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Psychiatric Pharmaceuticals as Emerging Contaminants in Wastewater



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Preface

The industrial revolution brought different benefits to society, some translated into the exponential development of medicine and pharmacy. The identification and differential diagnosis of some not so uncommon psychiatric diseases implied the generalized usage of specific pharmaceuticals, mainly by the so-called developed societies and, as a consequence, some very complex molecules reach urban wastewater treatment plants, which are not prepared to deal with them, to remove or degrade them, before accumulating into environment.

This condensed text tackles with the definition of the environmental problem resulting from the generalized consumption of psychiatric pharmaceuticals observed in the last few decades as a consequence of the degradation of social and economic circumstances of modern society. Classification, production and consumption of psychiatric pharmaceuticals are reviewed, as well as the processes through which these molecules reach and accumulate in the environment. The metabolic pathways of such pharmaceuticals are referred, and this justifies the toxicological assessment in terms of nontarget organisms. The text continues with the state of the art of conventional and advanced processes to remove and to degrade the main molecules associated with psychiatric pharmaceuticals. The analytical methods to quantify trace concentrations of such complex molecules are crucial to the success of the monitoring of this specific contamination, so they are reviewed and compared in a specific chapter. Finally, new perspectives on greener and more sustainable products and processes within pharmaceutical industry are considered and discussed in the final chapter.

This SpringerBriefs book aims to present a broad but summarized approach that may help researchers, students and engineers to build a solid perspective of this emerging issue.

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Chapter 1

Introduction

Abstract This first chapter is devoted to the definition of the environmental problem, in size and depth, resulting from the consumption of psychiatric pharmaceuticals. Classification of pharmaceuticals and overall figures concerning production and consumption are presented, substantiated by national, regional and worldwide examples. The lifecycle of pharmaceuticals is addressed in order to justify the environmental impact expected from the generalized usage of medicines. A global explanation and discussion is presented to clarify the processes through which those molecules reach and accumulate in environment. Particular attention is paid to main groups of psychiatric drugs and their relevant physical-chemical characteristics in terms of environmental impact are listed.

Keywords Environmental impact • Life-cycle • Pharmaceuticals • Psychiatric pharmaceuticals

1.1 Pharmaceuticals: An Overview

Pharmaceuticals are a large and diverse group of organic compounds used for the prevention and treatment of diseases in humans and animals. As a result of the rapid advances in medical science, new medications and treatments have been developed resulting in an increasing amount of drugs that are consumed. Currently, in the European Union there are more than 3000 different active pharmaceutical substances in the market such as analgesics, anti-inflammatories, contraceptives, antibiotics, neuroactive compounds, beta-blockers, lipid regulators, among many others (Fent et al. 2006). Similarly, a large number of these compounds are used in veterinary medicine, among them antibiotics and anti-inflammatories (Fent et al. 2006).

Although every aspect related to pharmaceutical efficacy and patient safety are under scrutiny, the full extent and consequences of the presence of pharmaceutical compounds in the environment have not been sufficiently studied yet. These

compounds are considered as emerging pollutants since they still remain unregulated or are currently under a regularization process (Esplugas et al. 2007).

Pharmaceutical compounds have been detected at trace concentrations (ng/L levels) in a wide variety of environmental water samples including sewage flows, rivers, lakes, groundwater aquifers and drinking water (Santos et al. 2010). Although the concentrations of these compounds in water bodies are very low, their continuous input may constitute in a potential hazard for living organisms. The adverse side effects that pharmaceuticals may have in wildlife and ecosystem health are still largely unknown, since these compounds are not tested for low doses and long-term exposure or when present in mixtures. Moreover, pharmaceutical compounds are frequently synthesized in order to remain unchanged during their passage through the human body, which makes them persistent pollutants in environmental matrices (EEA 2010). Therefore, over the past few years pharmaceuticals have been considered to be an emerging environmental problem.

Human pharmaceuticals are consumed in high quantities worldwide, in the range of tons per year per pharmaceutical compound, depending on the country. In 2004, the global consumption of pharmaceuticals used in human medicine was expected to be 100,000 tons per year, which corresponds to an average annual consumption of 15 g per capita. This value is estimated to be between 50 and 150 g in developed countries (Alder et al. 2006). In Germany, almost 5000 pharmaceuticals were registered for human use, 2700 of which accounted for 90 % of the total consumption, which in turn contained about 900 different active substances (Kümmerer 2001), whereas in the United Kingdom approximately 3000 actives substances are licensed. Within Europe, these two countries account for 46 % of the market volume of active substances, being followed by Spain, Russia and Italy (EEA 2010).

The trends on pharmaceuticals consumption clearly vary between different countries. According to the World Health Organization, 0.4 % of Japanese women of reproductive age take a contraceptive pill containing ethinyloestradiol, in comparison with 16 % in North America. Even though it is possible to find a similar consumption pattern for several pharmaceuticals among the members of the European Union, clear differences can also be observed for specific pharmaceutical compounds, namely amoxicillin, paracetamol and metformin (Table 1.1).

In Portugal, according to INFARMED (Portuguese National Authority of Medicines and Health), the 10 most commercialized pharmaceuticals compounds over the years 2010, 2011 and 2012 are listed in Table 1.2. As one can observe, simvastatin highlights in the first position of the ranking for the three years, while paracetamol, metformin and amoxicillin also find place in the “top 5” for the three years.

Table 1.1 Average annual consumption of selected pharmaceuticals, in g per person and year, for France, Germany, Poland, Spain and the UK, for the period from 1999–2006, adapted from Sadezky et al. (2010)

Class	Compound	Annual per capita consumption of pharmaceuticals (g/cap/y)				
		France	Germany	Spain	UK	Poland
Antibiotic	Amoxicillin	6.50	1.20	–	1.54	–
	Ciprofloxacin	0.21	0.17	0.09	0.12	0.13
	Clarithromycin	0.25	0.12	0.13	0.08	0.27
	Sulfamethoxazole	0.34	0.65	–	0.02	0.17
Mood stabilizer/ Antiepileptic	Carbamazepine	0.61	0.98	–	0.77	0.84
Analgesic	Tramadol	0.44	0.30	–	0.27	–
	Ibuprofen	3.4	3.2	2.6	2.8	5.04
	Paracetamol	47.14	4.46	3.60	15.68	4.84
Antidiabetic agent	Metformin	12.1	6.3	–	5.9	–

1.2 Sources of Contamination and Lifecycle of Pharmaceuticals

The widespread use of pharmaceuticals in human and veterinary medicine and agricultural products has led to the continual release of several pharmaceutical drugs into environmental matrices. After the administration and absorption by humans or animals, pharmaceuticals are metabolized, although substantial fractions of the original compounds are often excreted in unmetabolized forms or as metabolites via urine or feces. Therefore, a mixture of pharmaceuticals and their metabolites will enter into the wastewater systems or directly into the environment (Monteiro and Boxall 2010; Khetan and Collins 2007). During wastewater treatment many pharmaceutical compounds have poor biodegradability, resulting in the incomplete removal from the water phase and in the partitioning into solid phases including biosolids (such as sewage sludge). Pharmaceutical residuals have been found at concentrations up to $\mu\text{g/L}$ levels in effluents and up to mg/kg levels in biosolids (Wu et al. 2010; Heidler and Halden 2008).

Pharmaceuticals may reach the environment by a number of different routes, including human or animal excretions, wastewater effluents, industrial waste from manufacturing, medical waste from health-care and veterinary facilities, agriculture, landfill leachate and biosolids (WHO 2011). The lifecycle of pharmaceuticals (Fig. 1.1) starts with their production in the manufacturing process, during which wastewater may suffer contamination. After production, pharmaceuticals are used in human or veterinary medicine. After their excretion in urine and feces, human and veterinary drugs have quite different fates in the environment. Veterinary residues get into soil and groundwater without any sewage treatment, mainly through the deposition of manure on agricultural land. On the other hand, the excreted human pharmaceuticals and their active metabolites pass through wastewater treatment

Table 1.2 Pharmaceutical compounds ordered from the highest to the lowest sales amount in Portugal, over the years 2010/2011/2012 (INFARMED)

Ranking	2010		2011		2012	
	Active substance	Packages	Active substance	Packages	Active substance	Packages
1	Simvastatin	3,522,044	Simvastatin	3,440,703	Simvastatin	3,567,650
2	Paracetamol	3,261,561	Paracetamol	3,239,035	Paracetamol	2,912,093
3	Metformin	2,421,990	Metformin	2,482,609	Metformin	2,685,739
4	Alprazolam	2,394,980	Amoxicillin + clavulanic acid	2,406,428	Acetylsalicylic acid	2,456,275
5	Amoxicillin + clavulanic acid	2,259,992	Alprazolam	2,384,299	Amoxicillin + clavulanic acid	2,552,594
6	Omeprazole	2,249,083	Acetylsalicylic acid	2,296,395	Omeprazole	2,337,542
7	Trimetazidine	2,121,618	Omeprazole	2,263,145	Alprazolam	2,201,702
8	Acetylsalicylic acid	2,070,650	Trimetazidine	2,075,409	Ibuprofen	2,100,226
9	Lorazepam	1,972,538	Ibuprofen	2,063,414	Trimetazidine	1,888,458
10	Ibuprofen	1,952,067	Lorazepam	1,947,305	Lorazepam	1,766,388

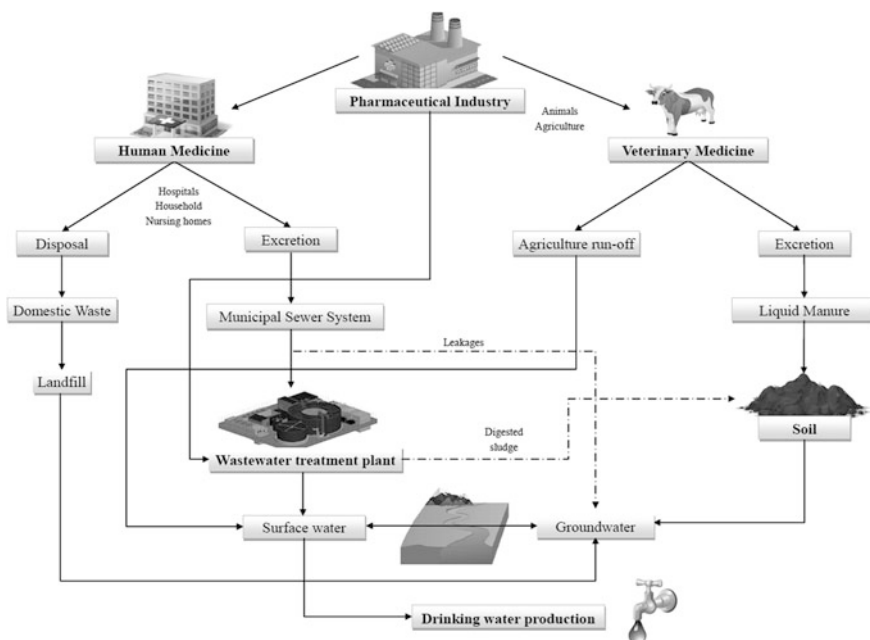


Fig. 1.1 Major pathways of pharmaceuticals released in the environment

plants before entering the watercourses. In addition to metabolic excretion, the improper disposal of unused or expired drug residues and drug-containing waste from pharmaceutical industries, are another source of environment contamination (Khetan and Collins 2007). The conventional wastewater treatment plants (WWTP) are not prepared for the treatment of complex pharmaceuticals, as they were designed with the principal aim of removing biodegradable carbon, as well as nitrogen and phosphorus compounds (Verlicchi et al. 2012). Therefore, these pharmaceuticals residues may pass through the treatment plants and reach surface water such as rivers, streams and lakes. Additional emissions can result from sewers leakages after rainfall, or come from agricultural runoff from fields treated with digested sludge or livestock slurries (Khetan and Collins 2007). As a consequence of these emissions, pharmaceutical residues can be detected in surface water (Moldovan 2006; Moreno-González et al. 2014), groundwater (Barnes et al. 2008; Sacher et al. 2001) or even in drinking-water (Loos et al. 2007; Houtman et al. 2014; Wen et al. 2014), although at very low concentration. Once in the environment, pharmaceuticals and their metabolites undergo natural attenuation by adsorption, dilution or degradation in the environment (e.g. photolysis, biodegradation, other chemical reactions), depending on their hydrophobicity and biodegradability and environmental conditions (Moreno-González et al. 2014; WHO 2011).

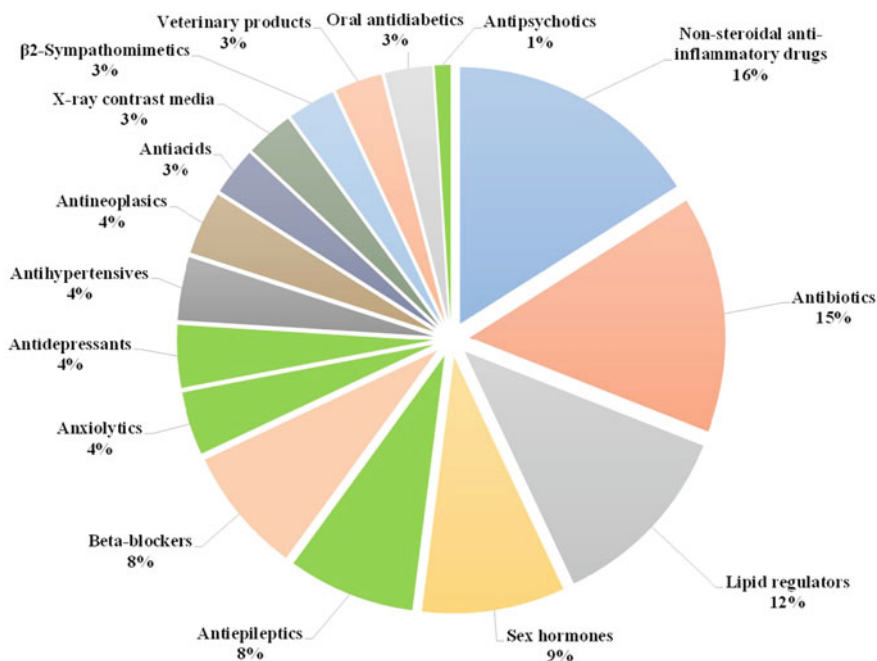


Fig. 1.2 Therapeutic classes of pharmaceuticals detected in the environment (expressed in relative percentage), adapted from Santos et al. (2010)

The occurrence of pharmaceuticals in WWTP is related to local sales and consumption patterns. After being consumed, large amounts of pharmaceuticals and their metabolites can be discharged into the aquatic environment, which will further allow their detection in wastewater, surface water, groundwater and even drinking water, at concentrations ranging from ng/L to several μ g/L (Matamoros and Bayona 2006; Pedrouzo et al. 2007). According to data collected from 134 articles published between 1997 and 2009, the main therapeutic classes found in the environment are non-steroidal anti-inflammatory drugs, blood lipid lowering agents, antibiotics and sex hormones (Fig. 1.2). The group of psychotropic drugs, comprising 4 therapeutic classes of pharmaceuticals (antipsychotics, antidepressants, anxiolytics and antiepileptics), represents an overall occurrence of 17 % in environmental matrices.

