the same concentrations; the adsorbed quantities of ibuprofen being of the same order of magnitude. However, the values of the adsorbed amounts of ibuprophen in mixture are slightly higher than those obtained with ibuprofen alone, which allows us to say that the presence of both molecules improves the affinity of TpBD-$(CF_3)_2$ towards ibuprofen.

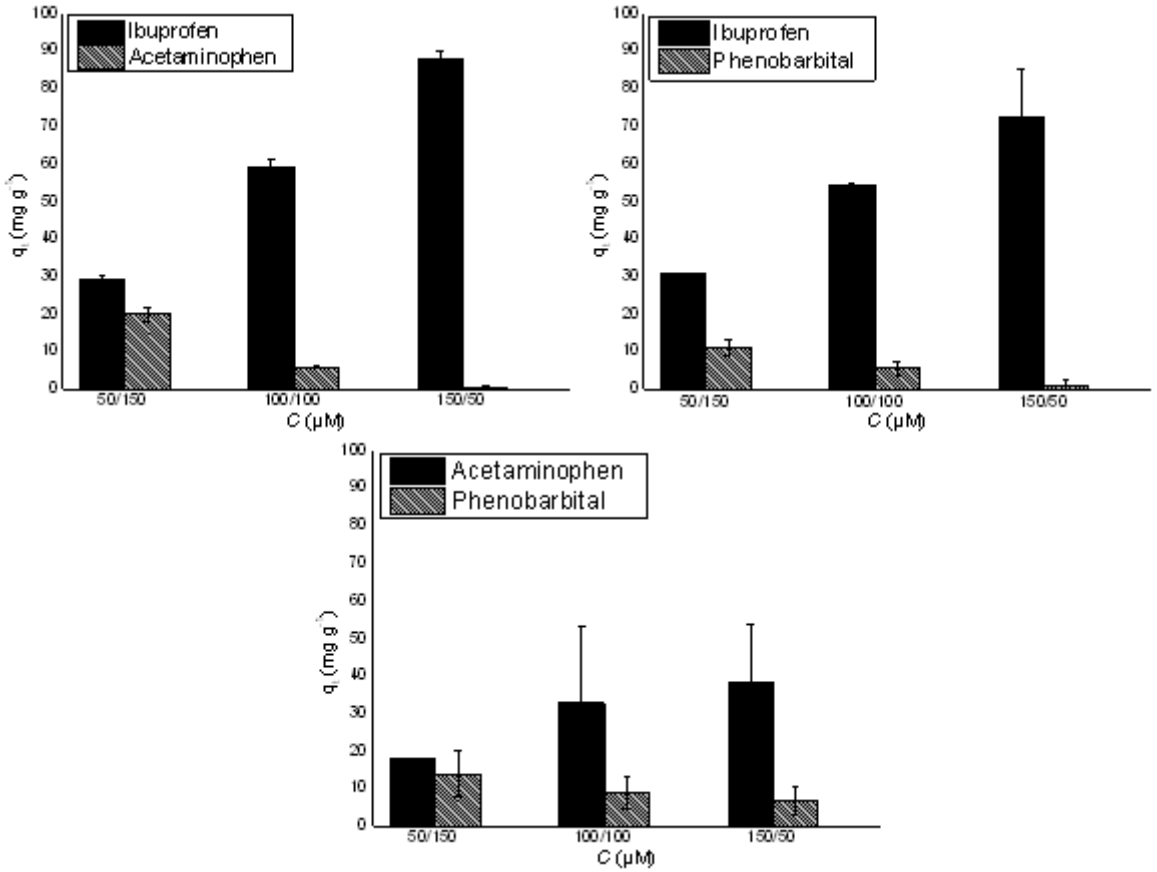

Figure 80 Adsorption of mixed ibuprofen/acetaminophen, ibuprofen/phenobarbital, and acetaminophen/phenobarbital by TpBD-$(CF_3)_2$ expressed as the quantity adsorbed q_t (mg g^{-1}) at 21°C in lake water at proportional concentrations (C_0(pharmaceutical) = 50/150, 100/100, 150/50 µM; C(COF) = 333 mg L^{-1}).

Table 39 Adsorption of mixed IBU/ACE, IBU/PHEN, and ACE/PHEN at different proportional concentrations by TpBD-$(CF_3)_2$ in lake water at 21°C expressed as the quantity adsorbed q_t (mg g^{-1}).

	q_t (mg g^{-1})/ lake water/ TpBD-$(CF_3)_2$		
C(µM)	IBU/PHEN	IBU/ACE	ACE/PHEN
50/150	31/11	29/20	18/14
100/100	54/6	59/6	33/9
150/50	72/1	88/1	38/7
	IBU	PHEN	ACE
50 µM (10 mg L^{-1})	22	4	o
100 µM (21 mg L^{-1})	45	10	15
150 µM (31 mg L^{-1}),	88	12	20
q_t (mg g^{-1}) / ultra pure water			
50 mg L^{-1}	133		80

Acetaminophen is preferentially adsorbed by TpBD-$(CF_3)_2$ in the presence of phenobarbital but with smaller amounts than ibuprofen (Figure 80) but the presence of phenobarbital appears to improve the affinity of the adsorbent towards this molecule, its adsorbed quantities being even greater than those given by its adsorption alone.

Phenobarbital is poorly adsorbed either in the presence of ibuprofen or acetaminophen which itself is poorly adsorbed in the presence of ibuprofen.

TpBD-$(CF_3)_2$ does not present a good affinity towards phenobarbital, because of its lower adsorbed quantities ether alone or as a mixture in lake water (Table 39).

V.3.1.3. In estuary water

The adsorption on TpBD-$(CF_3)_2$ of the 3 pairs of pharmaceuticals at the three ratios of concentrations of 1/3, 1/1, 3/1 in estuary water gives less adsorbed amounts than in other waters. The competitiveness of each molecule compared to other is directly related to its concentration; the molecule with highest concentrations being the most competitive molecule (Figure 81).

Ibuprofen presents a lower adsorption in estuary water than its adsorption in other waters and seems less competitive compared to the other two molecules.

Acetaminophen presents the best competitiveness followed by phenobarbital (Table 40).

The adsorption of ibuprofen in ultrapure water at an initial concentration of 50 mg L^{-1} onto TpBD-$(CF_3)_2$ was 133 mg g^{-1}, much higher than its adsorbed quantity in estuary water ether alone or in binary mixture at the same concentrations. Contrariwise, these values are fairly close to what was obtained when ibuprofen is in a mixture and it is preferentially adsorbed at ratio concentration of 3/1 with the other two molecules.