1.3 Psychiatric Pharmaceuticals

Nowadays, the worldwide prevalence of psychiatric disorders led to an increased number of prescriptions for psychiatric pharmaceuticals, particularly antidepressants, anxiolytics, sedatives and hypnotics (Calisto and Esteves 2009). According to

the Eurobarometer of 2010 regarding mental health, one in fourteen EU citizens (7 %) has taken antidepressants in the year of 2009 (Eurobarometer 2010). The same report claims that Portugal has the highest consumption of antidepressants, where the prevalence of use is 15 %. The latest OECD Health Statistics reveal that the consumption of this class of pharmaceuticals has doubled on average in OECD countries in the period between 2000 and 2012 (OECD 2014). In USA, 35 of the top 200 prescriptions in 2010 were psychiatric pharmaceuticals, including 17 sedatives-hypnotics-anxiolytics, 16 antidepressants, and 2 anti-schizophrenia drugs (Yuan et al. 2013). In addition to the increased consumption of psychotropic pharmaceuticals, the required chronic administration of such drugs suggests a higher environmental exposure (Silva et al. 2012). As other pharmaceuticals, psychoactive drugs enter the environment through human excretion or by direct disposal of unused or expired medications in toilets and household waste, being the discharge from WWTP the major pathway for the entrance of pharmaceuticals into environmental matrices. Together with treated wastewater, these compounds are released into the aquatic environment, contaminating the receiving water bodies.

Psychiatric drugs can be classified according to their chemical structure, pharmacological actions on specific biological processes or by their therapeutic actions (Leonard 2010). According to their therapeutic use, the four main classes of the most prescribed psychoactive drugs are: antidepressants, anxiolytics, sedatives and hypnotics, antipsychotics and mood stabilizers. The most relevant psychiatric pharmaceuticals and their daily dosage range are listed in Table 1.3. Moreover, structural and chemical properties of the most significant pharmaceuticals in an environmental context are presented in Table 1.4.

1.3.1 *Antidepressants*

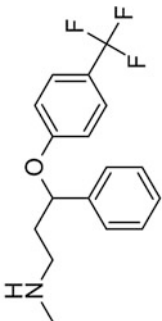
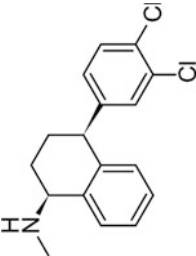
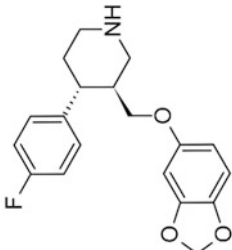
Depressive disorders are a leading cause of disability, especially in developed countries. A World Health Organization report estimates the 12-month prevalence of depression in developed countries ranges from 3.1 % in Japan to 9.6 % in U.S.A. (Nandi et al. 2009). Antidepressants are used in the symptomatic treatment of depression and act through the action on various neurotransmitter systems, namely serotonin, norepinephrine and dopamine. The most important classes of antidepressants are the selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAOI). Tricyclic antidepressants were the first agents successfully used. However, they exhibit neuro-pharmacological effects in addition to their original action. Nowadays, SSRI have emerged as a major therapeutic advance in psychopharmacology. The SSRI acts by modulating the levels of the neurotransmitter serotonin, specifically by blocking the function of the serotonin transporter on cell membranes leading to elevated levels of serotonin. This class of antidepressants is largely prescribed to treat depression, anxiety, panic disorder, obsessive-compulsive disorder, eating disorders and social phobia. Currently there are five SSRIs available in the

Table 1.3 Several relevant psychiatric drugs and dosage range (Sethi 2008)

Therapeutic class	Category	Pharmaceuticals	Dosage range (mg/d)
Antidepressants	SSRI	Fluoxetine	20–60
		Sertraline	50–200
		Paroxetine	20–50
		Fluvoxamine	50–200
		Citalopram	20–40
		Escitalopram	10–40
	SNRI	Venlafaxine	75–225
		Duloxetine	40–120
	TCA	Clomipramine	100–250
		Imipramine	150–300
		Amitriptyline	150–300
		Doxepin	150–300
		Nortriptyline	50–150
	MAOI	Phenelzine	45–90
		Tranylcypromine	30–60
		Moclobemide	300–600
	Others (atypical)	Bupropion	200–450
Anxiolytics/sedatives/hypnotics	Benzodiazepines	Diazepam	5–40
		Alprazolam	0.5–10
		Clonazepam	1–6
		Lorazepam	1–6
		Oxazepam	30–120
		Temazepam	20–40
Antipsychotics	Typical antipsychotics	Chlorpromazine	50–1200
	Atypical antipsychotics	Risperidone	4–8
Mood stabilizers/anticonvulsants	–	Carbamazepine	400–1200
		Oxcarbazepine	1200–2400

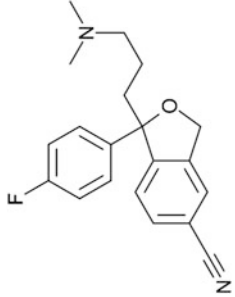
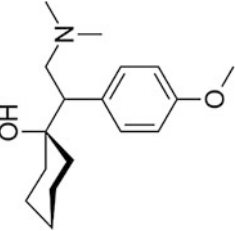
market—fluoxetine, fluvoxamine, paroxetine, sertraline and citalopram. Fluoxetine, paroxetine and sertraline, commonly known as Prozac, Paxil and Zoloft, are very similar in efficacy and safety, although Paxil has more indicators in its label and Prozac has more convenience in a weekly dosage form (Khetan and Collins 2007). When these three SSRI are not effective, other antidepressants such as venlafaxine, duloxetine (selective serotonin and norepinephrine re-uptake inhibitors—SSNRI), bupropion, tricyclic and tetracyclic antidepressants—amitriptyline and mianserin, respectively—are prescribed (Calisto and Esteves 2009).

Table 1.4 Structural and chemical properties of the most common psychiatric pharmaceuticals found in the environment (SRC 2011)

Compound	Therapeutic class	CAS number	Molecular formula	Structural formula	<i>M</i> (g/mol)	Water solubility
Fluoxetine	Antidepressants	54910-89-3	$C_{17}H_{18}F_3NO$		309.3	60.3 mg/L (at 25 °C)
Sertraline		79617-96-2	$C_{17}H_{17}Cl_2N$		306.2	3.51 mg/L (at 25 °C)
Paroxetine		61869-08-7	$C_{19}H_{20}FNO_3$		329.3	35.27 mg/L (at 25 °C)

(continued)

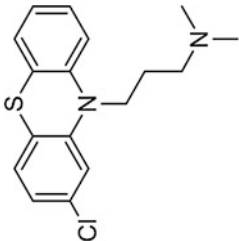
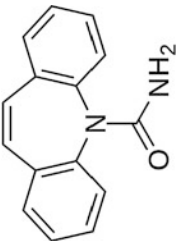
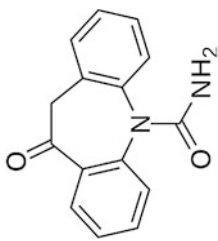
Table 1.4 (continued)

Compound	Therapeutic class	CAS number	Molecular formula	Structural formula	M (g/mol)	Water solubility
Citalopram		59729-33-8	C ₂₀ H ₂₁ FN ₂ O		324.4	31.09 mg/L (at 25 °C)
Venlafaxine		93413-69-5	C ₁₇ H ₂₇ NO ₂		277.4	266.7 mg/L (at 25 °C)

(continued)

Table 1.4 (continued)

Table 1.4 (continued)

Compound	Therapeutic class	CAS number	Molecular formula	Structural formula	M (g/mol)	Water solubility
Chlorpromazine	Antipsychotics	50-53-3	$C_{17}H_{19}ClN_2S$		318.9	2.55 mg/L (at 24 °C)
Carbamazepine	Mood stabilizers	3564-73-6	$C_{15}H_{12}N_2O$		238.3	16.8 mg/L (at 25 °C)
Oxcarbazepine		28721-07-5	$C_{15}H_{12}N_2O_2$		252.3	308.1 mg/L (at 25 °C)

1.3.2 Anxiolytics, Sedatives and Hypnotics

This class of compounds acts on the central nervous system, being mainly indicated to treat anxiety symptoms and to induce sedation and amnesia. It is also effective as anticonvulsants (Calisto and Esteves 2009). This is the most widely prescribed class of psychotropic drugs and includes benzodiazepines, barbiturates, non-barbiturate sedative-hypnotics and non-benzodiazepines (Sethi 2008). Among these, the most extensively studied and traded group are the benzodiazepines, with special relevance to diazepam (Calisto and Esteves 2009). Currently, there are 35 benzodiazepines under international control for therapeutic use (INCB 2009). However, these compounds are not exclusively used for human therapeutics, being also prescribed in veterinary treatments due to their anxiolytic and appetite stimulant effects in domestic and wild animals (Courtheyn et al. 2002).

1.3.3 Antipsychotics

The term antipsychotic is applied to a group of drugs used to treat a number of psychiatric disorders, including schizophrenia, mania, dementia and delusional disorder. This group of pharmaceuticals is also known as neuroleptics. There are two types of antipsychotics drugs, the typical antipsychotics and the atypical antipsychotics. The typical antipsychotics pharmaceuticals (first generation of antipsychotics) are chlorpromazine, haloperidol, flupenthixol, perphenazine, thioridazine, thiothixene and trifluoperazine. The atypical antipsychotics (second generation of antipsychotics) pharmaceuticals such as olanzapine, quetiapine risperidone, aripiprazole, clozapine and ziprasidone, represent a new generation of drugs prescribed for schizophrenia and delusional disorders (Sethi 2008). The antipsychotics pharmaceuticals act by regulating serotonin and dopamine levels in the brain (Khetan and Collins 2007). Recently, a new atypical antipsychotic drug acting as a partial agonist of dopamine has been discovered (Ciccone 2007).

1.3.4 Mood Stabilizers

These pharmaceuticals are used in the treatment of acute phase of mania and depressive phase of bipolar disorder. Drugs commonly classed as mood stabilizers include carbamazepine, oxcarbamazepine, valproate and lithium (Sethi 2008). Antiepileptics and anticonvulsants such as carbamazepine (commonly known as Tegretol) are central nervous system (CNS) pharmaceuticals that help to decrease the abnormal firings of nerves in the brain and in the CNS (Khetan and Collins 2007).

Despite the high-volume production and consumption of psychoactive drugs worldwide, relatively little is known about their occurrence in environmental

matrices compared to other pollutants. Therefore, the occurrence of such kind of drugs in the environment and their potential harmful effects on human health and environment, have become a matter of major concern. In Chap. 2, the occurrence and effects of psychiatric pharmaceuticals in the environment will be discussed in detail.

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Chapter 2

Pharmaceuticals in the Environment: Case Study of Psychiatric Drugs

Abstract The ecotoxicological assessment of pharmaceuticals is discussed in this chapter, under the light of a growing local and international legal framework that is meant to control the environmental impact of an intensive consumption of such molecules, mainly those used in psychiatric conditions. The specific pathways for pharmaceuticals metabolism are evaluated and the resulting accumulation of those medicines in different matrices is presented. Non-target organisms may suffer different effects when exposed to those pharmaceuticals or to their metabolites and the first attempts to quantify this contamination are reviewed.

Keywords Ecotoxicological assessment • Metabolic pathways • Non-target organisms

2.1 Introduction

Pharmaceuticals are a vast and diverse group of chemicals with different functionalities, physicochemical and biological properties (Kümmerer 2009), that have been used worldwide by the human and veterinary medicine (Calisto and Esteves 2009; Christen et al. 2010; Fent et al. 2006; Furuhausen et al. 2014). In order to achieve optimal therapeutic function, pharmaceuticals are chemically designed to pass through the cellular membrane, to fit a specific molecular target, which is often evolutionary conserved and have orthologs in a variety of organisms (Furuhausen et al. 2014), and to resist inactivation before having the desired therapeutic effect (Calisto and Esteves 2009; Christen et al. 2010). These properties raise concerns for the following reasons:

- (i) As pharmaceuticals do not occur individually in the environment, but as complex mixtures, the interaction of these compounds with wildlife that might have high similarity with the molecular targets, the so-called non-target organisms (Furuhausen et al. 2014; Rand-Weaver et al. 2013), may occur at

- relevant environmental concentrations, due to combined and synergistic effects (Calisto and Esteves 2009);
- (ii) For some pharmaceuticals, the specific mode of action is not well characterized and often different modes of action are possible;
 - (iii) Some pharmaceuticals are responsible for antibiotic resistance, while others have the aptitude to directly affect the central nervous system and disrupt neuro-endocrine signaling (Calisto and Esteves 2009; Chen et al. 2006; Jones et al. 2001; Saussereau et al. 2013).

Considering that regulations over the development and production of pharmaceuticals are usually extremely supervised by human health agencies, which generally have limited experience and knowledge on issues of environmental scope and that, until recently: (a) pharmaceuticals were not considered as potential pollutants, thus not being subjected to detailed research regarding their impact on the environment (Jones et al. 2001); (b) the ecotoxicological assessments of pharmaceuticals have been based on acute toxicity experiments performed by standard tests according to the existing guidelines using laboratory organisms belonging to different trophic levels such as algae, zooplankton, other invertebrates and fish, it is possible to infer that the information about the chronic toxicity or bioaccumulation potential of pharmaceuticals in biota and food chains is extremely scarce (Christen et al. 2010).

Pharmaceuticals, either in their original form or as metabolites with residual activities, are being introduced into the environment at variable degrees and on a continuously basis, mainly through wastewater and sewage treatment plants (WWTP and STP, respectively), as a consequence of the inadequacy of the treatment processes applied in these facilities (Chen et al. 2006; Furuhaugen et al. 2014; Ginebreda et al. 2010; Saussereau et al. 2013; Zuccato et al. 2006). According to Calisto and Esteves (2009) the first reports referring explicitly to the incomplete removal of some pharmaceuticals by wastewater treatments and their discharge into the environment by WWTP were published in the 60s and 70s. However, only in the 90s was it established that some pharmaceuticals have the ability to interfere with the ecosystem, even in concentrations as low as few nanograms per litre (ng/L). Since then, and as a consequence of the growing number of published studies focused on pharmaceuticals and their persistence in the environment, as well as of the large amount of pharmaceuticals produced, their increasing use, diversity and potential toxicological effects on non-target organisms, pharmaceuticals and pharmaceutically active metabolites are now unanimously considered as an important group of emergent environmental pollutants (Calisto et al. 2011; Calisto and Esteves 2009).

Although knowledge concerning the removal pathways, fate, environmental transformation and the effects of these compounds once they are released into the environment, is reduced, it is possible to reach a general consensus on the main features of this emerging problem (Ginebreda et al. 2010): (a) pharmaceuticals are intrinsically bioactive compounds, being therefore able to cause potential damage on living systems, target and non-target organisms; (b) there is a continuous and

worldwide increase on their use and thus on their subsequent introduction into the environment; (c) there are plenty of different pharmaceuticals that are currently and regularly used simultaneously, being therefore susceptible to interaction and synergistic effects that are basically unknown and (d) information regarding effects on the aquatic and terrestrial ecosystems resulting from long-term low-dose exposure to pharmaceuticals is scarce.

This chapter will be specifically focused on the psychiatric pharmaceuticals as emergent pollutants, their occurrence in environmental matrices and the effect on non-target organisms.