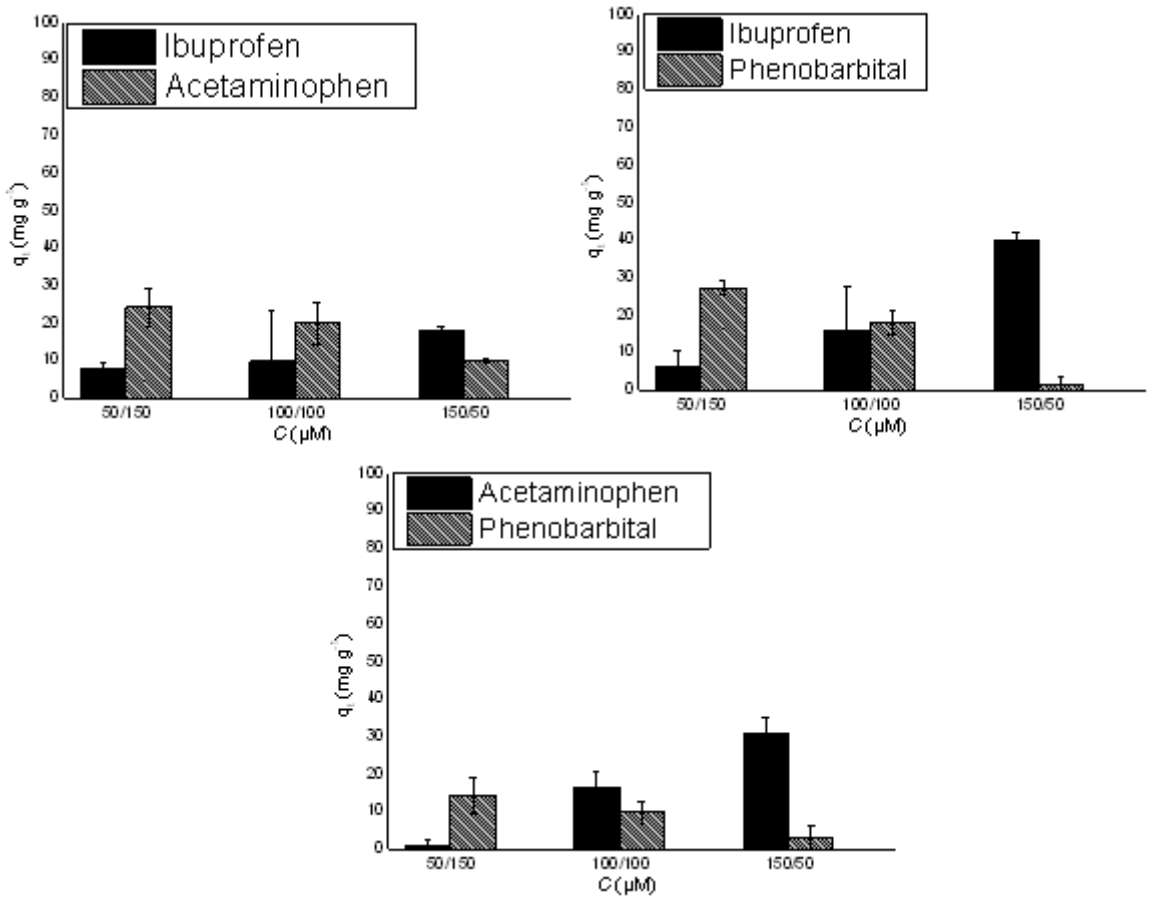

Figure 81 Adsorption of mixed ibuprofen/acetaminophen, ibuprofen/phenobarbital, and acetaminophen/phenobarbital by TpBD-$(CF_3)_2$ expressed as the quantity adsorbed q_t (mg g^{-1}) at 21°C in Estuary water at proportional concentrations (C_0(pharmaceutical) = 50/150, 100/100, 150/50 µM; C(COF) = 333 mg L^{-1}).

Table 40 Adsorption of mixed IBU/ACE, IBU/PHEN, and ACE/PHEN at different proportional concentrations by TpBD-$(CF_3)_2$ in Estuary water at 21°C expressed as the quantity adsorbed q_t (mg g^{-1}).

	q_t (mg g^{-1})/ Estuary water		
C(µM)	IBU/PHEN	IBU/ACE	ACE/PHEN
50/150	6/27	8/24	1/14
100/100	16/18	10/20	16/10
150/50	40/2	18/10	31/7
	IBU	PHEN	ACE
50 µM (10 mg L^{-1})	14	5	2
100 µM (21 mg L^{-1})	18	8	20
150 µM (31 mg L^{-1}),	39	25	29
q_t (mg g^{-1}) / ultra pure water			
50 mg L^{-1}	133		80

The adsorbed quantity of phenobarbital in estuary water does not present an important difference compared to its individual adsorption (Table 40, Figure 76, 81). It is more competitive with ibuprofen than with acetaminophen.

Conclusion

The adsorption of the three molecules alone and in binary mixtures on TpBD-$(CF_3)_2$ in different real waters has shown that ibuprofen is the best adsorbed products on this COF whether alone or in binary mixture with other molecules; even if its adsorbed amount is lower than that given on ultrapure water with the same adsorbent.

Summarizing the results given by the adsorption of ibuprofen, as shown in Table 41, it is adsorbed preferentially compared to other two pharmaceuticals. Even in some waters, it is noticed an improvement in the amount adsorbed in the presence of the other molecules at the concentration ratios of 1/3 for IBU/PHEN and IBU/ACE. On the other hand, at this low concentration (1/3), ibuprofen is not preferentially adsorbed except in the lake water, but there is inversion as soon as this ratio goes to 1/1, that is to say for an equimolar mixture.

The best affinity of TpBD-$(CF_3)_2$ towards ibuprofen is in lake water where the adsorbed amounts exceed, even, the values given by the adsorption of ibuprofen alone, and it is preferentially adsorbed, even atthe weakest concentration (1/3).

Table 41 Adsorption of ibuprofen alone, and in binary mixture IBU/PHEN and IBU/ACE at different proportional concentrations 1/3 ; 1/1 et 3/1 by TpBD-$(CF_3)_2$ in different real waters at 21°C expressed as the quantity adsorbed q_t (mg g^{-1}).

	q_t (mg g^{-1}) IBU; IBU/PHEN/ TpBD-$(CF_3)_2$							
	Rivière Lima		Eau du Lac		Fonte de Forjães		Estuaire	
50/150	8	28 / 40	22	31/11	10	24 / 11	14	6/27
100/100	29	44 / 32	45	54/6	44	28 / 6	18	16/18
150/50	37	85 / 4	88	72/1	57	36 / 2	39	40/2
	q_t (mg g^{-1}) IBU/ACE; ACE/ TpBD-$(CF_3)_2$							
50/150	2 / 12	14	29/20	20	2 / 12	18	8/24	29
100/100	17 / 7	10	59/6	15	32 / 5	7	10/20	20
150/50	25 / 5	1	88/1	0	78 / 1	11	18/10	2

Estuary is the water that gave the least good results for the adsorption of ibuprofen by TpBD- $(CF_3)_2$.

V.3.2. Adsorption of different binary mixtures by TpBD-Me_2 in real water

The mixed adsorption between ibuprofen, acetaminophen, and phenobarbital onto TpBD-Me_2 in different real water samples such as Lima River, estuary, lake, and Fonte de Forjães is presented in Figures 82–85. The adsorbed quantity of phenobarbital onto TpBD-Me_2 at different initial concentrations in all real water samples is near null, which can be explained

by the lack of affinity of TpBD-Me_2 towards phenobarbital.

On the other hand, as already verified in the ultrapure water and the different water samples with the molecules alone, the adsorbed quantities increase proportionately with the concentration of the adsorbate

V.3.2.1. In Lima river water

Figure 82 shows the mixed adsorption between IBU/PHEN, IBU/ACE and ACE/PHEN on TpBD-Me_2 in Lima River water; ibuprofen showed the best adsorptions and is preferentially adsorbed in its binary mixture with phenobarbital. This is no longer evident for phenobarbital in the presence of acetaminophen; both of them present a low and comparable adsorbed amount. Contrariwise, acetaminophen seems having a better selectivity with respect to phenobarbital while still having relatively low adsorbed amounts. Phenobarbital as it is a product that present the very little adsorbed amounts by TpBD-Me_2 in the Lima River water whatever in the presence of ibuprofen or acetaminophen.

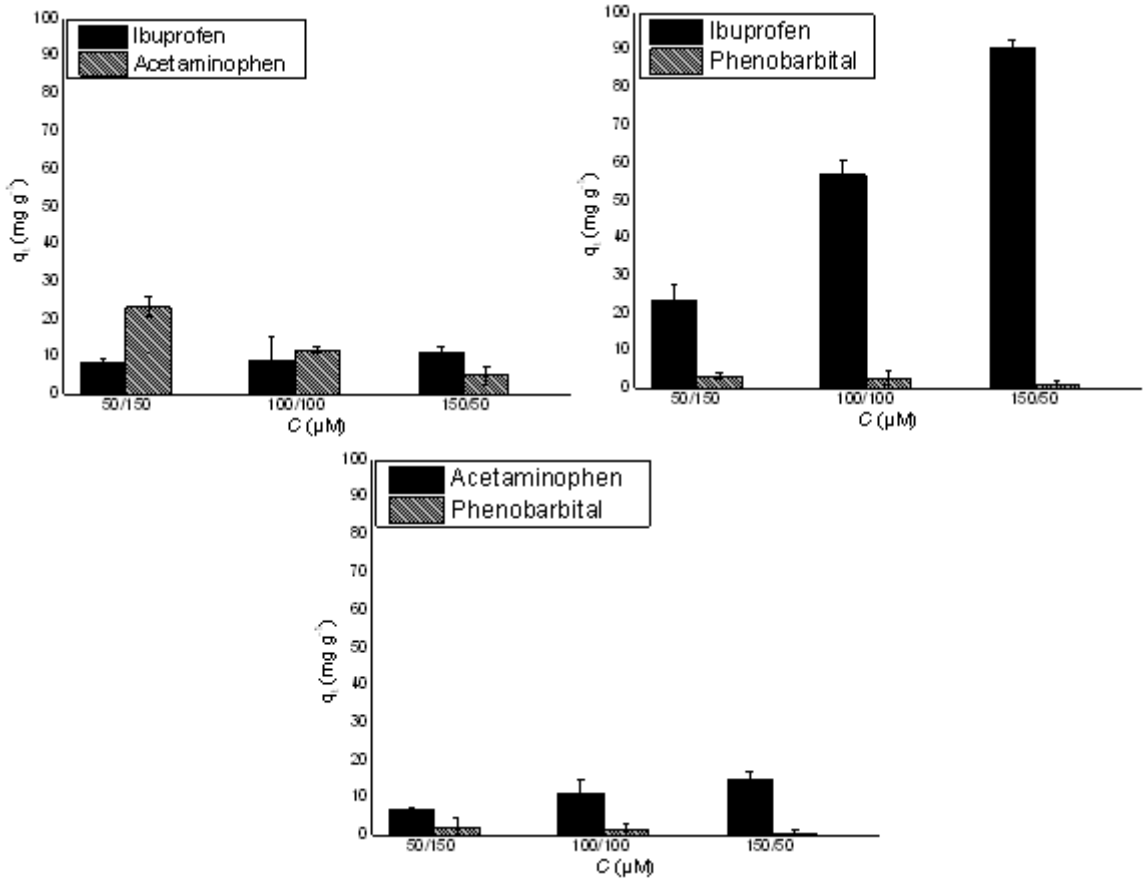

Figure 82 Adsorption of mixed ibuprofen/acetaminophen, ibuprofen/phenobarbital, and acetaminophen/phenobarbital by TpBD-Me_2 expressed as the quantity adsorbed q_t (mg g^{-1}) at 21°C in Lima river at proportional concentrations (C_0(pharmaceutical) = 50/150, 100/100, 150/50 µM; C(COF) = 333 mg L^{-1}).

Table 42 Adsorption of mixed IBU/ACE, IBU/PHEN, and ACE/PHEN at different proportional concentrations by TpBD-Me_2 in Lima River water at 21°C expressed as the quantity adsorbed q_t (mg g^{-1}).

	q_t (mg g^{-1})/ *Lima River water/* TpBD-Me_2		
C(µM)	IBU/PHEN	IBU/ACE	ACE/PHEN
50/150	23/3	8/23	7/2
100/100	57/3	9/12	11/1
150/50	91/1	11/5	15/1
	IBU	PHEN	ACE
50 µM (10 mg L^{-1})	21	0	8
100 µM (21 mg L^{-1})	25	1	11
150 µM (31 mg L^{-1}),	32	3	19
q_t (mg g^{-1}) / ultra pure water			
50 mg L^{-1}	113		57

The adsorption of ibuprofen in ultrapure water at an initial concentration of 50 mg L^{-1} on TpBD-Me_2 is 113 mg g^{-1}, higher than its adsorbed amount in Lima River water. The adsorbed amounts of ibuprofen mixed with phenobarbital in Lima River water are better than those obtained for its adsorption alone and it is preferentially adsorbed compared to phenobarbital which has a negligible adsorption next to ibuprofen. This competitiveness is no longer evident in the presence of acetaminophen, and the adsorbed amounts are much lower (Table 42).

The adsorption of acetaminophen in ultrapure water is 57 mg g^{-1}, much higher than the adsorbed amounts obtained in Lima River water, but very close to the adsorbed amounts of the mixed acetaminophen with phenobarbital (Table 42). In addition, it is preferentially adsorbed. Its adsorption in the presence of ibuprofen is also very close to its adsorption individually without obvious preference towards one or to other.

Phenobarbital presents very low adsorbed amounts in Lima River water on TpBD-Me_2 whether alone or mixed with either of the other two molecules.

V.3.2.2. In lake water

In lake water, ibuprofen was adsorbed more efficiently than acetaminophen, with 30 mg g^{-1} in equimolar solution (100/100 µM) mixed with acetaminophen with 14 mg g^{-1} on TpBD-Me_2 (Table 42, Figure 83). The adsorption of acetaminophen at 50 µM mixed with 150 µM of ibuprofen is close to zero, while the adsorbed quantity of ibuprofen is 41 mg g^{-1}. The adsorbed quantity of acetaminophen at 150 µM is 26 mg g^{-1} compared to 11 mg g^{-1} of ibuprofen at an initial concentration of 50 µM.

In lake water, the adsorption of ibuprofen in binary mixture presents the highest adsorbed amounts in the mixture when its presence is with sufficient quantity (equimolar or more) and becomes more competitive than the other two molecules (Figure 83).

Acetaminophen presents a preferal adsorption in binary mixture with phenobarbital onto TpBD-Me_2 in lake water even at concentration ratios 1/3. (Figure 83), in fact, phenobarbital is practically not adsorbed in its presence.

Even if it is poorly adsorbed, phenobarbital presents a slight higher adsorbed quantity in the presence of ibuprofen and it is adsorbed preferentially at concentration of three times higher than ibuprofen which is preferentially adsorbed at equimolar initial concentrations.

Acetaminophen is preferentially adsorbed in the presence of ibuprofen at concentration of three times more concentrated, but the phenomenon reverses as soon as the concentration of ibuprofen increases and the adsorption of acetaminophen became nul at the ratio of 3/1 for IBU/ACE pair (Table 43).

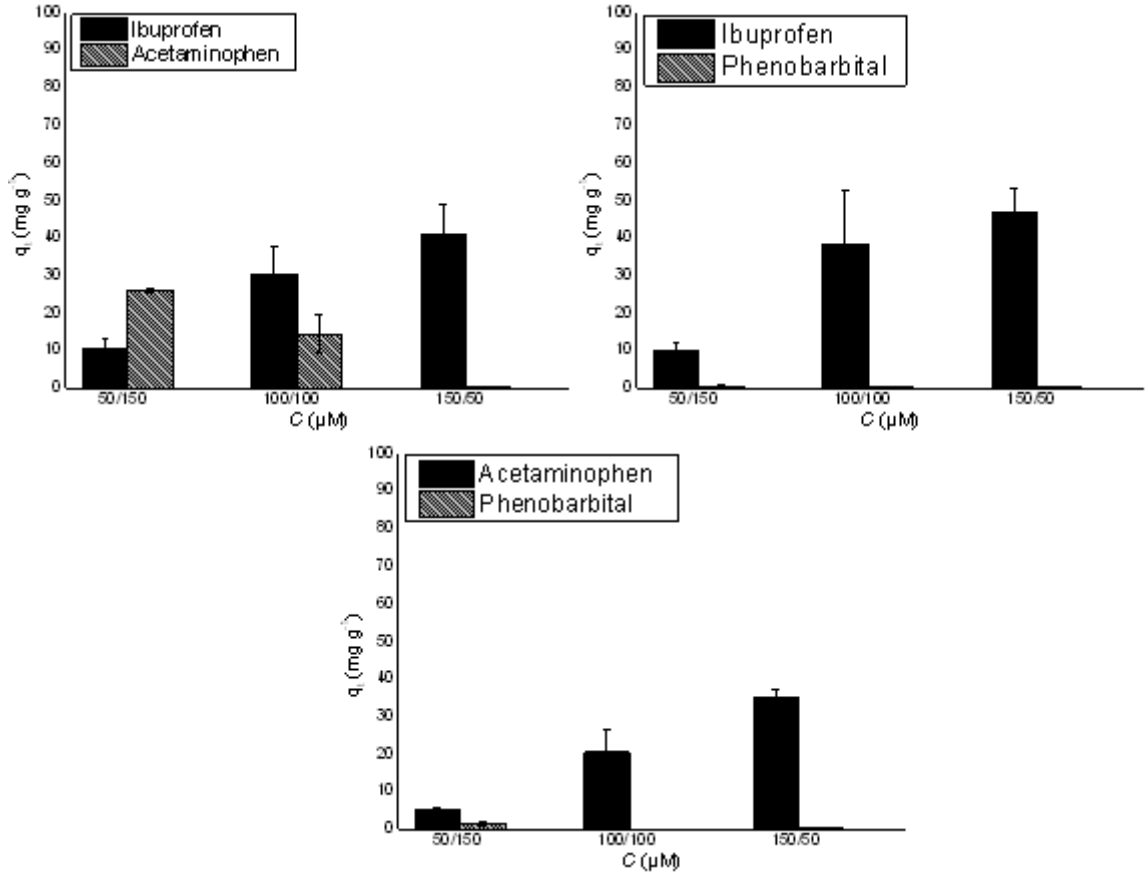

Figure 83 Adsorption of mixed ibuprofen/acetaminophen, ibuprofen/phenobarbital, and acetaminophen/phenobarbital by TpBD-Me_2 expressed as the quantity adsorbed q_t (mg g^{-1}) at 21°C in lake water at proportional concentrations (C_0(pharmaceutical) = 50/150, 100/100, 150/50 µM; C(COF) = 333 mg L^{-1}).