2.2 Pharmaceuticals as Emerging Pollutants: Occurrence of Psychiatric Drugs in Environmental Matrices

The term *pharmaceutical* comprise a large and diverse group of synthetic or natural chemicals with substantial variability in structure, function, behaviour and activity (Jones et al. 2001, 2005; Monteiro and Boxall 2010). The intensive use and increasing consumption of pharmaceuticals worldwide, which is intrinsically associated with the continuous ageing of the population, better access to health care and life quality improvement (Verlicchi et al. 2012a), have made pharmaceuticals a crucial and indispensable element of modern society. This situation is particularly relevant in high-income countries due to the increased number of obese and elderly people with chronic health problems (Arnold et al. 2014).

Most of pharmaceutical substances are polar compounds with a molecular weight that ranges typically from 200 to 500/1000 Da (Kümmerer 2009) and present low volatility, thus increasing the probability of pharmaceuticals to be transported to surface waters (Brausch et al. 2012). Both administration and production of pharmaceuticals may vary between countries and over time, fluctuating not only on an annual basis, but also through the years (Verlicchi et al. 2012b). Table 2.1 and Fig. 2.1 summarize, respectively, the main psychiatric pharmaceuticals consumed in the last years in several countries and the volume of antidepressants consumed between 2000 and 2012 in daily dose (DDD) units.

The consumption of antidepressants has practically doubled on average in EU countries between 2000 and 2012 (Fig. 2.1). This exponential increase is strictly related with the epidemiological context as it is the insecurity created by the economic crisis.

There are many scattered ways by which pharmaceuticals can enter the environment (Chen et al. 2006; Zuccato et al. 2006). The main pathway from human and animals contribution includes ingestion, following excretion and disposal in wastewater (Fent et al. 2006). Once administered, pharmaceuticals are metabolized to varying degrees and excreted in urine and feces as metabolite and/or unaltered parent compounds.

Table 2.1 Volume of pharmaceutically active compounds sold in different countries (kg/year)

Therapeutical class	Pharmaceutical	Countries				
		France (2004) ^a	UK (2004) ^b	Spain (2004) ^c	Austria (1997) ^d	Switzerland (2004) ^d
Antidepressants SSRIS	Fluoxetine	3740	4826	4200	–	
	Paroxetine	5515	2663	–	–	
	Citalopram	3487	4799	1600	368	
	Sertraline	6224				
Anxiolytic	Bromazepam	2604				
	Diazepam	526			207	51
	Prazepam	2166				
	Oxazepam	6195				

^aBesse et al. (2008)

^bMonteiro and Boxall (2010)

^cCarballa et al. (2008)

^dFent et al. (2006)

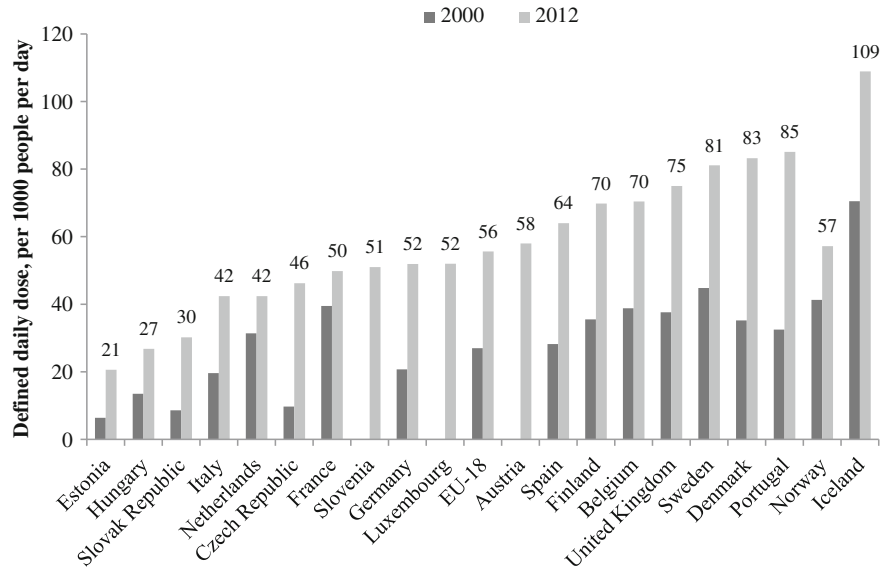


Fig. 2.1 Consumption of antidepressants in the EU countries between 2000 and 2012 (adapted from OECD 2014)

A significant amount of the original substance may also be excreted in their native form and undergo further modification due to biological, chemical and physical processes in sewage treatment facilities, receiving water bodies (Jones et al. 2005). It is estimated that 30–90 % of an administered dose of most antibiotics, human and veterinary, may be excreted as active substances. As a

The annual production of this hormone lies in a couple of hundreds kilograms per year in the EU, nevertheless it is extremely potent, very persistent in the environment and shows estrogenic activity in fish at 1–4 ng/L, or lower. Therefore, pharmaceuticals having environmental relevance share the following properties: often, but not always, high production volume combined with environmental persistence and biological activity, mainly after long-term exposure (Fent et al. 2006).

In this chapter, special attention will be given to the psychiatric pharmaceuticals, particularly their occurrence in environmental matrices. Psychiatric pharmaceuticals, such as sedatives, hypnotics, anxiolytics (including antiepileptics), antidepressants and antipsychotics are among the most prescribed substances. These are defined as a group of pharmaceuticals that directly act on the central nervous system and disrupt neuro-endocrine signaling (Calisto et al. 2011; Calisto and Esteves 2009). Emerging pollutants, also known as contaminants of emerging concern—CEC, are defined as substances that are not currently covered by existing water-quality regulations and are thought to be potential threats to environmental ecosystems, human health and safety (Deblonde et al. 2011). Emerging pollutants do not necessarily need to be new compounds. Some have been present in the environment for decades and were only recently discovered through the use of advanced analytical methods.

For example, the sedative-hypnotic diazepam (the most extensively studied psychiatric pharmaceutical) has been found in all environment matrices—wastewater, surface, ground and drinking water, soils, sediments, bio-solids and tissues (Calisto et al. 2011). Diazepam was found in concentrations lower than 1 µg/L in sewage effluent, in concentrations of 10 ng/L in rivers and potable water (Waggot 1981). Caffeine was detected in sewage water in concentrations of 1 µg/L, in potable water in concentrations higher than 1 µg/L (Richardson and Bowron 1985) and in wastewater effluents in concentrations between 16 and 292 µg/L (Rogers 1996). Recent analytical studies in Italy, confirm that several pharmaceuticals are poorly removed in STP and that several commonly used pharmaceuticals such as erythromycin, cyclophosphamide, naproxen, sulphamethoxazole or sulphasalazine, persist in the environment for periods of time longer than one year (Zuccato et al. 2006). López-Serna et al. (2012) reported the occurrence of pharmaceuticals, their metabolites and transformation products in the Ebro river basin, in the Northeast of Spain. Twenty-four samples of water were collected along the basin and subsequently analyzed. In total, 17 metabolites, 7 of which still had pharmacologic activity, 2 transformation products, along with 58 parent pharmaceuticals were detected. Metabolites and transformation products were found at concentrations of the same order of magnitude as their corresponding parent pharmaceuticals, with the exception of 10,11-epoxycarbamazepine which was found in a concentration approximately 10 times higher than its corresponding parent pharmaceutical carbamazepine. These authors also reported that, with the exception of 14 compounds, among them the aforementioned 10,11-epoxycarbamazepine with a maximum concentration of more than 1600 ng/L, the levels of all target compounds were below 100 ng/L. Other pharmaceuticals such as propyphenazone (analgesic), carbamazepine (psychiatric), clarithromycin and sulfadiazine (antibiotic), propranolol

(β -blocker), tamoxifen (antineoplastic) were found to be ubiquitous in all analyzed samples. Studies conducted in Europe and North America demonstrated that carbamazepine is one of the most frequently detected pharmaceuticals in WWTP effluents, river water (Mohapatra et al. 2014), final sewage effluents, surface water, drinking water and groundwater (Monteiro and Boxall 2010). Different studies conducted in Portuguese regions confirm the presence of several pharmaceuticals such as citalopram and paroxetine (Silva et al. 2014), carbamazepine, fenobric acid, propranolol, sulphamethoxazole and trimethoprim (Madureira et al. 2011a, b), acetaminophen, acetylsalicylic acid, carboxyibuprofen, diclofenac, hydroxyibuprofen, ibuprofen, naproxen, nimesulide and ketoprofen in seawater (Lolić et al. 2015). Brooks et al. (2005) reported the occurrence of fluoxetine, norfluoxetine, sertraline and desmethylsertraline in tissue samples (muscle, liver and brain) of several fishes—*Lepomis macrochirus* (bluegill), *Ictalurus punctatus* (channel catfish) and *Pomoxis nigromaculatus* (black crappie)—from Pecan Creek Water Reclamation Plant, Denton County, Texas (U.S.A). For all fish samples, the highest concentrations was observed in brain (fluoxetine, 1.58 ± 0.74 ng/g; norfluoxetine, 8.86 ± 5.9 ng/g; sertraline, 4.27 ± 1.4 ng/g; desmethylsertraline, 15 ± 14.3 ng/g) and liver tissues (fluoxetine, 1.34 ± 0.65 ng/g; norfluoxetine, 10.27 ± 5.73 ng/g; sertraline, 3.59 ± 1.67 ng/g; desmethylsertraline, 12.94 ± 10.45 ng/g). The lowest concentrations were detected in the muscle tissue (fluoxetine, 0.11 ± 0.03 ng/g; norfluoxetine, 1.07 ± 0.41 ng/g; sertraline, 0.34 ± 0.09 ng/g; desmethylsertraline, 0.69 ± 0.59 ng/g). According to those authors, the fact that the average levels of norfluoxetine and desmethylsertraline were higher in the brain, liver and muscle tissue, compared to the average fluoxetine and sertraline levels, reveal a general similarity to the data obtained by Fuller et al. (1995), DeVane et al. (2002) and Weigel et al. (2004), documenting slow accumulation and dispositional differences among these compounds in rat models and humans. Ramirez et al. (2007) also reported the presence of psychiatric medicines (carbamazepine 1.16 ng/g of wet weight, and norfluoxetine 4.37 ng/g of wet weight) in muscle tissues of *Lepomis* sp., also collected in Pecan Creek Water Reclamation Plant. Studies conducted by Beretta et al. (2014) in sediments from the Todos os Santos Bay (Brazil), identified in all sediments samples concentrations of several pharmaceuticals such as carbamazepine, ibuprofen, diclofenac, atenolol, diazepam and erythromycin, at levels of parts per billion of dry sediment.

These observations reinforce the importance and the need to study the effect and impact of psychiatric drugs in non-target organisms, as well as to develop accurate and precise methods for their quantification in different and diversified matrices. A factor that influences the accuracy of the quantification process of pharmaceuticals is the sensibility of the equipment and the development of an internationally standardized analytical protocol. The existence of such protocol would help to ensure both quality and comparability of data.

The effects that psychiatric pharmaceuticals exert on non-target organisms which are summarized in Table 2.2, will be addressed in the next section whereas the analytical techniques used for the detection and quantification of psychiatric pharmaceuticals will be discussed in Chap. 4.

Table 2.2 Main psychiatric pharmaceuticals used extensively by the population and detected in the environment

Therapeutical class	Pharmaceutical	Commercial name	Concentration found in the environment	Matrix	Country
Antidepressants	Fluoxetine	Prozac	0.012 µg/L	Surface water	USA ^a , Canada ^a
			17 ± 3 ng/L	Psychiatric hospitals WWTP influents	China ^f
			21 ± 2 ng/L	Psychiatric hospitals WWTP primary effluents	China ^f
			10 ± 1 ng/L	Psychiatric hospitals WWTP secondary effluents	China ^f
			na	WWTP, Wastewaters effluents and influents	Portugal ^d
			nd–0.099 µg/L	STP effluents	USA ^e , Canada ^c
			0.1–10 ng/g	Tissues (muscle, brain, and liver) of fish residing in a municipal effluent-dominated stream	USA ^a
			0.14–1.02 µg/kg	Fish tissues	Canada ^a
			0.099 µg/L	STP effluents	Canada ^a
			0.055–0.19 µg/L; 0.010–0.063 µg/L	WWTP influents and effluents	Italy ^b
			0.024–0.033 µg/L; 0.035–0.069 µg/L	Hospital effluents	Italy ^b

(continued)

Table 2.2 (continued)

Therapeutic class	Pharmaceutical	Commercial name	Concentration found in the environment	Matrix	Country
Antidepressants	Paroxetine	Paxil	2.1 ± 0.4 ng/L; 3 ± 1 ng/L; 2.2 ± 0.2 ng/L	Pecan creek water reclamation plant	USA ^a
			na	WWTP, wastewaters effluents and influents	Portugal ^d
			0.020–0.080 µg/L; 0.010–0.018 µg/L	WWTP influents and effluents	Italy ^b
			0.056–0.076 µg/L	Hospital effluents	Italy ^b
			0.48–0.58 µg/kg	Fish tissues	Canada ^a
	Citalopram	Celexa	90 ± 20 µg/L; 40 ± 30 µg/L; 80 ± 30 µg/L	Pecan creek water reclamation plant	USA ^a
			67 ± 5 ng/L; 261 ± 14 ng/L	Psychiatric hospitals WWTP influents	China ^f
			322 ± 23 ng/L	Psychiatric hospitals WWTP primary effluents	China ^f
			19 ± 1 ng/L; 162 ± 9 ng/L	Psychiatric hospitals WWTP secondary effluents	China ^f
			0.4 ng/L; 3 ng/L; 4 ± 1 ng/L	Municipal WWTP influents	China ^f
			1 ng/L	Municipal WWTP primary effluents	China ^f
			2 ng/L; 4 ng/L; 5 ± 2 ng/L	Municipal WWTP secondary effluents	China ^f
			na	WWTP, Wastewater effluents and influents	Portugal ^d

(continued)

Table 2.2 (continued)

Therapeutical class	Pharmaceutical	Commercial name	Concentration found in the environment	Matrix	Country
Antidepressants	Sertraline	Zoloft	0.1–10 ng/g	Tissues (muscle, brain, and liver) of fish residing in a municipal effluent-dominated stream	USA ^a
			29 ± 8 ng/L; 106 ± 28 ng/L	Psychiatric hospitals WWTP influents	China ^f
			99 ± 7 ng/L	Psychiatric hospitals WWTP primary effluents	China ^f
			9 ± 5 ng/L; 59 ± 3 ng/L	Psychiatric hospitals WWTP secondary effluents	China ^f
			na	WWTP, Wastewater effluents and influents	Portugal ^d
	Duloxetine	Cymbalta	36 ± 5 ng/L; 49 ± 9 ng/L; 33 ± 8 ng/L	Pecan creek water reclamation plant	USA ^a
			1.5 ± 0.2 ng/L; 2 ± 2 ng/L; 1.2 ± 0.9 ng/L	Pecan creek water reclamation plant	USA ^a
			600 ± 200 µg/L; 1000 ± 400 µg/L; 900 ± 300 µg/L	Pecan creek water reclamation plant	USA ^a
	Venlafaxine	Effexor	50 ± 20 µg/L; 60 ± 40 µg/L; 50 ± 10 µg/L	Pecan creek water reclamation plant	USA ^a
	Bupropion	Wellbutrin			

(continued)

Table 2.2 (continued)