The adsorption of ibuprofen in ultrapure water at an initial concentration of 50 mg L^{-1} onto TpBD-Me_2 was 113 mg g^{-1}, which is much higher than its quantity adsorbed in lake water. The adsorbed amount of ibuprofen in binary mixture is much lower than the initial amount adsorbed in ultrapure water but is similar to the adsorbed amounts obtained during its adsorption individually (Table 43).

The adsorption of acetaminophen in ultrapure water at an initial concentration of 50 mg L^{-1} onto TpBD-Me_2 presents a quantity of 57 mg g^{-1} much higher than that obtained during its adsorption alone in lake water. In mixture with the two other molecules, it gives an adsorption practically nul at low concentration. At equimolar concentration, its adsorbed quantities exceed those obtained individually, and it is preferentially adsorbed on the TpBD-Me_2 (Table 43).

Table 43 Adsorption of mixed IBU/ACE, IBU/PHEN, and ACE/PHEN at different proportional concentrations by TpBD-Me_2 in lake water at 21°C expressed as the quantity adsorbed q_t (mg g^{-1}).

	q_t (mg g^{-1}) / Lake water/ TpBD-Me_2		
C(µM)	IBU/PHEN	IBU/ACE	ACE/PHEN
50/150	11/14	11/26	5/2
100/100	38/7	30/14	20/0
150/50	47/2	41/0	35/0
	IBU	PHEN	ACE
50 µM (10 mg L^{-1})	0	0	2
100 µM (21 mg L^{-1})	30	1	6
150 µM (31 mg L^{-1}),	35	2	14
q_t (mg g^{-1}) / ultra pure water			
50 mg L^{-1}	133		57

The adsorbed quantity of phenobarbital in lake water at initial concentrations of 50 µM/150 µM, 100 µM/100 µM, and 150 µM/50 µM phenobarbital/ibuprofen were 0 mg g^{-1}, 0 mg g^{-1}, and 1 mg g^{-1}, respectively, and do not present an important difference compared to its individual adsorption, in which 0 mg g^{-1}, 1 mg g^{-1}, 2 mg g^{-1} were adsorbed at initial concentrations of 50 µM 100 µM 150 µM, respectively (Table 42, Figure 77, 83).

Phenobarbital do not practically adsorbed on TpBD-Me_2 in lake water either individually or in binary mixture with acetaminophen. Contrariwise, its adsorption improves in the presence of ibuprofen, and it is also preferentially adsorbed at concentration ratio 3/1 of PHE/IBU (Table 43). This is reversed at the ratio 1/1 of the two molecules, and the adsorption of phenobarbital became nul at concentration ratio 1/3 of PHE/IBU.

V.3.2.3. In estuary water

The results of adsorption of mixed ibuprofen, acetaminophen, and phenobarbital onto TpBD-Me_2 at different concentrations ratios in Estuary water are presented in Figure 84. The adsorbed amounts of ibuprofen and acetaminophen are quite close and they do not show a preferential adsorption in binary mixture. On the other hand, they are preferentially adsorbed in the presence of phenobarbital, which is very poorly adsorbed on TpBD-Me_2 (Figure 84, Table 44).

The adsorption of ibuprofen in ultrapure water at an initial concentration of 50 mg L^{-1} onto TpBD-Me_2 was 113 mg g^{-1}, then much higher than its adsorbed quantity alone in estuary water. These values remain virtually unchanged in binary mixture of ibuprofen with other molecules (Table 44).

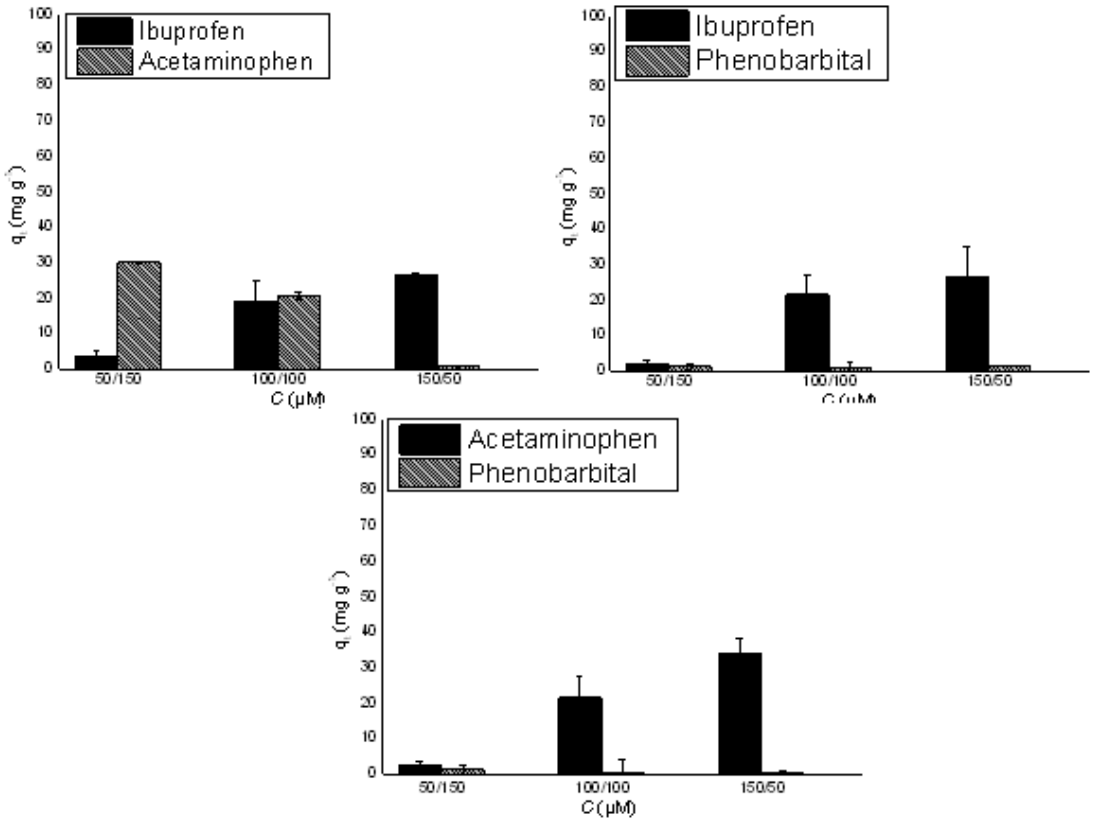

Figure 84 Adsorption of mixed ibuprofen/acetaminophen, ibuprofen/phenobarbital, and acetaminophen/phenobarbital by TpBD-Me_2 expressed as the quantity adsorbed q_t (mg g^{-1}) at 21°C in Estuary water at proportional concentrations (C_0(pharmaceutical) = 50/150, 100/100, 150/50 µM; C(COF) = 333 mg L^{-1}).

The adsorption of acetaminophen in ultrapure water at an initial concentration of 50 mg L^{-1} onto TpBD-Me_2 was 57 mg g^{-1}, then much higher than the quantity adsorbed in estuary water. The adsorbed amounts of acetaminophen in binary mixture with other molecules in the estuary water are slightly higher than those given by its individual adsorption (Table 44).

Table 44 Adsorption of mixed IBU/ACE, IBU/PHEN, and ACE/PHEN at different proportional concentrations by TpBD-Me$_2$ in Estuary water at 21°C expressed as the quantity adsorbed q_t (mg g^{-1}).

	q_t (mg g^{-1})/Estuary water/ TpBD-Me$_2$		
C(µM)	IBU/PHEN	IBU/ACE	ACE/PHEN
50/150	2/1	3/30	3/1
100/100	22/1	19/21	22/0
150/50	27/1	26/1	34/0
	IBU	PHEN	ACE
50 µM (10 mg L^{-1})	2	1	2
100 µM (21 mg L^{-1})	25	0	16
150 µM (31 mg L^{-1}),	30	1	17
q_t (mg g^{-1}) / ultra pure water			
50 mg L^{-1}	113		57

Phenobarbital is not practically adsorbed by TpBD-Me$_2$ either alone or in mixture in Estuary waters.