Therapeutical class	Pharmaceutical	Commercial name	Concentration found in the environment	Matrix	Country
Antipsychotics	Chlorpromazine	Thorazine	5 ± 4 ng/L;	Psychiatric hospitals WWTP influents	China ^f
			364 ± 173 ng/L		
			217 ± 21 ng/L	Psychiatric hospitals WWTP primary effluents	China ^f
Anxiolytics/Hypnotics	Diazepam	Valium	99 ± 6 ng/L	Psychiatric hospitals WWTP secondary effluents	China ^f
			0.053 µg/L	Municipal STP effluents	Germany ^a , UK ^a , Italy ^a
			0.002–0.010 µg/L	WWTP influents and effluents	Italy ^b
			0.021–0.038 µg/L	Hospital effluents	Italy ^b
			0.88 µg/L	Surface water	Germany ^a
			0.033 µg/L	Rivers and Streams	Germany ^a
			3–62 ng/L	Lake mead	USA ^a
			>0.01 µg/L;	STP influents	Belgium ^a
			0.59 µg/L; 1.18 µg/L		
			33.6 ± 7.1 ng/L	River water	Romania ^a
			23.5 ng/L	Drinking water	Italy ^a
			0.13–2.13 ng/L	Po and Lambro rivers	Italy ^a
			nd–0.053 (Germany)	STP effluents	Germany ^c , UK ^c , Italy ^c ,
			0.39 ± 0.24 ng/g dry weight	Sediments collect in the Todos os Santos Bay	Brasil ^g
			~ 10 ng/L	Potable water	UK ^a
Nordiazepam	Nordiazepam	Nordaz	8.3 ng/L	WWTP effluent	France ^a
			2.4 ng/L	Surface waters	France ^a

(continued)

Table 2.2 (continued)

Therapeutic class	Pharmaceutical	Commercial name	Concentration found in the environment	Matrix	Country
Anxiolytics/Hypnotics	Oxazepam	Serax	0.25 µg/L	STP effluents	Germany ^a , USA ^a
			942 ± 155 ng/L; 286 ± 42 ng/L	Psychiatric hospitals WWTP influents	China ^f
			297 ± 10 ng/L	Psychiatric hospitals WWTP primary effluents	China ^f
			751.7 ± 34 ng/L; 186 ± 14 ng/L	Psychiatric hospitals WWTP secondary effluents	China ^f
	Zaleplon	Sonata	23 ± 7 ng/L	Psychiatric hospitals WWTP influents	China ^f
			30 ± 2 ng/L	Psychiatric hospitals WWTP primary effluents	China ^f
			33 ± 1 ng/L	Psychiatric hospitals WWTP secondary effluents	China ^f
	Alprazolam	Xanax	na	WWTP, Wastewaters effluents and influents	Portugal ^d
			30 ± 1 ng/L	Psychiatric hospitals WWTP influents	China ^f
			32 ± 0.2 ng/L	Psychiatric hospitals WWTP primary effluents	China ^f
			29 ± 2 ng/L	Psychiatric hospitals WWTP secondary effluents	China ^f

(continued)

Table 2.2 (continued)

Therapeutical class	Pharmaceutical	Commercial name	Concentration found in the environment	Matrix	Country
Anxiolytics/Hypnotics	Lorazepam	Ativan	0.8–54.5 ng/L	Wastewater influents	Portugal ^d
			0.3–49.2 ng/L	Wastewater effluents	Portugal ^d
			294 ± 40 ng/L	Psychiatric hospitals WWTP influents	China ^f
			353 ± 22 ng/L	Psychiatric hospitals WWTP primary effluents	China ^f
			205 ± 22 ng/L	Psychiatric hospitals WWTP secondary effluents	China ^f
			0.62–0.79 µg/L; 0.17–0.20 µg/L; 0.46–0.70 µg/L	Hospital effluents	Italy ^b
Mood-stabilizers	Carbamazepine	Tegretol	0.17–0.25 µg/L; 0.08–0.14 µg/L	WWTP influents and effluents	Italy ^b
			0.64–0.87 µg/L; 0.76–1.2 µg/L; 0.75–1.1 µg/L	Hospital effluents	Italy ^b
			88 ± 16 ng/L; 161 ± 72 ng/L	Psychiatric hospitals WWTP influents	China ^f
			240 ± 10 ng/L	Psychiatric hospitals WWTP primary effluents	China ^f
			184 ± 10 ng/L	Psychiatric hospitals WWTP secondary effluents	China ^f
			(continued)		

Table 2.2 (continued)

Therapeutical class	Pharmaceutical	Commercial name	Concentration found in the environment	Matrix	Country
Mood-stabilizers	Carbamazepine	Tegretol	23 ± 2 ng/L;	Municipal WWTP influents	China ^f
			22 ± 3 ng/L;		
			19 ± 5 ng/L		
			24 ± 3 ng/L	Municipal WWTP primary effluents	China ^f
			22 ± 7 ng/L;	Municipal WWTP secondary effluents	China ^f
			13 ± 2 ng/L;		
			17 ± 7 ng/L		
			291.1 ng/L	STPS	Italy ^e
			175.3 ng/L	Lambro River	Italy ^e
			23.1–34.2 ng/L	Po River	Italy ^e
0.0325*–6.3 (Germany)	STP effluents	Italy ^c , Canada ^c , Switzerland ^c , France ^c , Germany ^c , Greece ^c , Sweden ^c , USA ^c			
0.30–1.17 µg/L;	WWTP influents and effluents	Italy ^b			
0.28–0.44 µg/L					
0.41 ± ng/g dry weight					
				Sediments collect in the Todos os Santos Bay	Brasil ^g

The psychiatric pharmaceuticals are grouped according to their therapeutic class

na—not available; *nd*—not detected; * mean value

^aCalisto and Esteves (2009)

^bVerlicchi et al. (2012a)

^cMonteiro and Boxall (2010)

^dPereira et al. (2015)

^eZuccato et al. (2006)

^fYuan et al. (2013)

^gBeretta et al. (2014)

2.3 Effects of Psychotropic Drugs on Non-target Organisms

The presence of pharmaceuticals in the aquatic environment, due to their incomplete removal in wastewater treatments and their subsequent discharge into the environment was acknowledged in the 60s and 70s (Calisto and Esteves 2009; Jones et al. 2005). However, according to Brausch et al. (2012) the awareness of this subject emerged with the publication of two critical reviews performed by Halling-Sørensen et al. (1998) and Daughton and Ternes (1999), which coincided with a period of intensive concern and attention by the public and scientific community, on the presence and potential effects of endocrine active compounds, and with the advances in analytical detection. The fact that pharmaceutical formulations may also incorporate adjuvants, and in some cases pigments and dyes which are commonly considered of minor importance in terms of environmental significance and impact, intensifies the concern about the potential effects of these compounds when in the environment. This associated with the fact that pharmaceuticals development and synthesis are strictly regulated for efficiency, welfare and wellness of the patient, highlights the lack of knowledge regarding the environmental impact of these compounds, the lack of studies and research regarding their persistence in the environment, their biologic activity, forms of degradation and fate. It also highlights the lack of concise regulations for ecological risk assessment (Fent et al. 2006) and environmental legislation concerning the discharge of these compounds into surface water bodies (Verlicchi et al. 2012b).

The first ecotoxicity testing as pre-requisite for pharmaceuticals registration and the corresponding Note for Guidance (EMA 1998) for veterinary pharmaceuticals was established in 1995, according to the European Union (EU) Directive 92/18 EEC. The European Commission released a draft guideline, the Directive 2001/83/EC, specifying that an authorization for a medicinal product for human use must be accompanied by an environmental risk assessment (EMA 2005). In contrast to what happens with veterinary medicine, where environmental assessments of veterinary pharmaceuticals are required by the U.S.A Food and Drug Administration (FDA) since 1980 and by the EU since 1997 (Boxall et al. 2003), only in 1998 the FDA published a guidance for the assessment of human pharmaceuticals, requiring an environmental assessment report whenever the expected introduction concentration of the active compound of the pharmaceutical in the aquatic environment is $\geq 1 \mu\text{g/L}$ (FDA-CDER 1998).

As it was previously mentioned, pharmaceuticals are biologically active substances that specifically affect the control mechanisms in living organisms, influencing hormonal balance, regulating metabolism or relieving signal transmission between cells. Since most pharmaceuticals are administered by ingestion and almost none is completely metabolized, the excretion products contain relevant amounts of the active substance with different metabolites and conjugates, in urine and feces. As the excretion process by humans and animals is considered to be the main pathway for the appearance of pharmaceuticals into environment, the

understanding of human metabolism and excretion rates of psychiatric drugs is of vital importance to the assessment of environmental concentrations of this pharmacological subgroup (Calisto and Esteves 2009).

According to Kümmerer (2009), in order to avoid any misunderstanding in addressing different molecules and processes, the term metabolite should only be used for compounds which have been changed within or on the human body, the bodies of treated animals and plants, but not environmental bacteria or fungi, whereas the term transformation product should be used for molecules resulting from the change of the structure of a molecule after excretion (hydrolysis, photo-oxidation and oxidation) (Fig. 2.3).

The biochemical processes leading to the pharmaceutical metabolism, largely determine the duration of the action, of the elimination process and the toxicity of such a drug. How far may these processes be controlled to produce beneficial medical results on the patient, relies on numerous variables that have been the scope of considerable study (Jr et al. 2007). After administration of a medicine, its absorption and distribution must occur before the pharmaceutical reaches the interior of the body (Fig. 2.4). As with the vast majority of pharmaceuticals, psychiatric pharmaceuticals absorption occurs by simple diffusion and is usually affected by several physicochemical properties such as degree of ionization, molecular size and shape and relative lipid solubility (Wilkinson 2001). Cell

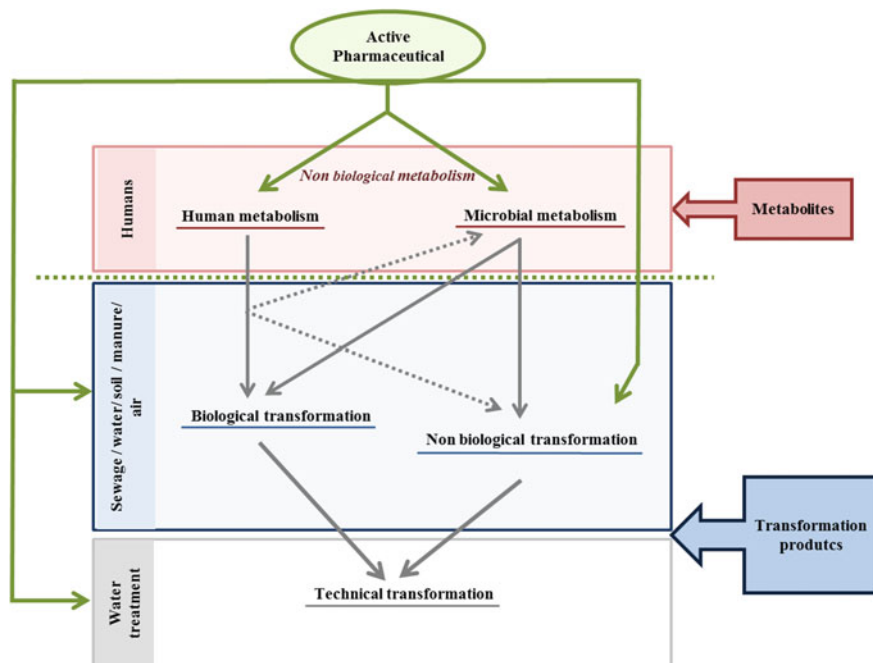


Fig. 2.3 Metabolites and transformation products of active pharmaceuticals (adapted from Kümmerer 2009)

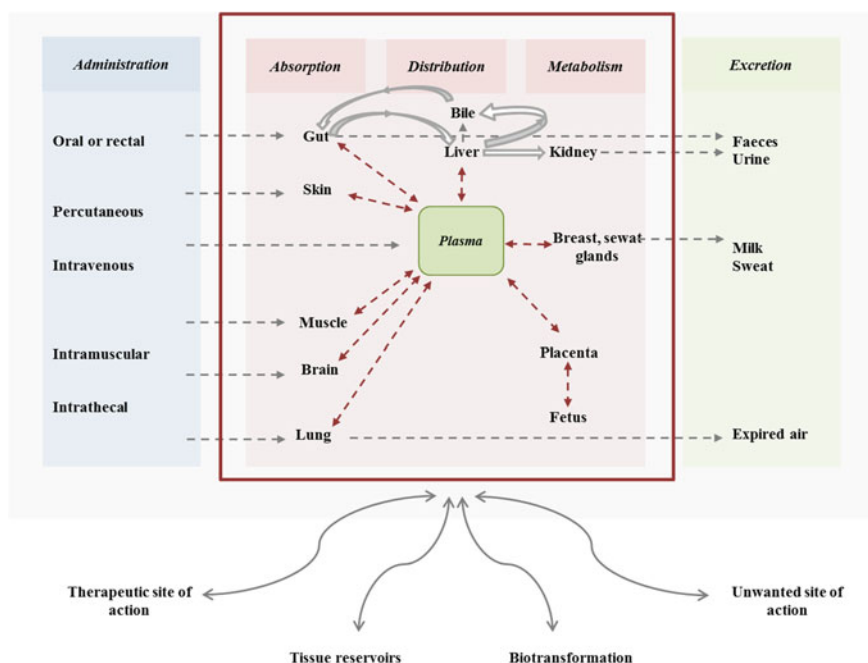


Fig. 2.4 Interrelationship between adsorption, distribution, metabolism and excretion of a pharmaceutical (adapted from Wilkinson 2001)

membranes retain lipid constituents that allow lipophilic substances to cross membranes rapidly and easily. After absorption, the pharmaceutical goes into circulation and after performing its action, it may be metabolized, usually through specialized enzymatic systems, to a more hydrophilic substance for excretion.

Pharmaceutical metabolism can result in toxification (activation) or detoxification (deactivation) of the active compound. Although both processes may occur, the majority of pharmaceutical metabolites are detoxification products.

According to Halling-Sørensen et al. (1998) the metabolism of pharmaceuticals involves two consecutive metabolic pathways: Phase I and Phase II (Fig. 2.5; Table 2.3).

The majority of pharmaceuticals are metabolized to either Phase I or Phase II metabolites. Both phases alter the physical-chemical behaviour of pharmaceuticals (metabolites are more soluble than the parent compounds and products of Phase I are often more toxic than the parent compound). Phase I biotransformations involve primary covalent chemical oxidative modification (hydroxylation, N-oxidation, deamination, reduction or hydrolysis reactions (Jr et al. 2007)). If Phase I metabolites are sufficiently polar, they may be immediately excreted. However, many metabolites of this phase are not quite eliminated and undergo a subsequent reaction in which an endogenous substrate combines with the recently incorporated functional group to form a highly polar conjugate.