V.3.2.4. In Fonte de Forjães water

In the water sample from Fonte de Forjães, the adsorption of mixed ibuprofen, acetaminophen, and phenobarbital onto TpBD-Me$_2$ at different concentrations is presented in Table 44 and Figure 85. Ibuprofen presents a high adsorbed quantity at different initial concentrations compared to acetaminophen and phenobarbital. It is preferentially adsorbed even at low concentration (ratio 1/3).

The adsorption of mixed acetaminophen with phenobarbital on TpBD-Me$_2$ in Fonte Forjães water is preferentially adsorbed at sufficient concentrations (ratio 1/1). For the ratio 1/3 of ACE/PHEN, neither of the two molecules is adsorbed. Acetaminophen exhibits the same behavior and practically the same adsorbed amounts in binary mixture with ibuprofen.

The adsorbent TpBD-Me$_2$ has no affinity to the mixed phenobarbital with ibuprofen or acetaminophen (Table 45).

The adsorption of ibuprofen in ultrapure water at an initial concentration of 50 mg L^{-1} onto TpBD-Me$_2$, 113 mg g^{-1}, was higher than its adsorbed quantity, alone, in Fonte de Forjães water (Table 45). These quantities are practically found for mixed ibuprofen with either phenobarbital or acetaminophen, with which it is preferentially adsorbed as soon as its concentration equals or exceeds that of acetaminophen.

The adsorption of acetaminophen alone in ultrapure water, 57 mg g^{-1}, is much lower than that obtained with ibuprofen and much decreases in the water of Fonte de Forjães. The adsorbed quantities of mixed acetaminophen in the Fonte de Forjães water do not present a significant difference compared to those given by its individual adsorption (Table 45).

Phenobarbital do not practically adsorbed alone by TpBD-Me$_2$ as well as in mixture (Table 45). This adsorbent has practically no affinity for this molecule.

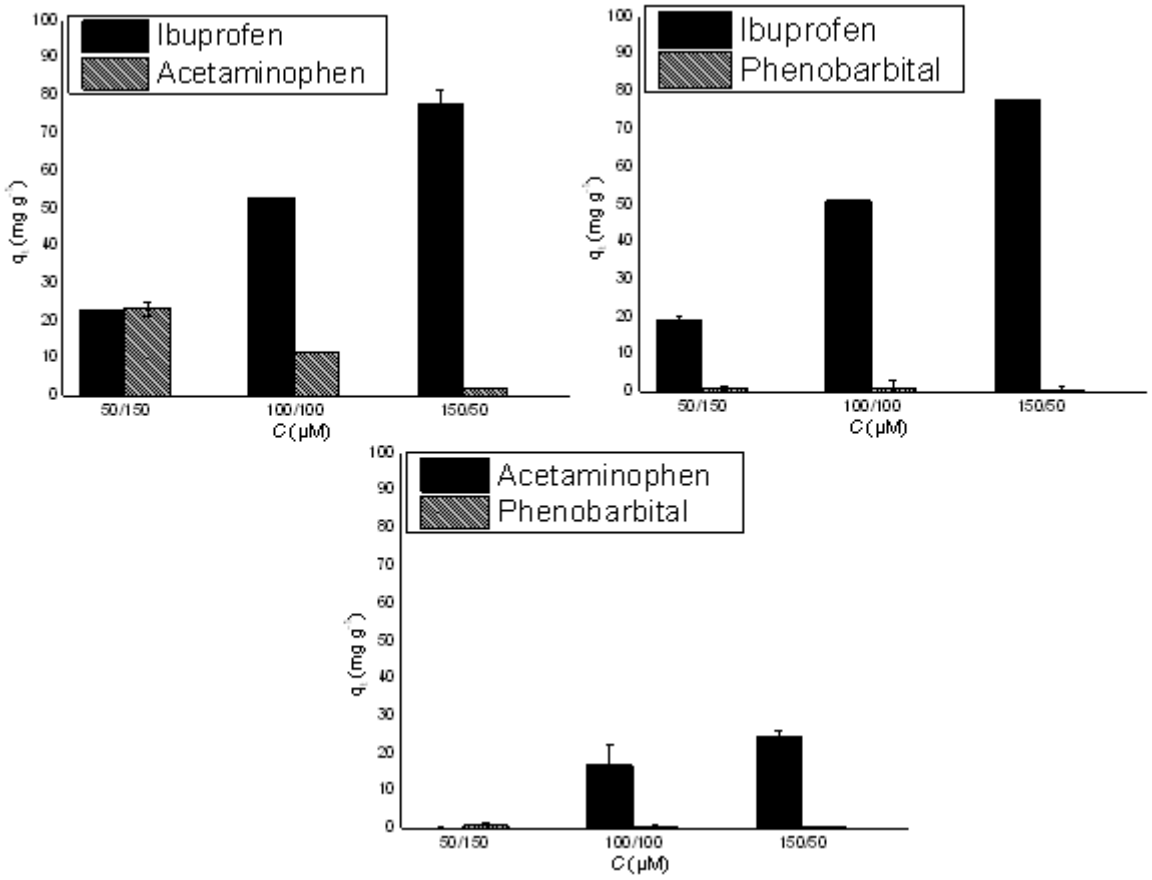

Figure 85 Adsorption of mixed ibuprofen/acetaminophen, ibuprofen/phenobarbital, and acetaminophen/phenobarbital by TpBD-Me$_2$ expressed as the quantity adsorbed q_t (mg g^{-1}) at 21°C in Fonte de Forjães water at proportional concentrations (C_0(pharmaceutical) = 50/150, 100/100, 150/50 µM; C(COF) = 333 mg L^{-1}).

Table 45 Adsorption of mixed IBU/ACE, IBU/PHEN, and ACE/PHEN at different proportional concentrations by TpBD-Me$_2$ in Fonte de Forjães at 21°C expressed as the quantity adsorbed q_t (mg g^{-1}).

	q_t (mg g^{-1})/ *Fonte de Forjães water/* TpBD-Me$_2$		
C(µM)	IBU/PHEN	IBU/ACE	ACE/PHEN
50/150	19/1	23/23	0/1
100/100	51/1	53/12	17/1
150/50	78/0	78/2	24/1
	IBU	PHEN	ACE
50 µM (10 mg L^{-1})	29	0.55	1.5
100 µM (21 mg L^{-1})	58	0.67	15
150 µM (31 mg L^{-1}),	82	0.82	26
q_t (mg g^{-1}) / ultra pure water			
50 mg L^{-1}	113		57

Table 46 summarizes the results obtained for the adsorption of ibuprophen and acetaminophen on TpBD-Me_2 in the different real waters.

Table 46 Adsorption of ibuprofen and acetaminophen alone, and in binary mixture IBU/PHEN and IBU/ACE at different proportional concentrations 1/3; 1/1 and 3/1 by TpBD-Me_2 in different real waters at 21°C expressed as the quantity adsorbed q_t (mg g^{-1}).

	q_t (mg g^{-1}) IBU; IBU/PHEN/ TpBD-Me_2							
	Rivière Lima		Eau du Lac		Fonte de Forjães		Estuaire	
50/150	21	23/3	0	11/14	29	19/1	2	2/1
100/100	25	57/3	30	38/7	58	51/1	25	22/1
150/50	32	91/1	35	47/2	82	78/0	30	27/1
	q_t (mg g^{-1}) IBU/ACE; ACE/ TpBD-Me_2							
50/150	8/23	19	11/26	14	23/23	26	3/30	17
100/100	9/12	11	30/14	6	53/12	15	19/21	16
150/50	11/5	8	41/0	2	78/2	1	26/1	2

Conclusion: The competitive adsorption on the COFs TpBD-$(CF_3)_2$ and TpBD-Me_2 using real water samples shows that the adsorbed quantities of pharmaceuticals in binary mixtures at different initial concentrations varied according to the type of water used. This variation indicates a competition between pharmaceuticals and other compounds to be adsorbed onto COFs. Extended previous studies of adsorption onto different adsorbents such as activated carbon on real water have been reported for some other pharmaceutical compounds **(Xiao et al, 2004; Mansouri et al, 2015)**. Morever, the adsorbed quantity of pharmaceuticals in binary mixtures in real water may be affected by the salinity, alkalinity, surface charge, and ionization state of the compounds leading to electrostatic interactions **(Mansouri et al, 2015)**, and the effect of porosity and surface area on the adsorption performance of the material (**Radovic et al., 1997).** TpBD-$(CF_3)_2$ shows the best adsorption performance in real water. This material has a surface area of 870 m^2 $g^{-1}$and a pore volume of 0.50 cm^3 g^{-1}. Its surface area and porosity are much greater than that of TpBD-Me_2 (520 m^2 g^{-1} and 0.38 cm^3 g^{-1}) **(Chandra et al, 2013)**.