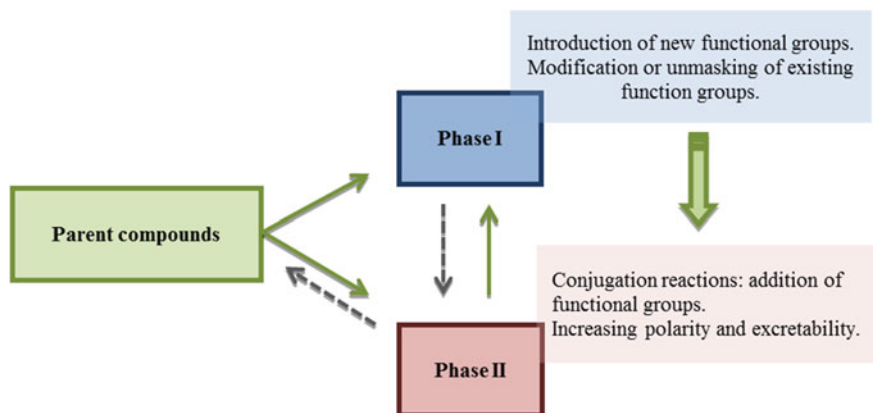
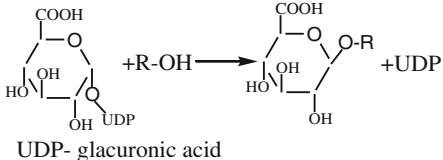


Fig. 2.5 An overview of the metabolization of parent compound into Phase I and Phase II metabolites. *Solid line*—transformation into more water-soluble compounds; *dotted line*—reactivation of the Phase II metabolites (adapted from Halling-Sørensen et al. 1998)

Phase II reactions comprise the synthesis or conjugation of an endogenous polar species to either the parent compound or the Phase I product (Jr et al. 2007), as for example the addition of a glucuronic acid, sulfate, acetate or amino acids, and are usually detoxifying in nature, involving the interaction of polar functional groups of Phase I metabolites (Monteiro and Boxall 2010). If the pharmaceutical remains lipophilic, it will be once again reabsorbed and will last in the body for a longer period (Monteiro and Boxall 2010; Galbraith et al. 2004). Usually, pharmaceuticals metabolism originates more polar metabolites with lower activity and easily excreted.

Only in the last years, regulatory agencies have issued detailed guidelines regarding on how pharmaceuticals should be assessed for possible unwanted effects on the environment (Fent et al. 2006). In 2006, the European Medicines Agency (EMA) delivered a guideline regarding the environment risk assessment of medicinal products for human purpose. This guideline aimed to estimate the potential environmental risks of human pharmaceuticals by a stepwise procedure described below. In a first stage (Phase I) the predicted environmental concentrations (PEC) of a particular medicine in surface water is assessed. This assessment is made taking into consideration several parameters such as maximum daily dose consumed per inhabitant, the volume of wastewater produced per inhabitant per day, the percentage of market penetration and the dilution effect that pharmaceuticals suffer when entering the environment. If the value obtained for PEC is lower than $0.01 \mu\text{g/L}$ and there are no other apparent environmental concerns, it can be assumed that the pharmaceutical is unlikely to represent a risk for the environment. However, if the value obtained for PEC is equal or higher than $0.1 \mu\text{g/L}$, it is necessary to proceed to a second stage (Phase II), which is divided in two sub-phases (Tier A and Tier B) and this aims to evaluate the environmental fate and effect of the pharmaceutical in question. In Tier A, the environmental fate of pharmaceutical is assessed in ready biodegradability tests, through the examination

Table 2.3 Reactions involved in pharmaceuticals metabolism (Adapted from Wilkinson 2001)

Phase I	Reaction	Examples
1. Oxidation reactions		
Aliphatic hydroxylation	$\text{RCH}_2\text{CH}_3 \longrightarrow \begin{array}{c} \text{OH} \\ \\ \text{RCHCH}_3 \end{array}$	Ibuprofen
Deamination	$\begin{array}{c} \text{RCHCH}_3 \\ \\ \text{NH}_2 \end{array} \longrightarrow \begin{array}{c} \text{OH} \\ \\ \text{R}-\text{C}-\text{CH}_3 \\ \\ \text{NH}_2 \end{array} \longrightarrow \begin{array}{c} \text{O} \\ \\ \text{R}-\text{C}-\text{CH}_3 \end{array} + \text{NH}_2$	Diazepam
N-Dealkylation	$\text{RNHCH}_3 \longrightarrow \text{RNH}_2 + \text{CH}_2\text{O}$	Diazepam, codeine, caffeine
2. Hydrolysis reactions	$\begin{array}{c} \text{O} \\ \\ \text{R}_1\text{COR}_2 \end{array} \longrightarrow \text{R}_1\text{COOH} + \text{R}_2\text{OH}$	Acetyl-salicylic acid, clofibrate
	$\begin{array}{c} \text{O} \\ \\ \text{R}_1\text{CNR}_2 \end{array} \longrightarrow \text{R}_1\text{COOH} + \text{R}_2\text{NH}_2$	Lidocaine
Phase II	Reaction	Examples
3. Conjugation reactions		
Glucuronation	<div></div>	Oxazepam, morphine

of: (a) the sorption behaviour of these substances towards sewage sludge and soil; (b) the distribution between water and octanol and finally (c) by a transformation test in water-sediment systems. According to the results obtained, additional analysis may be required. The pharmaceutical effect is also established by respiration inhibition tests, whereas the standard long-term toxicity analyses are performed in *Daphnia magna* fishes and aim to calculate the no-effect concentration ($\text{PNEC}_{\text{water}}$). The $\text{PNEC}_{\text{water}}$ is used to calculate the ratio $\text{PEC}_{\text{surface water}}$ versus $\text{PNEC}_{\text{water}}$. If the $\text{PNEC}_{\text{water}}$ value is lower than one, there is no additional necessity for ecotoxicological analyses for the aquatic compartment. However, if the obtained value is higher than one, additional analyses will be required on a second stage

(Tier B). The threshold recognized by the EMEA guideline is of 0.01 µg/L and may not be suitable for very specific and highly powerful pharmaceuticals such as synthetic hormones, which can have antagonistic effects in the environment at trace concentrations. These substances enter Phase II and are subject to a risk assessment taking into account the mode of action (Christen et al. 2010).

Similarly to others pharmacological compounds, psychiatric compounds occur in the environment in the range of ng/L to µg/L. However, although the concentrations in which they are found are below the levels considered to be harmful to humans, as well as causing acute or chronic toxicity to non-target organisms, it is vital to take into consideration that these compounds and their metabolites do not occur individually in the environment, but as complex mixtures. In this context, and due to their intrinsic biological activity that can affect nervous and endocrine systems, psychiatric pharmaceuticals are one of the most significant groups in what concerns the evaluation of ecotoxicological effects in terrestrial and aquatic non-target organisms (Calisto and Esteves 2009). Since the potential adverse effects of steroids and other estrogens on the endocrine systems were discovered (Brooks et al. 2003a), little attention has been paid to non-steroidal pharmaceuticals that have the same ability to affect the neuronal system, to disrupt neuro-endocrine signaling and to cause perturbations on the reproductive behaviour (Gust et al. 2009), Table 2.4. One example is fluoxetine, an antidepressant that is suspected to be hormonally active (Kolpin et al. 2002).

In primary producers, invertebrates and fish, the mechanistic responses to SSRI, serotonin-specific reuptake inhibitors, are not completely clarified, however, several fish species were identified for the possession of serotonin receptors, making it possible to predict that SSRI can modulate serotonin levels in these animals (Brooks et al. 2005). An investigation conducted by Henry et al. (2004) regarding the chronic and acute toxicity of SSRI to *Ceriodaphnia dubia*, a water flea, acknowledged that the production patterns of *C. dubia* were affected by the exposure to SSRI. Pascoe et al. (2003) compared the acute and chronic toxicity of diazepam to an aquatic invertebrate sedentary organism (*Hydra vulgaris*) and described visible adverse effects such as deficient regeneration of polyps, at concentrations of 10 µg/L.

The majority of the studies concerning the impact, effect and fate of psychiatric pharmaceuticals in non-target organism are conducted in laboratory conditions, where most of the times, only one drug is analyzed at a time, thus not reproducing the actual and natural conditions of their occurrence in the environment, as well as all the interactions involved (Table 2.4).

The fluctuating concentrations of pharmaceuticals through time and space (this last one, due either to the location of pharmaceuticals facilities, domestic and hospital sewages, near natural hydric resources, but also to the dilution effect that pharmaceuticals suffer when enter the environment) are another important factor that must be considered in environmental and toxicity studies as well in ecotoxicological risk assessments. These studies should always consider the environmental effects of metabolites and transformation products, the impact and the short and long term effect of pharmaceuticals accumulation via food-chain, drug

Table 2.4 Effects of several psychiatric pharmaceuticals on non-target organisms (SAICM 2014)

Therapeutical group	Antidepressants			
Pharmaceutical	Fluoxetine			
Non-target organism	<i>Pseudokirchneriella subcapitata</i>	<i>Ceriodaphnia dubia</i>	<i>Ceriodaphnia dubia</i>	<i>Dreissena polymorpha</i>
Effects	Growth inhibition; cell deformities	Increase fecundity in neonates female	Reduce the number of neonates and broods per female; increase in mortality with increasing fluoxetine concentration	Induce spawning in male zebra mussels
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Brooks et al. (2003b); Johnson et al. (2007)	Brooks et al. (2003b)	Henry et al. (2004)	Fong (1998)
Non-target organism	<i>Oryzias latipes</i>	<i>Elliptio complanata</i>	<i>Lampsilis fasciola</i>	<i>Lampsilis cardium</i>
Effects	Affect embryos development such as edema, curved spine, incomplete development (no pectoral fins, reduced eyes) and non-responsiveness; increase of steroids in females circulation; reduce growth	Induce parturition of nonviable larvae from female bivalves and release of spermatzeugmata in males; accumulation in mussel tissues and potential to disrupt reproduction in freshwater mussels	Stimulate lure display behaviour in female bivalves	Stimulate lure display behaviour in female bivalves
Study type	Laboratory	Wildlife	Wildlife	Wildlife
Reference	Brooks et al. (2003a, b)	Bringolf et al. (2010)	Bringolf et al. (2010)	Bringolf et al. (2010)
Non-target organism	<i>Potamopyrgus antipodarum</i>	<i>Valvata piscinalis</i>	<i>Rana pipiens</i>	<i>Xenopus</i>
Effects	Reduce the number of cumulated neonates per living adult; variation on the number of shelled embryos and the number of embryos in the brood pouch; loss of gonadal tissue	Decrease of the total number of eggs per living adult	Delay tadpole development	Tail flexure; faial malformations

(continued)

Table 2.4 (continued)

Therapeutical group	Antidepressants			
Pharmaceutical	Fluoxetine			
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Gust et al. (2009)	Gust et al. (2009)	Foster et al. (2010)	Richards and Cole (2006)
Non-target organism	<i>Hyalella azteca</i>	<i>Morone saxatilis</i> × <i>Morone chrysops</i>	<i>Chironomus tentans</i>	<i>Mytilopsis leucophaeata</i>
Effects	Stimulate young female reproduction; growth inhibition	Reduce the ability to capture the prey	Reduce survival; reduce growth	Induce spawning in male zebra mussels and dark false mussels
Study type	Laboratory	450 L circular flow-through holding tanks	Laboratory	Laboratory
Reference	Brooks et al. (2003b)	Gaworecki and Klaine (2008)	Brooks et al. (2003a, b)	Fong and Molnar (2008)
Therapeutical group	Antidepressants			
Pharmaceutical	Fluoxetine	Sertraline		
Non-target organism	<i>Sphaerium striatinum</i>	<i>Xenopus</i>	<i>Pseudokirchneriella subcapitata</i>	<i>Oryzias latipes</i>
Effects	Reduce number of neonates	Tail flexure	Growth inhibition	Increase in mortality; disruption of larval locomotor behaviour
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Fong (1998)	Richards and Cole (2006)	Johnson et al. (2007)	Chiffre et al. (2014)
Therapeutical group	Antidepressants			
Pharmaceutical	Fluvoxamine	Venlafaxine	Citalopram	
Non-target organism	<i>Dreissena polymorpha</i>	<i>Lymnaea stagnalis</i>	<i>Ceriodaphnia dubia</i>	<i>Oryzias latipes</i>
Effects	Induce spawning in male zebra mussels	Changes in immunocompetence (increased hemocyte count, ROS levels and phagocytosis, and decreased intracellular thiol levels)	Reduce number of neonates and increase mortality with increasing citalopram concentration	Increase in mortality; disruption of larval locomotor behaviour

(continued)

Table 2.4 (continued)

Therapeutical group	Antidepressants			
Pharmaceutical	Fluvoxamine	Venlafaxine	Citalopram	
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Fong (1998)	Gust et al. (2013)	Henry et al. (2004)	Chiffre et al. (2014)
Therapeutical group	Antidepressants			
Pharmaceutical	Paroxetine			Fluvoxamine
Non-target organism	<i>Dreissena polymorpha</i>	<i>Xenopus</i>	<i>Dreissena polymorpha</i>	<i>Dreissena polymorpha</i>
Effects	Induce spawning in male zebra mussels and dark false mussels	Tail flexure	Induce spawning in male zebra mussels	Induce spawning in male zebra mussels
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Fong and Molnar (2008)	Richards and Cole (2006)	Fong (1998)	Fong (1998)
Therapeutical group	Antidepressants			
Pharmaceutical	Venlafaxine		Norfluoxetine	
Non-target organism	<i>Lymnaea stagnalis</i>	<i>Daphnia magna</i>	<i>Mytilopsis leucophaeata</i>	<i>Sphaerium striatinum</i>
Effects	Changes in immunocompetence (increased hemocyte count, ROS levels and phagocytosis, and decreased intracellular thiol levels)	Decrease the offspring number	Induce spawning in male zebra mussels and dark false mussels	Reduce number of neonates
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Gust et al. (2013)	Minguez et al. (2015)	Fong and Molnar (2008)	Fong and Molnar (2008)
Therapeutical group	Antidepressants		Anxiolytics	
Pharmaceutical	Citalopram		Oxazepam	Diazepam
Non-target organism	<i>Ceriodaphnia dubia</i>	<i>Oryzias latipes</i>	<i>Perca fluviatilis</i>	<i>Lymnaea stagnalis</i>
Effects	Reduce number of neonates and increase mortality with increasing citalopram concentration	Increase in mortality; disruption of larval locomotor behaviour	Altered behaviour and feeding rate	Changes in immunocompetence (increased hemocyte count, ROS levels and phagocytosis, and decreased intracellular thiol levels)

(continued)

Table 2.4 (continued)

Therapeutical group	Antidepressants		Anxiolytics	
Pharmaceutical	Citalopram		Oxazepam	Diazepam
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Henry et al. (2004)	Chiffre et al. (2014)	Brodin et al. (2013)	Gust et al. (2013)
Therapeutical group	Anxiolytics			
Pharmaceutical	Diazepam		Carbamazepine	
Non-target organism	<i>Hydra vulgaris</i>	<i>Daphnia magna</i>	<i>Folsomia candida</i>	<i>Lymnaea stagnalis</i>
Effects	Deficient regeneration of polyps	Growth inhibition	Avoidance behaviour; decrease of acetylcholinesterase activity; peroxidative damages; glutathione S-transferase inhibition	Changes in immunocompetence (increased hemocyte count, ROS levels and phagocytosis, and decreased intracellular thiol levels)
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Pascoe et al. (2003)	Lilius et al. (1995)	Oliveira et al. (2015)	Gust et al. (2013)
Therapeutical group	Mood-stabilizers			
Pharmaceutical	Carbamazepine			
Non-target organism	<i>Venerupis decussate</i>	<i>Venerupis philippinarum</i>	<i>Salmo salar</i>	<i>Dreissena polymorpha</i>
Effects	Decrease on lipid peroxidation levels; Glutathione S-transferase activity stimulation; induction of glutathione reductase, superoxide dismutase and cytochrome P450 3A4 activities	Increase on lipid peroxidation levels; Glutathione S-transferase activity decrease; induction of glutathione reductase, superoxide dismutase and cytochrome P450 3A4 activities	Induces differential transcriptome expression in brain	Increase in gills mRNA levels of hsp70 able to cause protein damage in gills
Study type	Laboratory	Laboratory	Laboratory	Laboratory
Reference	Almeida et al. (2014)	Almeida et al. (2014)	Hampel et al. (2014)	Contardo-Jara et al. (2011)

target-conservation on non-target organisms and establish and validate international analytical methods for the detection and quantification of drugs in different environmental matrices. Although considerable information regarding psychiatric pharmaceuticals occurrence and effects are currently available in the public domain, there are still a lot of gaps. Based on the literature review it is possible to advocate that over the past years, countless and different pharmaceuticals such as antibiotics, analgesics, anti-inflammatories, hormones, lipid regulators and psychiatric pharmaceuticals, have been detected in several environmental matrices. Psychiatric pharmaceuticals are of especially importance since they have the aptitude to directly affect the central nervous system, disrupt neuro-endocrine signaling and alter reproduction patterns in non-target organisms. Although the sources of psychiatric pharmaceuticals are well known, the environmental effects and fate of these compounds, as well as their metabolites, in natural and actual conditions are far from being fully studied and understood.

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Chapter 3

Removal of Psychiatric Drugs in Water Treatment Systems

Abstract Wastewater treatment plants are not prepared to degrade or remove these new emergent contaminants. As a consequence this is becoming a much relevant environmental problem considering the impact that these pharmaceuticals and their transformation products may have on different organisms and systems. Herein this chapter the conventional methods to tackle this type of contaminants are reviewed in terms of their capabilities and insufficiencies. The flux of wastewater through WWTP is evaluated in terms of pharmaceuticals degradation and the need of a tertiary treatment is widely justified. This section will be focused in different advanced treatments and their efficiency on the removal of psychiatric drugs, centering on adsorption, membrane and advanced oxidation processes.

Keywords Activated carbon adsorption • Advanced oxidation processes • Environmental impact • Membrane separation processes • Pharmaceuticals degradation • Waste water treatment plants

3.1 Introduction

Pharmaceuticals are one of the most important classes of emerging contaminants. As addressed in the previous chapter, the occurrence of these compounds has been reported in several environmental matrices, such as surface and groundwater, wastewater, sediments, biosolids and soil. The low concentration and diversity of pharmaceuticals found in the environment not only difficult their detection and analysis procedures but also create challenges for water and wastewater treatment processes.

Although pharmaceutical compounds have been released into the environment for decades, the development and improvement of analytical tools (e.g. gas chromatography coupled to mass spectrometry [GC-MS], high performance liquid chromatography coupled to mass spectrometry [HPLC-MS], tandem MS [MS/MS], or HPLC-MS/MS) have allowed the detection of very low concentrations (range of

ng/L to $\mu\text{g/L}$) of these compounds in different environmental matrices (Richardson 2010). Although, currently there are no regulatory limits for the concentration of pharmaceuticals in wastewater or drinking water, the potential impact of these compounds on the environment and human health cannot be excluded.

Conventional wastewater treatment plants (WWTP) are specially designed to remove suspended solids, carbonaceous substances, nutrients (phosphorous and nitrogen) and pathogens from industrial and domestic effluents. Even though these substances can be successfully removed, the elimination of micropollutants such as pharmaceuticals is frequently ineffective, which results in their widespread presence in the environment (Fatta-Kassinos et al. 2011). Therefore, the development of new processes capable of efficiently remove such pollutants is a subject of increasing concern among the environmental science community. As previously addressed in Chap. 2, several studies have demonstrated the presence of a large number of pharmaceuticals in the effluents of WWTP as well as in surface and groundwater. Therefore, during the last decade intensive research has been done to improve the removal performance of these micropollutants, typically by introducing additional advanced treatment technologies to the existing primary and secondary treatments in conventional WWTP. However, in Europe most of the treatment plants comprise only the physical and biological treatment steps, with the latter based on conventional activated sludge, whereas a small number of those plants use a tertiary treatment, which may include membrane filtration, carbon adsorption or advanced oxidation processes. Even though the use of these technologies is not widespread because of their high cost in terms of energy consumption, several studies have been made on these processes considering the improvements they may yield in the removal of organic micropollutants, such as pharmaceuticals (Zorita et al. 2009). The optimization of a treatment process requires the evaluation of the fate and removal of the pollutants during wastewater treatment. The removal efficiency of pharmaceuticals in WWTP could vary significantly in different treatment plants or at different time periods (Vieno et al. 2007). Several factors may influence the removal ratios of these compounds, namely their physical-chemical properties (e.g. hydrophobicity), the processes employed, the environmental conditions (e.g. temperature and light intensity) and the hydraulic retention time (Zorita et al. 2009; WHO 2011).

In the next sections, the effectiveness of different treatment technologies in the removal of pharmaceuticals from various aqueous systems, particularly psychiatric drugs, will be reviewed and assessed.

3.2 Conventional Systems

Commonly, conventional WWTP consist of two main degrees of treatment, primary and secondary treatment (Fig. 3.1), even though some plants may include tertiary treatments. After the removal of coarse solids and large materials from raw wastewater (preliminary treatment), the primary treatment lead to the removal of settleable and floatable organic and inorganic solids by sedimentation. Secondary

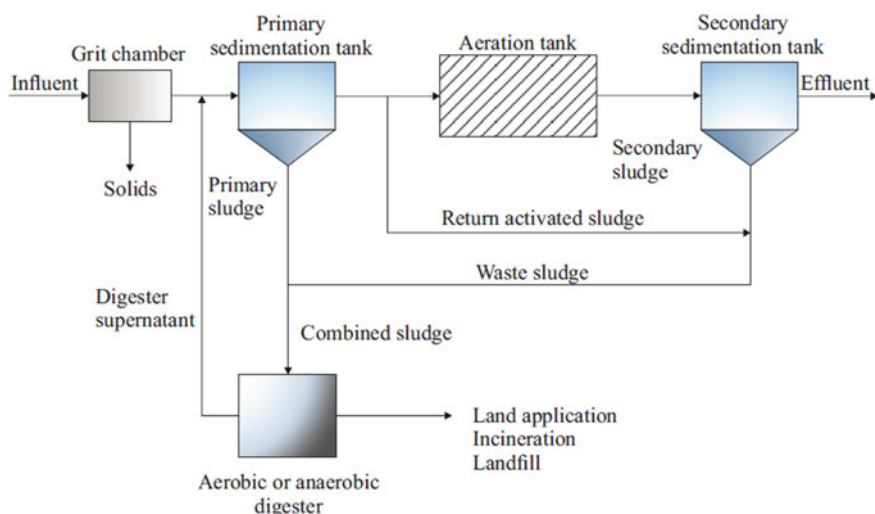


Fig. 3.1 Schematic representation of a conventional WWTP, adapted from Monteiro and Boxall 2010

treatment comprises a biological reactor formed by activated sludge that is designed to remove the biodegradable dissolved and colloidal organic matter (Fulekar 2010). Depending on the sorption behaviour of pharmaceuticals, some compounds will tend to adsorb onto the sewage sludge (Monteiro and Boxall 2010). When specific wastewater pollutants (e.g. pharmaceuticals) cannot be eliminated by secondary treatment, a tertiary treatment can be employed. The main goal of tertiary treatment is to enhance the global removal of suspended solids, organic matter, dissolved solids, heavy metals, refractory organics and nutrients (Fulekar 2010). This advanced treatment can be accomplished by a variety of methods such as sand filtration, ultraviolet radiation, physical-chemical processes, membrane filtration, activated carbon adsorption and advanced oxidation processes (AOP).

Conventional treatment systems have an insufficient capacity to completely remove pharmaceuticals from wastewater, since the microorganisms involved in the activated sludge process are not able to metabolize in a large extent most of these compounds as a source of carbon and the microbial activity can even be inhibited by their presence (Rivera-Utrilla et al. 2013). Nevertheless, in the secondary treatment step pharmaceuticals can be partially removed by biodegradation or sorption onto sludge in the biological reactor (Carballa et al. 2004). After the treatment, the effluent from WWTP is commonly discharged into surface water, while the solid wastes (sewage sludge) are mainly disposed of to landfill, applied as fertilizer on agricultural fields or incinerated (Monteiro and Boxall 2010). As a result, significant levels of pharmaceuticals compounds are released into water bodies through the discharge of the final effluent of WWTP. Moreover, the sewage sludge from treatment plants are also an important pollution source for the soil if they are spread on land (Carballa et al. 2004).

Several studies have been examining the behaviour of pharmaceuticals in conventional wastewater treatment. Recent reports have clearly revealed that the elimination of pharmaceutical products in treatment plants is frequently incomplete (Fernández et al. 2014; Luo et al. 2014; Kosma et al. 2014; Vieno and Sillanpää 2014), confirming that the processes employed in conventional systems are not effective in the removal of these contaminants. For the particular case of psychiatric pharmaceuticals, a short literature review on the removal of these compounds from wastewater by different treatment processes in WWTP is presented in Table 3.1.

It should be stressed that the removal efficiencies obtained in the aqueous phase (effluent) do not necessary indicate that the compounds were degraded to the same extent. Psychiatric compounds such as SSRI antidepressants present high sorption affinity for soil and sediments, with values of log *k*_{oc} (normalized soil organic carbon-water partitioning coefficient) between 4.17 and 5.63, for sertraline and citalopram, respectively (Silva et al. 2014). Thus, if no other processes are involved,

Table 3.1 Removal of psychiatric pharmaceuticals by different processes in WWTP

Pharmaceutical	Influent concentration/ average load	Process	Removal (%)	Reference
Carbamazepine	356.1 ± 5.8 ng/L	Activated sludge/UV	29	Miao et al. 2005
	1273 ± 175 µg/m ³ /d	Membrane bioreactor	13	Bernhard et al. 2006
	≈50 ng/L	Ozonation	99	Westerhoff et al. 2005
	139 ng/L	Ozone/H ₂ O ₂ (2.1/1.0 mg/L)	98	Snyder et al. 2006
Fluoxetine	≈45 ng/L	Aluminium treatment—coagulation	15	Westerhoff et al. 2005
		Activated carbon (5 mg/L)	92	
		Ozonation	91	Westerhoff et al. 2005
	14 ng/L 11 ng/L	Ozone/H ₂ O ₂ (2.1/1.0 mg/L)	81	Snyder et al. 2006
	127.97 ± 26.56	Activated sludge	100.00 ± 0.00	Silva et al. 2014
Citalopram	147.54 ± 35.40 ng/L	Activated sludge/trickling filters/biofiltration	78.83 ± 29.59	Silva et al. 2014
Paroxetine	169.97 ± 27.77	Activated sludge	80.37 ± 33.99	Silva et al. 2014
Sertraline	100.40	Activated sludge	100.00	Silva et al. 2014
Diazepam	≈40 ng/L	Activated carbon (5 mg/L)	67–90	Westerhoff et al. 2005
		Ozonation	81	

the concentration of these drugs in the solid phase increases while their concentration in liquid phase decreases. The discharge of treated effluents into water bodies, after incomplete removal in WWTP, as well as the disposal of contaminated solid wastes are therefore important releasing sources of psychiatric pharmaceuticals into the environment. As previously addressed in Sect. 2.3, the release of these compounds into the environment has been recognized as the cause of toxic effects to non-target organisms. The next sections will be focused in different advanced treatment and their efficiency on the removal of psychiatric drugs, centering on adsorption, membrane and advanced oxidation processes.

3.3 Activated Carbon Adsorption

Among the different advanced treatments, adsorption on activated carbon has been recognized as a highly efficient technique for the removal of emerging contaminants, such as pharmaceuticals (Snyder et al. 2007b; Vona et al. 2015; Rakić et al. 2015). Adsorption on activated carbon is a well-known technique for the removal of organic compounds in drinking water treatment (Delgado et al. 2012). The main benefits of this process are the relative low-cost, effectiveness at removing low levels of pollutants, flexibility of operation (batch or continuous mode) and possibility of regeneration and reuse (Delgado et al. 2012). Properties such as surface area, surface chemistry, pore size distribution, hydrophobicity and oxygen content are intrinsically related with the removal performance in activated carbon adsorption systems (Snyder et al. 2003). Due to its hydrophobic surface, activated carbon tends to adsorb nonpolar organic compounds, although ion-exchange interactions may allow the removal of polar contaminants. The functional groups of the surface, mainly composed by oxygen and hydrogen, contribute to the acid-base properties of the surface, which has an effect on particular interactions with adsorbed solutes (Vona et al. 2015). The removal capacity of pharmaceuticals tends to decrease in wastewater with a high contamination level, since the natural organic matter present in water competes for the adsorption sites in activated carbon (Snyder et al. 2003). Activated carbon can be found in powdered (powdered activated carbon—PAC) or granular form (granular activated carbon—GAC). Both PAC and GAC have been successfully used as adsorbents in the removal of organic micropollutants, such as pharmaceuticals (Kovalova et al. 2013; Grover et al. 2011). An advantage of using PAC is that it can be used seasonally or occasionally in the treatment of wastewater when the concentration of contaminants is higher than usual, for instance in low-flow events (Vona et al. 2015). The use of PAC in the activated sludge process or as a post treatment constitutes an upgrade to conventional WWTP, as it promotes the improvement of pharmaceuticals removal (Boehler et al. 2012). The main disadvantage of using PAC is the separation of the adsorbent from the aqueous phase, which can be achieved by the addition of a filtration unit (Gadipelly et al. 2014). While PAC is added occasionally or intermittently in wastewater flow, GAC is used in packed bed filters or columns. One limitation of this technique is the

faster breakthrough of the more hydrophilic contaminants in comparison to those hydrophobic compounds that are strongly bound to GAC (Delgado et al. 2012). Although the initial cost of PAC is lower in comparison with the granular form, GAC can be regenerated by heating or steaming, saving more than 60 % of the initial cost, while the regeneration of PAC is economically unsustainable (Levy et al. 2011). The use of GAC in packed bed filters has also demonstrated to be a highly efficient process in the removal of pharmaceutical compounds from water (Kennedy et al. 2015; Huerta-Fontela et al. 2011; Kim et al. 2007) and wastewater (Ek et al. 2014; Luo et al. 2014; Rivera-Utrilla et al. 2013; Margot et al. 2013). In particular, some recent research data concerning the removal of psychiatric pharmaceuticals by activated carbon adsorption, either in powdered or granular form, is presented in Table 3.2. The requirement of disposal of spent PAC or GAC after successive regeneration cycles, is another drawback of this process, since it involves important operating costs (Rakić et al. 2015). Nevertheless, activated carbon can be manufactured from several biological materials such as wood, coal, lignin, and coconut shells, which is a low-cost alternative for the treatment of wastewater contaminated with pharmaceutical compounds (Delgado et al. 2012).

3.4 Membrane Processes

In membrane filtration processes, the membrane acts as a selective barrier that limits the passage of contaminants such as organic compounds, particles in suspension, metal ions, nutrients and microorganisms, allowing the passage of treated water through the membrane (Shon et al. 2007). The retention of pollutants in the membrane is controlled by different mechanisms, namely size exclusion, adsorption onto membrane and charge repulsion. These mechanisms are related to membrane characteristics, operation conditions and to specific properties of pollutants (Luo et al. 2014). The different membrane processes commonly used can be classified into four main categories: microfiltration (MF), ultrafiltration (UF), nanofiltration (NF), and reverse osmosis (RO). Table 3.3 presents the pore sizes, applied pressures and some of the applications of each type of membrane.