The pharmaceutical adsorption is greatly influenced as well by the pH of water samples for both individual and mixed adsorption. Individual ibuprofen presented the highest adsorbed quantity in Fonte of Forjães and lake water which were characterized by a low pH of 4.9 and 6.5, respectively. A quantity of 88 mg g^{-1} of individual ibuprofen was adsorbed onto TpBD-$(CF_3)_2$ compared to 11 mg g^{-1} and 19 mg g^{-1} of acetaminophen and phenobarbital, respectively, at an initial concentration of 150 µM. The adsorbed quantity of ibuprofen onto

TpBD-Me_2 presented a high adsorbed quantity in Fonte of Forjães water with 82 mg g^{-1} compared to 25 mg g^{-1} and 1 mg g^{-1} of acetaminophen and phenobarbital, respectively (Figure 76, 77). Those results are confirmed by the adsorption of ibuprofen and acetaminophen onto TpBD-$(CF_3)_2$ in ultrapure water at different pH, where ibuprofen presented a high adsorbed quantity of 140 mg g^{-1} at pH 2 compared to 2 mg g^{-1} of acetaminophen.

The pH had influence on the competitive adsorption of pharmaceuticals onto COFs as well. The adsorption of ibuprofen mixed with acetaminophen onto TpBD-$(CF_3)_2$ in Fonte of Forjães and lake water presented a high quantity adsorbed with 78 mg g^{-1} and 88 mg g^{-1}, respectively, at an initial concentration of 150 µM, similar to 85 mg g^{-1} of its mixed adsorption with phenobarbital at 50 µM in Lima River (Figure 78, 79). The mixed adsorption of ibuprofen with acetaminophen and phenobarbital onto TpBD-$(CF_3)_2$ showed the least adsorbed quantity compared to its adsorption in other real water samples.

The pH also influenced the competitive adsorption of ibuprofen mixed with acetaminophen and phenobarbital onto TpBD-Me_2 in Fonte of Forjães water which presented a same adsorbed quantity of 78 mg g^{-1} at an initial concentration of ibuprofen at 150 µM with 50 µM of mixed acetaminophen and phenobarbital (Figure 85). The adsorption of ibuprofen onto TpBD-Me_2 in Lima River water presented a high adsorbed quantity of 91 mg g^{-1} at initial proportional concentration of 150 µM/50 µM ibuprofen/phenobarbital. The mixed adsorption of ibuprofen with acetaminophen and phenobarbital onto TpBD-Me_2 in estuary water showed as well the least adsorbed quantity compared to its adsorption in other real water samples (Figure 84).

Ibuprofen is adsorbed in greater quantity onto both TpBD-$(CF_3)_2$ and TpBD-Me_2 in real water compared to acetaminophen and phenobarbital, showing that the least polar pharmaceutical has the highest affinity to the COFs.

CONCLUSIONS AND OUTLOOK

Conclusions and outlook

This work intended to be a contribution to the elimination of residues of four drug molecules present in waters: ibuprofen, acetaminophen, ampicillin and phenobarbital, products widely used in Algeria and in the world, by adsorption, interesting technique to fight against contaminants due to its simplicity, low cost, and wide applicability.

The survey conducted on pharmaceuticals in Algeria, based on statistics showing a high consumption of pharmaceuticals by the people compared with global statistics. Expired pharmaceuticals that have been eliminated by consumers show that 64% are thrown in the trash by consumers and 32% in the toilet, which increases the potential risks associated with the presence of pharmaceutical compounds in the environment. This study has allowed us to situate the consumption and the management of pharmaceutical products in Algeria compared to the rest of the world, highlighting the products widely used whether in Algeria or worldwide and to select among these products the four molecules to be studied, namely: ibuprofen, acetaminophen, ampicillin and phenobarbital.

The experimental tests were carried out using a batch adsorption technique to compare the adsorption and co-adsorption effect of the four pharmaceutical products onto the COFs (Covalent Organic Frameworks) TpBD-$(CF_3)_2$ and TpBD-Me_2 and activated carbon PAC (F400) in ultrapure water and in real water samples.

The interest is focused about this type of emerging adsorbents, COFs, which are a new class of porous materials, composed of crystalline and porous covalent bonds, which have rigid structures, exceptional thermal stability and a permanent porosity whose high specific surfaces allow them to be good and promising adsorbents.

The adsorption processes of two pharmaceuticals, ibuprofen and phenobarbital on activated carbon were evaluated in ultrapure water. Activated carbon PAC F400 can effectively remove the pharmaceuticals in the solution. It was found that logK_{ow}, pKa value, and molecular weight affected the adsorption capacities of the target compounds on activated carbon. This study showed that non-polar ibuprofen had a good adsorption capacity compared to phenobarbital.

According to, Tow COFs TpBD-$(CF_3)_2$ and TpBD-Me_2 have tested as adsorbents, where the obtained results show that the Covalent Organic Frameworks adsorb ibuprofen better than ampicillin and acetaminophen, confirming that COFs have a preferential affinity towards

lipophilic pharmaceuticals as typical for organic adsorbents. This confirms the obtained results with activated carbon, which also adsorbed lipophilic ibuprofen better than phenobarbital, which justifies the fact that the adsorption of phenobarbital was not monitored on the COFs. In addition to polarity, the size of the pharmaceutical molecules also influences the process of adsorption. Indeed, COFs, due to their restricted pore size, can function as size-selective adsorbents.

A state of equilibrium was reached after about 1h, 45min, 10min of contact between the adsorbate TpBD-Me_2 and the adsorbent ibuprofen, ampicillin and acetaminophen, respectively, and after 10 min for all drugs adsorbed on TpBD-$(CF_3)_2$. These time periods are very short compared to the results of the adsorption of ibuprofen and phenobarbital onto PAC (F400), where the equilibrium is reached after 180 min, and 4h when adsorbing naproxen onto MOFs **(Seo et al, 2016).**

The pseudo second-order kinetic model was found to describe well the adsorption kinetics of ibuprofen, acetaminophen, and ampicillin onto TpBD-$(CF_3)_2$ and TpBD-Me_2, as well as ibuprofen and phenobarbital adsorbed onto PAC (F400). The intra-particle Weber–Morris diffusion model also fit the experimental values obtained.

The adsorption isotherms of ibuprofen, acetaminophen, and ampicillin on TpBD-Me_2 and TpBD-$(CF_3)_2$ are of type H (high affinity) for both ibuprofen and ampicillin. Type H isotherms are observed with porous materials, in which a single layer of molecules adsorbs at low pressure, a multilayers start to form and the pores are filled at intermediate pressure and a saturation at high pressure (**Butt et al., 2003)**. The type of isotherm for the adsorption of acetaminophen is type L. The type L isotherms exhibit a downward concavity at low concentrations of the solution, which reflects a decrease in free sites as the adsorption of acetaminophen on the COFs progresses **(Belmouden, 2008)**.

The high values of the correlation coefficient R^2 given by the Langmuir model allows to conclude that the experimental data are well described by this model for ibuprofen and ampicillin on TpBD-Me_2. It fits best, as well, the experimental data of the adsorption of ibuprofen on TpBD-$(CF_3)_2$ and PAC (F400). This model of Langmuir fits, as well, best the adsorption of phenobarbital onto PAC (F400)

The pH effect on the adsorption capacity of lipophilic ibuprofen and both hydrophilic pharmaceuticals acetaminophen and ampicillin onto TpBD-$(CF_3)2$ in an low acidic medium (pH=2) and in basic medium (pH =10) showed that ibuprofen is adsorbed at pH 2 with high

efficiency due to enhanced interaction with TpBD-$(CF_3)_2$ caused by the protonation of the carboxylic acid moiety and the increased water−octanol distribution coefficient log*D* at pH 2 of ~3.5. The ibuprofen adsorption capacity is dramatically decreased at pH 10, due to repulsions between ibuprofen and TpBD-$(CF_3)_2$.

The adsorption studies of ibuprofen, acetaminophen, and phenobarbital individually and in binary mixtures in four real water samples: Lima River, lake, estuary, and Fonte de Forjães, to evaluate the capacity of COFs to simultaneously remove these pollutants from real water. The adsorbed quantity q_t of ibuprofen, acetaminophen, and ampicillin on both COFs in real water samples was decreased as compared to ultrapure water. Ibuprofen alone presented a high adsorption capacity in both COFs in different real waters compared to acetaminophen and phenobarbital. This may be explained by its lipophilic character as illustrated by its high logK_{ow}. The adsorption capacity of phenobarbital alone is nearly zero on TpBD-Me_2. This adsorption capacity of phenobarbital is very close to the adsorption capacity of ibuprofen by TpBD-$(CF_3)_2$ in Lima River, and smaller than ibuprofen in the other real water samples. This can be explained by the hydrophobic character and molecule size and the competition with other compounds from the water matrix have an effect on the slight of phenobarbital.

Acetaminophen alone presents relatively a low adsorption capacity onto COFs.

The studied real waters are characterized by different features, which clearly have an effect on the competitive adsorption of the pharmaceuticals by COFs. The variation of the adsorption capacity can be related with the competition between the pharmaceuticals and other compounds to be adsorbed onto COFs. The water characteristics such as salinity, alkalinity, density of surface charges on the COFs and the ionization state of the compounds leading to electrostatic interactions and pH solution (Table 12) affect the adsorption capacity of the adsorption of pharmaceuticals in binary mixtures in real water.

Also, the factors of porosity and surface area play an important role in adsorption. TpBD-$(CF_3)_2$ with a high surface area compared to TpBD-Me_2 presents a preferential adsorption capacity towards pharmaceuticals. These results justify the interest towards these adsorbents for serving in the elimination of pharmaceutical pollutants by the competitive adsorption.

This study carried out in synthetic water and real waters for four pharmaceutical molecules, gave very promising results with regard to the possibility of eliminating residues of pharmaceuticals from water by Covalent Organic Frameworks. It would be interesting on the one hand to carry out these studies on Algerian real waters and on the other hand, to

deepen this work by studying the behavior of other pharmaceutical molecules with regard to these adsorbents and to carry out these studies with other COFs with more suitable structures that will allow the total elimination of pharmaceutical residues from water that can harm human health.

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ANNEX

Presentation of the questionnaire addressed to pharmacists suppliers manufacturers, consumers

The questionnaire consists of four parts:

- The first part is devoted to the activity of pharmacies and information on the quantities and types of pharmaceuticals sold, thus the methods used to get rid of outdated products, and collects their views on the recent regulatory evolution.
- The second part is devoted to the activity of the manufacturers and information on the quantities and types of pharmaceuticals sold, thus the methods used to get rid of outdated products.
- The third part collects information on consumers about the quantities of drugs consumed, the types of diseases for which drugs are consumed and how to get rid of expired products.
- Finally, the fourth part asks the suppliers about their possible involvement in the collection of obsolete products of their ways to rid them, the quantities supplied and gather their opinions on the recent evolution of the regulation.
- The questions asked are most often closed-ended questions.

Enquête sur la commercialisation, la consommation et l'utilisation des médicaments (Officines)

1- Are you:

-owner :	☐	-employee :	☐
Private :	☐	-state :	☐

2- Exercice place:…….

3- Address: ……..

4- Training: ……

5- Since when do you practice this profession? :

……

6- Do you know the regulations relating to the marketing of pharmaceutical products? :

- Yes :	☐	-No :	☐

7- Does it happen that drug inspectors inspect your pharmacy? :

- Yes :	☐	-No :	☐

8- The command of pharmaceutical products:

- Is according to your choice:	☐
- Is imposed by the supplier:	☐
- Is done according to the recommendations of the health service:	☐

9-Your choice of products is according to:

- Most requested:	☐	- The active ingredient:	☐
- The most effective:	☐	-The good brands:	☐
- Other: indicates:	☐		

10- What are the most requested brands:

-……..…… -……..

-……..…… -……..

-……..…… -……..

-……..…… -……..

-……..…… -……..

-……..…… -……..

-……..…… -……..

-……..…… -……..

11- Do you check that your products are approved? :

- Yes :	☐	-No :	☐

12- Do you ever receive unapproved products? :

- Yes :	☐	-No :	☐

13- Do you ever receive expired products? :

- Yes :	☐	-No :	☐

14- What do you do with these expired products? :

- You send them back to the supplier:

- Yes :	☐	-No :	☐

- Do you sell them? :

- Yes :	☐	-No :	☐

- You store them:

- Yes :	☐	-No :	☐

If yes where? : .....

- Duration of this storage? : .....

- You destroy them? :

- Yes :	☐	-No :	☐

If yes where? : .....

15- Have you noticed an extension of the expiry times for certain products? :

- Yes :	☐	-No :	☐

16- Does it happen that products are withdrawn from the market?

- Yes :	☐	-No :	☐

17- Do Algerians consume too much medicine?:

- Yes :	☐	-No :	☐

18- How to choose the type of products made? :

-Price:	☐	-Performance:	☐
-The most requested:	☐	-Other	☐

19- Which products are the most sold?

Product Name	Product Type	Quantity Sold / Me (%)

20-How is the sale made of your products (pharmacist)? :

- The finding of the existence of a disease that spreads.	☐
- At the request of one or more products specified by the medicine.	☐

21- The choice of the product is based on:

- From the price:	☐	- From the commercial name	☐
-Of availability:	☐	-Other	☐

22- Do you notice an evolution in the consumption of medicines? :

- Yes :	☐	-No :	☐

23- How many medications do you deliver per day on average? : ....

24- What are the most common symptoms for which patients ask for medication? :

1)	2)	3) .....
4)	.5)	6) .....
7)	.8)	9) .....

25- Which are the most often sold drug classes (1 answer or several classified by priority)?

-Antalgic, Antipyretic:	☐	-Antigrippals	☐	-An inflammatory:	☐
-Antiptic and disinfectant:	☐	-Antihistamine:	☐	-Antibiotic	☐
- Antitussive, Expectorants:	☐	-Antiasthenic:	☐	-Contraceptives:	☐
-Complements(vitamin, anti-anemia):	☐	-Medicines of the digestive tract:	☐	-Other:	☐

26- Do you sell toxic, radioactive and dangerous drugs:

- Yes:	☐	-No :	☐

If yes

Which: .....

27- What are the high-use medications:

- ..... - .....

- ..... - .....

- ..... - .....

28- Give you advice to consumers regarding the clearance of medicines:

- Yes :	☐	-No :	☐

29- Do you throw away the rest of the expired medicines in the sanitary facilities?

- Yes :	☐	-No :	☐

PRIVATE SECTOR:

1-Number of wholesale distributors:

☐	-Not Evaluated:	☐

2-Number of private pharmacies:

☐	-Not Evaluated:	☐

3-Number of private medical clinics:

☐	-Not Evaluated:	☐

4-Number of private hospitals:

☐	-Not Evaluated:	☐

1-Percentage of drugs managed by the private sector:

☐	-Not Evaluated:	☐

Norm, Regulations, Laws and Policies Relating to Pharmaceutical and Sanitary Products:

1-Is there a national policy for the control of drugs consumed?:

-Yes:	☐	-No:	☐	-Not Evaluated:	☐

Note ……

2- Is there a national policy of environmental protection against the risks of contamination by drugs?

-Yes:	☐	-No:	☐	-Not Evaluated:	☐

Note: ……

3-Is there a plan for the implementation of the national policy of environmental protection against the risks of contamination by drugs?

-Yes:	☐	-No:	☐	-Not Evaluated:	☐

Note:

……

Enquête sur la commercialisation, la consommation et l'utilisation des médicaments (Fabricant)

1- Are you:

-owner :	☐	-employee :	☐
Private :	☐	-state :	☐

2- Exercice place: …….

3- Address: ……..

4- Training: ……

5- Since when do you practice this profession?:

…….

7- Do you know the regulations relating to the manufacture of pharmaceutical products ?:

- Yes :	☐	-No :	☐

8- Does it happen that inspectors of pharmaceutical products inspect your factory? :

- Yes :	☐	-No :	☐

9- The manufacture of pharmaceutical products:

- Is done according to the supplier's choice:	- Yes:	☐	No:	☐
- Is imposed by the supplier:	- Yes:	☐	No:	☐
- Is done according to the supplier's recommendations:	- Yes:	☐	No:	☐

10- Your choice of products to manufacture is according to:

- The most recommended by the suppliers:	☐	- The availability of the raw material:	☐
- The requirements of the state:	☐	-The needs of the market:	☐
-Other,	☐	Give details: ……	

11- What are the most requested products:

- .... - ....
- .... - ....
- .... - ....
- .... - ....
- .... - ....
- .... - ....