MF refers to membranes with the largest pore size that can be used to filter particles in suspension, large colloids, bacteria and organic compounds. The main separation mechanism in MF membrane systems is physical sieving of solutes larger than the membrane pore size. This type of membrane is also used as a pre-treatment for NF and RO processes, to reduce fouling potential.

UF membranes allow the separation of colloids up to 0.1 μm , being widely used in the recovery of raw materials and products from effluents in industrial WWTP. UF is also commonly used as a pretreatment step to NF and RO processes (Shon et al. 2007). MF and UF systems are strongly suggested when there are space limitations and/or the feed water has variable quality (Gadipelly et al. 2014).

NF is a new class of pressure-driven membranes with pore size between UF and RO, which allow the rejection of molecules with a size in the order of 1 nm. NF

Table 3.2 Removal of psychiatric pharmaceuticals from water and wastewater by activated carbon adsorption

Target pharmaceutical	Operation conditions	Results/observations	References
Carbamazepine (mood stabilizer, anticonvulsant)	Carbamazepine 79.7 ng/L Granular activated carbon (GAC) Matrix: sewage treatment works (STW), England	Removal of carbamazepine: 65 % Improvement of 23 % in the removal of carbamazepine after the use of GAC as a post-tertiary treatment	Grover et al. 2011
	Carbamazepine 0.235 ± 0.128 mg/L Powdered activated carbon (PAC Norit SAEe Super) Matrix: hospital wastewater treatment plant (WWTP), Baden, Switzerland	Removal of carbamazepine: PAC 8 ± 4 mg/L: 98 ± 0 mg/L PAC 23 ± 7 mg/L: 99 ± 1 mg/L PAC 43 ± 14 mg/L: 100 ± 0 mg/L	Kovalova et al. 2013
	Carbamazepine ~230 ng/l Granular activated carbon (GAC) Matrix: wastewater reclamation plant, Gwinnett County, USA	Removal of carbamazepine: ~88 %	Yang et al. 2011
	Carbamazepine 1.2 to 3.3 ng/L Granular activated carbon (GAC) Matrix: STP effluents, Henriksdal, Stockholm	0.4 % of the original concentration	Ek et al. 2014
	Carbamazepine 482 ± 586 ng/L Powdered activated carbon (PAC) and ultrafiltration (UF) Matrix: municipal WWTP, Lausanne, Switzerland	Removal of carbamazepine: 90 ± 9 %	Margot et al. 2013
Oxazepam	Carbamazepine 20 µg/L Granular activated carbon (GAC) Matrix: sewage from a municipal WWTP, Spain	Removal of carbamazepine: <43 %	Serrano et al. 2010
	Oxazepam 1.06 ± 0.34 mg/L Powdered activated carbon (PAC Norit SAEe Super) Matrix: hospital wastewater treatment plant (WWTP), Baden, Switzerland	Oxazepam elimination efficiency: PAC 8 ± 4 mg/L: 98 ± 0 mg/L PAC 23 ± 7 mg/L: 99 ± 0 mg/L PAC 43 ± 14 mg/L: 100 ± 0 mg/L	Kovalova et al. 2013
	Oxazepam 0.9 ng/L Granular activated carbon (GAC) Matrix: STP effluents, Henriksdal, Stockholm	Removal of oxazepam: 90 to 98 %	Ek et al. 2014
	Oxazepam 305 ± 134 ng/L Powdered activated carbon (PAC) and ultrafiltration (UF) Matrix: municipal WWTP, Lausanne, Switzerland	Removal of oxazepam: 69 %	Margot et al. 2013
(continued)			

Table 3.2 (continued)

Target pharmaceutical	Operation conditions	Results/observations	References
Venlafaxine	Venlafaxine 0.681 ± 0.275 mg/L Powdered activated carbon (PAC Norit SAE Super) Matrix: hospital wastewater treatment plant (WWTP), Baden, Switzerland	Venlafaxine elimination efficiency: PAC 8 ± 4 mg/L: 99 ± 0 mg/L PAC 23 ± 7 mg/L: 100 ± 0 mg/L PAC 43 ± 14 mg/L: 100 ± 0 mg/L	Kovalova et al. 2013
	Venlafaxine 235 ± 21 ng/L Powdered activated carbon (PAC) and ultrafiltration (UF) Matrix: municipal WWTP, Lausanne, Switzerland	Removal of venlafaxine: 46 %	Margot et al. 2013
Citalopram	Citalopram $0.5-1.5$ ng/L Granular activated carbon (GAC) Matrix: STP effluents, Henriksdal, Stockholm	Removal of citalopram: 90 to 98 %	Ek et al. 2014
Sertraline	Sertraline $0.7-1.6$ ng/L Granular activated carbon (GAC) Matrix: STP effluents, Henriksdal, Stockholm	Removal of sertraline: 90 to 98 %	Ek et al. 2014
10,11-dihydro-10,11-dihydroxycarbamazepine	10,11-dihydro-10,11-dihydroxycarbamazepine 975 ± 106 Powdered activated carbon (PAC) and ultrafiltration (UF) Matrix: municipal WWTP, Lausanne, Switzerland	Removal of 10,11-dihydro-10,11-dihydroxycarbamazepine: 52 %	Margot et al. 2013
Diazepam	Diazepam 20 µg/L Granular activated carbon (GAC) Matrix: sewage from a municipal WWTP, Spain	Removal of diazepam: 32-35 % Removal of sertraline: 90-98 %	Serrano et al. 2010

Table 3.3 Characteristics and applications of pressure-driven membranes for water and wastewater treatment (Wang et al. 2011)

Membrane	Pore size	Working pressure	Applications
Microfiltration	50–10 ⁴ nm	5–500 kPa	Particle and microorganisms removal Pharmaceutical industry Water treatment
Ultrafiltration	5–100 nm	<1 MPa	Water pollution treatment Sterile filtration of water Products recovery
Nanofiltration	1–10 nm	<4 MPa	Desalination of water Micropollutants removal Product separation
Reverse osmosis	Non porous	>5–10 MPa	Production of ultrapure water Municipal wastewater reclamation Desalination of seawater

membranes are generally used in water softening, industrial wastewater treatment and reuse, product separation and desalination (Van der Bruggen and Geens 2008). NF membranes have a molecular weight cut off (MWCO) in the range of 150–300 Da and a unique property that distinguishes themselves from RO that is the higher rejection of multivalent ions than of monovalent ions, making NF a cost-effective alternative when retention of monovalent salts is not necessary (Schäfer et al. 2003; Koyuncu and Cakmakci 2010). NF membranes have overcome the drawbacks of UF and RO membranes, since they have a higher rejection of organics compared to UF and a lower operating pressure compared to RO (Shon et al. 2007; Ng and Mohammad 2015). Both physical sieving and ion interactions play an important role in the rejection mechanisms of NF membranes (Bowen and Welfoot 2002).

RO was the first membrane process to be commercialized at large scale. RO process is characterized by high operating pressure, being widely used in the separation of dissolved salts and ions with low molecular weight (<200 g/mol). The applications of RO membrane systems range from the desalination of seawater for drinking purposes to the production of ultrapure water and the purification of effluents in industrial WWTP (Peters 2010).

Membrane filtration has demonstrated a great potential in various fields of water and wastewater treatment. Nowadays, there is an increasing interest in the implementation of membrane technology due to its attractive advantages, namely the quality of the treated water, the moderate operating temperatures, the absence of chemicals and the low energy requirements in most of the applications (Javier Benitez et al. 2011). Despite the many advantages, the main drawback to the widespread application of membranes is their proneness to fouling, observable as the flux decline through the membrane along time (Wiesner and Aptel 1996).

Membrane filtration using NF or RO membranes has demonstrated to be an efficient technique for the treatment of contaminated raw water to be used for

Table 3.4 Removal of psychiatric pharmaceuticals from water and wastewater by membrane processes

Target pharmaceutical	Membrane process	Experimental conditions	Results/observations	References
Diazepam (anxiolytic)	Ultrafiltration	Diazepam 0.98 ± 0.10 mg/L Hollow fiber ultra-filtration membrane (UF-HF) Spiral wound ultra-filtration membrane (UF-SW)	Diazepam removal: 82.1 % (UF-HF) 90.4 % (UF-SW)	Sulaiman et al. 2014
	Nanofiltration and ultrafiltration	Diazepam 2 to <250 ng/L ESNA nano-filtration membrane (NF) GM ultra-filtration membrane (UF) NF—724 to 779 kPa, MWCO 600 ± 200 Da UF—445 to 504 kPa; MWCO 8000 ± 1000 Da	Diazepam recovery: 100 % (NF) ~90 % (UF) Diazepam retention vs adsorption: ~15 % (NF retention) ~90 % (NF adsorption)	Yoon et al. 2006
Carbamazepine (mood-stabilizer)	Nanofiltration and ultrafiltration	Carbamazepine to <250 ng/L ESNA nano-filtration membrane (NF) GM ultra-filtration membrane (UF) NF—724 to 779 kPa, MWCO 600 ± 200 Da UF—445 to 504 kPa; MWCO 8000 ± 1000 Da	Carbamazepine recovery: 100 % (NF) ~85 % (UF) Carbamazepine retention vs adsorption: ~20 % (NF retention) ~0 % (NF adsorption)	Yoon et al. 2006
	Ultrafiltration	Carbamazepine 10 ppm Hollow fiber ultra-filtration membrane in cross-flow mode (HF-UF) HF-UF—polysulfone; 20 ± 0.4 kPa; MWCO 100 kDa	Carbamazepine removal: ~20 % (after 20 min)	Secondes et al. 2014

(continued)

Table 3.4 (continued)

Target pharmaceutical	Membrane process	Experimental conditions	Results/observations	References
	Microfiltration/ Reverse-osmosis	Carbamazepine $<2.5 \times 10^3$ ng/L	Recovery in influent of WWTP: 82 ± 3.4 % Removal in effluent of WWTP: 50–75 %	Al-Rifai et al. 2011
	Nanofiltration/ Reverse osmosis	Carbamazepine 8.7 to 166.5 ng/L Nano-filtration membranes (NF)—1st stage: 31 membranes modules equipped with 6 NF 90–400 membranes; 2nd stage: 15 membranes modules equipped with 6 NF 90–400 membranes; MWCO: 200 Da Reverse-osmosis (RO)—1st stage: 40 BW30LE-440 membranes modules; 2nd stage: 20 BW30LE-440 membranes modules;	Carbamazepine removal: 95–100 % for NF and RO	Radjenović et al. 2008
	Nanofiltration and ultrafiltration	Ultrafiltration (UF) PT-UF: PES; MWCO 5000 Da, 6 bar Nanofiltration (NF) HL-NF: MWCO 150–300 Da, 30 bar	Rejection coefficient in PT-UF: 56 % Rejection coefficient in HL-NF: 81 %	Acero et al. 2010
Meprobamate (anxiolytic)	Nanofiltration and ultrafiltration	Meprobamate 2 to <250 ng/L ESNA nano-filtration membrane (NF) GM ultra-filtration membrane (UF) NF—724 to 779 kPa, MWCO 600 ± 200 Da UF—445 to 504 kPa; MWCO 8000 ± 1000 Da	Meprobamate recovery: 100 % (NF) ~80 % (UF) Meprobamate retention versus adsorption: ~15 % (NF retention) ~0 % (NF adsorption)	Yoon et al. 2006

(continued)

Table 3.4 (continued)

Target pharmaceutical	Membrane process	Experimental conditions	Results/observations	References
Phenytoin (antiepileptic)	Microfiltration/Reverse-osmosis	Phenytoin 11–38 µg/L	Phenytoin recovery in influent of WWTP: 80 ± 2.4 % Phenytoin removal in effluent of WWTP: 100 %	Al-Rifai et al. 2011
Venlafaxine (antidepressant)	Nanofiltration and ultrafiltration	Ultrafiltration (UF) PT-UF: PES; MWCO 5000 Da, 6 bar Nanofiltration (NF) HL-NF: MWCO 150–300 Da, 30 bar	Rejection coefficient in PT-UF: 45 % Rejection coefficient in HL-NF: 87 %	Acero et al. 2010

drinking water production (Radjenović et al. 2008; Lipp et al. 2010; Verliefde et al. 2007; Vergili 2013). In wastewater treatment, an increasing number of studies has devoted special attention to membrane filtration processes, including membrane bioreactors (typically based on MF or UF technology), NF and RO for the removal of micropollutants such as pesticides, pharmaceuticals, endocrine disruptors and other trace organics (Zaviska et al. 2013; Sun et al. 2015; Siegrist and Joss 2012; Plakas and Karabelas 2012; Snyder et al. 2007a; Kimura et al. 2004).

Generally, pharmaceuticals have molecular weights higher than 250 Da and therefore can be removed from solution by using membrane technologies (Gadipelly et al. 2014). Several recent studies have shown the high efficiency of membrane processes in the elimination of pharmaceutical products from water matrices (Kim et al. 2008; Yoon et al. 2006; Yoon et al. 2007; Urtiaga et al. 2013; Al-Rifai et al. 2011). More specifically, in Table 3.4 are presented some recent reports concerning the efficiency of membrane technology in removing psychiatric pharmaceuticals from water and wastewater. The removal efficiency of each pharmaceutical compound is affected by several factors such its concentration, the operational conditions and the presence of organic matter in the water matrix. Although low-pressure-driven membrane techniques such as MF or UF are capable of removing in some extent selected pharmaceuticals, they might be applied to complement an existent treatment (Heberer and Feldmann 2008). By contrast, UF and RO processes have been shown to provide an effective retention of pharmaceutical compounds (Dolar and Košutić 2013; Radjenović et al. 2008). Nevertheless, NF and RO processes produce a large amount of concentrate (Roccaro et al. 2013) that requires proper treatment and disposal and this should be considered as an additional operating cost.

3.5 Advanced Oxidation Processes (AOP)

Advanced oxidation processes (AOP) are considered clean processes designed for the oxidation of a wide variety of organic pollutants present in water and wastewater. AOP are a set of processes involving the production of highly reactive hydroxyl radicals ($\text{HO}\cdot$), which are the second strongest oxidizing species after fluorine with an oxidation potential of 2.80 V (Pera-Titus et al. 2004). Due to their unselective nature, hydroxyl radicals can attack indiscriminately a large number of organic contaminants via hydroxylation or dehydrogenation, yielding CO_2 , H_2O or less complex products (Brillas et al. 2009; Mohapatra et al. 2014). When complete mineralization is not achieved, a post-treatment is usually required, leading to the improvement of the global removal efficiency. In several AOP applications, reaction byproducts are more biodegradable and less toxic than the parent compounds, which is a desirable benefit when biological post-treatment is applied (Klavarioti et al. 2009). Over the past years, there has been an increasing interest in the development of new AOP due to the diversity of technologies involved and the fields of potential application. The main advantages of these methods are: possibility of complete

mineralization, high degree of oxidation even for recalcitrant compounds and flexibility concerning water quality variations. However, the high capital and operating costs, the special safety requirements due to the use of very reactive chemicals as well as the need of high energy sources are the main drawbacks of these technologies (Kochany and Bolton 1992; Mohapatra et al. 2014).