12- What are the manufactured products:

- .... - ....

- .... - ....

- .... - ....

- .... - ....

- .... - ....

- .... - ....

13- The raw materials that you use are:

- local:	☐	- imported:	☐

14- The raw materials you use are subject to state control:

- Yes :	☐	-No :	☐

15- Do you ever receive raw materials that are out of date?

- Yes :	☐	-No :	☐

16- Do you check that your raw materials are approved?

- Yes :	☐	-No :	☐

17- Do you ever receive unapproved raw materials? :

- Yes :	☐	-No :	☐

18- Are all your manufactured products approved? :

- Yes :	☐	-No :	☐

19- What do you do with outdated raw materials? :

- You send them back to the supplier:

- Yes :	☐	-No :	☐

- You store them:

- Yes :	☐	-No :	☐

- If yes where? : .....

- Duration of this storage? : .....

- Do you sell them? :

- Yes :	☐	-No :	☐

- You destroy them? :

- Yes :	☐	-No :	☐

If yes where? : .....

20- Do you have outdated products?

- Yes :	☐	-No :	☐

21- What do you do with these outdated products? :

- You send them back to the supplier:

- Yes :	☐	-No :	☐

- You store them:

- Yes :	☐	-No :	☐

- If yes where? : .....

- Duration of this storage? : .....

- Do you sell them? :

- Yes :	☐	-No :	☐

- You destroy them?

- Yes :	☐	-No :	☐

22- Have you noticed an extension of the expiry periods for certain products? :

- Yes :	☐	-No :	☐

23- Does it happen that products are withdrawn from the market:

- Yes :	☐	-No :	☐

24- how many products do you make per day on average? : ....

25- How is the choice of products made? :

-Prices:	☐	-Performance	☐
-Most requested:	☐	-Other	☐

7- Do you notice an evolution in the consumption of medicines? :

- Yes :	☐	-No :	☐

28- What are the most common symptoms for which providers ask for medicines? :

1)	2)	3) .....
4)..... .	5).....	6).....

29- Do you have a treatment plant (Step) in your manufacturing unit? :

- Yes :	☐	-No :	☐

30- Do you manufacture toxic and dangerous drugs:

which:

.....

.....

.....

31- Do you have a system designed for plumb water in your manufacturing unit:

- Yes :	☐	-No :	☐

32- Give you advice to suppliers regarding the removal of your products:

- Yes :	☐	-No :	☐

33- Throw the rest of raw materials or obsolete manufactured products in the toilets:

- Yes :	☐	-No :	☐

Drug Marketing, Use and Use Survey (Suppliers)

1- Are you:

-Owner :	☐	-Employee	☐
-Private :	☐	state :	☐

2- Exercice place: …….

3- Address: ……..

5- Training : ……..

5- Since when do you practice this profession? :……

6- Do you know the regulations on the marketing of pharmaceutical products ?:

- Yes :	☐	-No :	☐

7- Does it happen that drug inspectors inspect your store? :

- Yes :	☐	-No :	☐

8- The order of pharmaceutical products:

- Is according to market demand	☐
- Is imposed by the pharmacies:	☐
- According to the pharmacist's recommendations:	☐

2- Your choice of products is according to:

- Most requested:	☐	- Active products:	☐
- The most effective:	☐	-The good brands:	☐
-Other,	☐	Give details: ……	

3- Which brands are the most sold?

- .... - ....

- .... - ....

- .... - ....

- .... - ....

- .... - ....

4- Do you check that your products are approved? :

- Yes :	☐	-No :	☐

5- Do you ever receive unapproved products? :

- Yes :	☐	-No :	☐

6- Do you ever receive expired products? :

- Yes :	☐	-No :	☐

7- What do you do with these expired products? :

- You send them back to the manufacturers:	- Yes:	☐	No:	☐
- You store them: -If yes where? : ..... - Duration of this storage? :	- Yes:	☐	No:	☐
Do you sell them? :	- Yes:	☐	No:	☐
- You destroy them? : If yes where? :	- Yes:	☐	No:	☐

8- Have you noticed an extension of the expiry periods for certain products? :

- Yes :	☐	-No :	☐

9- Does it happen that products are withdrawn from the market?

- Yes :	☐	-No :	☐

10- Do Algerians consume too much medicine?

- Yes :	☐	-No :	☐

11- How is the choice of products made? :

-Price:	☐	-Performance:	☐
-The most requested:	☐	-Other,	☐

12- How is your product ordered? :

- The finding of the existence of a disease that spreads.	☐
At the request of one or more products specified by the medicine.	☐

13- The choice of the product is based on:

- From the price:	☐	- From the commercial name:	☐
-Of availability:	☐	-Other,	☐

14- Do you see an evolution in the consumption of drugs? :

- Yes :	☐	-No :	☐

15- Which products are the most sold?

Product Name	Product	Quantity Sold / Me (%)

21- How much medicine do you deliver per day on average? :

……...……

……..…..

22- What are the most common symptoms for which pharmacies ask for medicines? :

1)	2)	3) .....
4)	.5)	6) .....
7)	.8)	9) .....
10)	.11)	12) .....

11- What are the most frequently used medication brands

1)	2)	3) .....
4)	.5)	6) .....
7)	.8)	9) .....
10)	.11)	12) .....

12- Do you sell toxic and dangerous drugs?

- Yes :	☐	-No :	☐

- If so why:

……

……

……

13- What are the high-use drugs?

- ..... - .....

- ..... - .....

- ..... - .....

- ..... - .....

14- Give you advice to consumers regarding the clearance of medicines:

- Yes :	☐	-No :	☐

Marketing Survey, consumption and use of medicines (Consumer)

1- Are you:

-Owner :	☐	-Employee	☐
-Private :	☐	state :	☐

2- Exercice place: …….

3- Address: ……..

4- Level of study: .....

5- Place of exercise: .....

6- Do you have an illness?

- Yes :	☐	-No :	☐

Which? : ..... .

7- When do you see a doctor for a mild illness?

- First symptoms	☐	Later	☐	Not at all	☐

7- Your purchase of pharmaceutical products:

- Is done according to a prescription:	☐
- Without a prescription:	☐
- On the advice of a friend:	☐

8- Your choice of pharmaceutical products is according to:

- Availability:	☐	Local products:	☐
- The most effective:	☐	- The known brands:	☐
- Imported products:	☐	- Advised by doctors	☐
- Other	☐	Specify:……	

9- How many medications do you use per month / year on average? :

....

10 - What are the most common symptoms for which you consume medications?

1)	2)	3) .....
4)	.5)	6) .....

11 - Which drug classes are most often used in your home (1 answer or several prioritized)?

-Antalgic, Antipyretic:	☐	-Antigrippals:	☐	-An inflammatory:	☐
-Antiptic and disinfectant:	☐	Antihistamine:	☐	Antibiotic:	☐
- Antitussive, Expectorants:	☐	-Antiasthenic:	☐	-Contraceptives:	☐
-Complements (vitamin, anti-anemia):	☐	-Other:	☐		
-Medicines of the digestive tract:	☐				

12- What brands do you know? :

- .... - ....

- .... - ....

- .... - ....

- .... - ....

- .... - ....

13- Do you notice an evolution in your consumption of medicines?

- Yes :	☐	-No :	☐

14 - How is your choice of products made? :

- Price:	☐	- Performance:	☐
- Most requested:	☐	- Other	☐

15 - Do you check the expiry date of your medications?

- Yes :	☐	-No :	☐

16 - What do you do with these unused or expired products?

- You give them to the pharmacies:

- Yes :	☐	-No :	☐

- You store them at home:

- Yes :	☐	-No :	☐

- If yes where? : .....

- Duration of this storage? : .....

- You throw them in the trash?

- Yes :	☐	-No :	☐

- Do you throw them in the toilets?

- You destroy them? :

- Yes :	☐	-No :	☐

- If yes,

in what way ? ....

17 - Do you think that pharmaceuticals are harmless:

- For the man

- Yes :	☐	-No :	☐

- For the environment

- Yes :	☐	-No :	☐

If so,

What risks can they present?

.....

19 - What method do you recommend to rid these products?

……

……..….

……