Depending on the specific properties of the water matrix to be treated and the level of treatment required, different AOP can be employed. These processes can be implemented by ultraviolet radiation (UV), oxygen (O_2), ozone (O_3), hydrogen peroxide (H_2O_2), or even the combination of some of them. In compliance with the method used to generate hydroxyl radicals, AOP can be classified into chemical, photochemical, electrochemical, sonochemical, and thermochemical. Conventional AOPs can be also classified as homogeneous (single-phase) or heterogeneous when they make use of solid catalysts, such as TiO_2 or supported metal catalysts (Oliveira et al. 2014). The main AOP systems are presented in Fig. 3.2. Some of the most representative AOP are the heterogeneous photocatalysis using semiconductors, ozonation, Fenton process, wet oxidation, catalytic wet oxidation and electrochemical oxidation. A brief description of the most commonly applied AOP to the treatment of wastewater is given in Table 3.5.

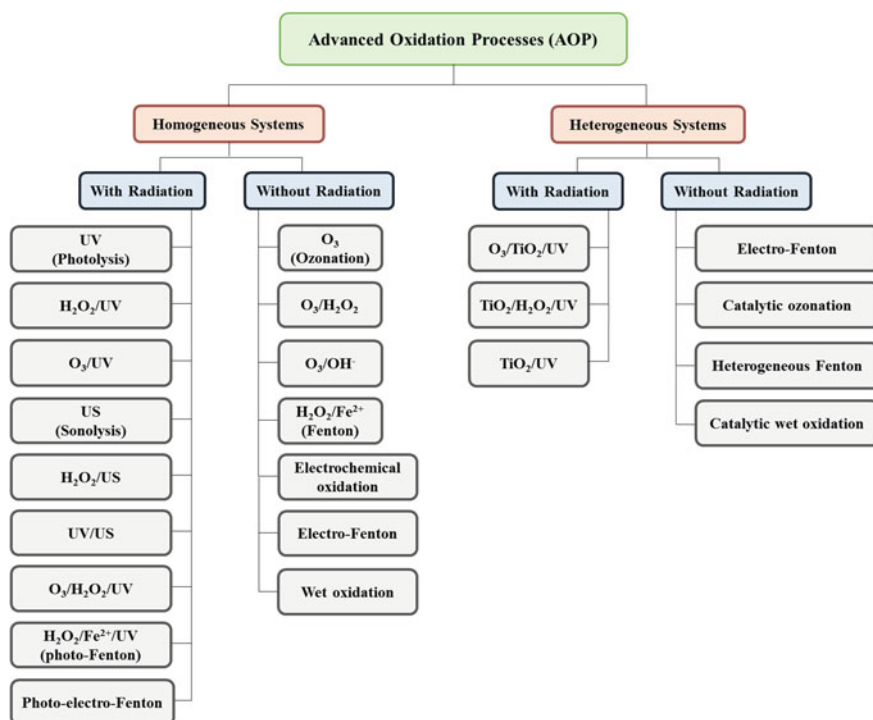


Fig. 3.2 AOP classification and possible combinations

Table 3.5 Classification and description of the most representative AOP applied to the treatment of wastewater

AOP type	Classification	Description
Ozonation	Homogeneous chemical	In ozonation processes, the contaminants can be degraded by direct or indirect reaction mechanisms: ozone can attack selectively certain functional groups of organic molecules or can be decomposed in water to form hydroxyl radicals which are even stronger oxidizers than ozone itself. Ozonation is usually enhanced at high pH values due to the increased production of hydroxyl radicals. The treatment can be improved with the combination of light irradiation, hydrogen peroxide or with metal complexes that act as catalysts
Heterogeneous photocatalysis	Heterogeneous photochemical	When semiconductors in aqueous suspension are illuminated with energy greater than their band gap, valence band holes and conduction band electrons are generated. Holes can generate reactive hydroxyl radicals, or can also react with species adsorbed on the catalyst surface, while electrons can react with dissolved oxygen reducing it to superoxide radicals and later to hydroxyl radicals. TiO_2 is the catalyst employed for almost all the photocatalytic treatments applied for pharmaceuticals removal
Fenton	Homogeneous chemical	Homogeneous oxidation with the Fenton's reagent (mixture of H_2O_2 and ferrous or ferric ions) is a process that involves the reaction of hydrogen peroxide with the iron catalyst through a free radical chain reaction which generates hydroxyl radicals. It is a catalytic reaction that occurs at room temperature and pressure and does not require special equipment. The photo-Fenton process is mediated by ultraviolet or solar irradiation which accelerates the regeneration rate of Fe^{2+} from Fe^{3+} complexes
Photo-Fenton	Homogeneous photochemical	
Wet oxidation	Homogeneous thermochemical	Wet oxidation is a thermochemical process in which hydroxyl radicals are produced at high temperature (200–300 °C) and pressure (20–200 bar) and where dissolved oxygen is used as oxidizing agent. The performance can be improved by the addition of homogeneous or heterogeneous catalysts that allow less severe operating temperatures (120–250 °C) and pressures (5–50 bar)
Catalytic wet oxidation	Homogeneous or Heterogeneous thermochemical	
Electrochemical oxidation	Homogeneous electrochemical	In electrochemical oxidation process, hydroxyl radicals are formed via the oxidation of water on the anode surface in the presence of a suitable electrolyte. Different types of electrodes can be used in this process, such as electrodes made of graphite, Pt, TiO_2 , IrO_2 , Ti-based alloys or boron doped diamond (BDD)

Table 3.6 Removal of psychiatric pharmaceuticals from water and wastewater by advanced oxidation processes

Target pharmaceutical	AOP type	Experimental conditions	Results/observations	References
Fluoxetine (antidepressant)	UV/TiO ₂ UV/TiO ₂ /H ₂ O ₂ UV/O ₃ /H ₂ O ₂	Fluoxetine 0.11 mM at pH 11 Matrix: deionized water TiO ₂ loading, 0.050 g/L H ₂ O ₂ (0.12 mM), O ₃ (25 mg/L) UV at 360 nm	Fluoxetine mineralization: UV/TiO ₂ (50 %) UV/TiO ₂ /H ₂ O ₂ (>70 %) UV/O ₃ (100 %) UV/O ₃ /H ₂ O ₂ (97 %)	Méndez-Arriaga et al. 2011
	Ozonation	Fluoxetine (30 ng/L; 66 ng/L; 82 ng/L) pH (8.2; 7.6; 7.1) Matrix: 3 tertiary-treated wastewaters O ₃ : TOC = 0.2; O ₃ : TOC = 0.6; O ₃ : TOC = 1.0	When O ₃ : TOC = 0.6 Fluoxetine removal: 90–100 %	Wert et al. 2009
	Ozonation	Fluoxetine 82 ng/L at pH 7.79 Matrix: surface water O ₃ (2.4 mg/L) 2, 6 and 24 min of reaction time	Fluoxetine removal >99 %, for all reaction times	Snyder et al. 2006
Duloxetine, (antidepressant)	Photolysis	Antidepressant concentration, 1 mM UV at 350 nm, 22 °C Suwannee river humic acid (SRHA) 25 mg/L	Duloxetine was the most susceptible to direct photolysis, with a half-life <1 h Bupropion degrades at a much slower rate and venlafaxine is not degraded by direct photolysis All compounds degraded faster in the presence of SRHA	Santoke et al. 2012
Bupropion (antidepressant)				
Venlafaxine (antidepressant)				

(continued)

Table 3.6 (continued)

Target pharmaceutical	AOP type	Experimental conditions	Results/observations	References
Venlafaxine (antidepressant)	Ozonation	Venlafaxine 7 ng/L Matrix: raw water (after pretreatment) O ₃ (0.2 mg/L) 15–20 min of reaction time	Venlafaxine removal: 86 %	Huerta-Fontela et al. 2011
	Ozonation	Diazepam 0.5 µM at pH 8, 10 °C Matrix: natural water O ₃ (2 mg/L) 10 min reaction time	Degradation follows second-order kinetics; second-order rate constant: k_{O_3} (T = 20 °C) = $0.75 \pm 0.15 \text{ M}^{-1} \text{ s}^{-1}$ Removal: 24–65 %	Huber et al. 2003
Diazepam (anxiolytic)	Ozonation	Diazepam (2.6 ng/L; 7.4 ng/L; 5.7 ng/L) pH (8.2; 7.6; 7.1) Matrix: 3 tertiary-treated wastewaters O ₃ : TOC = 0.2; O ₃ : TOC = 0.6; O ₃ : TOC = 1.0	When O ₃ : TOC = 1.0 Diazepam removal >90 %	Wert et al. 2009
	Ozonation	Diazepam 107 ng/L at pH 7.79 Matrix: surface water O ₃ (2.4 mg/L) 2, 6 and 24 min of reaction time	Diazepam removal: 46 % (t = 2 min) 70 % (t = 6 min) 82 % (t = 24 min)	Snyder et al. 2006
	Ozonation	Diazepam 1 ng/L Matrix: raw water (after pretreatment) O ₃ (0.2 mg/L)	Diazepam removal: 50 %	Huerta-Fontela et al. 2011

(continued)

Table 3.6 (continued)

Target pharmaceutical	AOP type	Experimental conditions	Results/observations	References
Buspirone (anxiolytic)		15–20 min of reaction time		
	UV/TiO ₂	Buspirone 15 mg/L at pH, 50 °C Matrix: water TiO ₂ loading, 200 mg/L UV at 340 nm	Removal of buspirone: 100 %	Calza et al. 2004
Carbamazepine (mood stabilizer, anticonvulsant)	UV/TiO ₂	Carbamazepine 5000 µg/L at pH 7 Matrix: wastewater TiO ₂ nanofiber UV at 254 nm, 4 h reaction time	Removal of carbamazepine: 78 %	Chong and Jin 2012
	Photo-Fenton	Carbamazepine 100 µg/L and 5 µg/L at pH 3 Matrix: wastewater Fe (5 mg/L and 20 mg/L), H ₂ O ₂ (50 mg/L) solar UV radiation (400 nm) 150 min reaction time	Removal of carbamazepine: 100 %	Klamerth et al. 2010
	Ozonation and UV/H ₂ O ₂	Carbamazepine 1 µM Matrix: wastewater O ₃ (1.5 mM), H ₂ O ₂ (0.2–5 mM) UV (254–320 nm), 1 h reaction time	Removal of carbamazepine: 100 %	Lee and von Gunten 2010

(continued)

Table 3.6 (continued)

Target pharmaceutical	AOP type	Experimental conditions	Results/observations	References
Carbamazepine (mood stabilizer, anticonvulsant)	Ozonation UV/H ₂ O ₂ TiO ₂ photocatalysis	Carbamazepine 7070 µg/L at pH 7.6 Matrix: water O ₃ (36 dm ³ /h), TiO ₂ (0.3 g/L) UV at 254 nm, H ₂ O ₂ (5–10 mM)	Removal of carbamazepine: Ozonation (100 %) UV/H ₂ O ₂ (100 %) Photocatalysis (80 %)	Andreozzi et al. 2004
	Ozonation	Carbamazepine 0.5 µM at pH 8, 10 °C Matrix: natural water O ₃ (0.2 mg/L)	Degradation follows second-order kinetics; second-order rate constant: k_{O_3} (T = 20 °C) $\approx 3 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ Removal: 98 %	Huber et al. 2003
	Ozonation	Carbamazepine 0.5 µM at pH 5.5, 25 °C Matrix: water O ₃ (1 mg/L)	Removal: 100 % Mineralization: 30 %	Andreozzi et al. 2002
	Ozonation	Carbamazepine 1 µg/L at pH 7.8 Matrix: surface water O ₃ (0.5 mg/L)	Removal of carbamazepine: > 90 %	Temes et al. 2002
	Ozonation	Carbamazepine (170 ng/L; 350 ng/L; 260 ng/L) pH (8.2; 7.6; 7.1) Matrix: 3 tertiary-treated wastewaters O ₃ ; TOC = 0.2; O ₃ ; TOC = 0.6; O ₃ ; TOC = 1.0	When O ₃ : TOC = 0.6 Carbamazepine removal: 100 %	Wert et al. 2009

(continued)

Table 3.6 (continued)

Target pharmaceutical	AOP type	Experimental conditions	Results/observations	References
	Ozonation	Carbamazepine 122 ng/L at pH 7.79 Matrix: surface water O ₃ (2.4 mg/L) 2, 6 and 24 min of reaction time	Carbamazepine removal >99 %, for all reaction times	Snyder et al. 2006
	Electrochemical oxidation	Carbamazepine 10 mg/L at pH 7 Matrix: water Ti/PbO ₂ circular anode electrodes Na ₂ SO ₄ electrolyte, 400 mg/L Current intensity: 1.37 A electrolysis time: 101 min Recirculation flow rate: 232 mL/min	Removal of carbamazepine: 88 ± 1.2 %	García-Gómez et al. 2014

AOP are very promising, powerful and eco-friendly methods for the treatment of several organic contaminants such as aromatics, pesticides, dyes, volatile organic compounds, as well as pharmaceutical products (Oturán et al. 2011; Rey et al. 2011; Biard et al. 2011; Bouafia-Chergui et al. 2010; Isarain-Chávez et al. 2011). Increasing attention has been paid to the application of AOP to the treatment of water/wastewater contaminated with pharmaceuticals, which is reflected in the large number of studies published in the last years on this subject. In a recent study, Klavarioti et al. (2009) reviewed and assessed the effectiveness of various AOP for pharmaceutical removal from aqueous systems. According to data collected from 94 studies, these authors found that heterogeneous photocatalysis (32 %), ozonation (31 %) and Fenton and similar reactions (13 %) were the most popular among the AOP techniques used for the removal of pharmaceutical compounds from water and wastewater. Carbamazepine, a psychotropic compound, finds place in the top 5 of the most common pharmaceuticals that have been treated by AOP. An overview of the recent work carried out in this field describing which psychiatric pharmaceuticals have been treated so far by AOP, is given in Table 3.6.

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Chapter 4

Analytical Methods for the Quantification of Pharmaceuticals

Abstract Pharmaceutical compounds have been detected at trace concentrations ranging from ng/L to $\mu\text{g/L}$ in different environmental systems and considering the threat that these substances present to non target organisms, the development and the optimization of analytical methods for their identification and quantification are crucial. A condensed evaluation on analytical methods such as high performance liquid chromatography or gas chromatography combined with mass spectrometry is presented, as well as a review on the main studies on the pharmaceuticals contamination issue and respective sample collection process and analytical method employed. Particular attention is devoted to immunoassay techniques.

Keywords Immunoassay techniques • Gas chromatography • High performance liquid chromatography • Mass spectrometry • Sample extraction and collection procedures • Trace concentrations

4.1 Introduction

The increasing demand for pharmaceutical products is strongly due to the number and the average age of world's population which act as driving forces to the growth of the production, use and disposal of these compounds (SAICM 2007). Still, the concentrations of these compounds present in water are generally below the minimum therapeutic doses. These pharmaceutical compounds have been detected at trace concentrations ranging from ng/L to $\mu\text{g/L}$ (Calisto and Esteves 2009; Calisto et al. 2011). Due to the risk and the biological effects of these pharmaceutical molecules in the aquatic medium with harmful effect on the living organisms, the development and the optimization of analytical methods for their identification and quantification are crucial. Analytical methods such as high performance liquid chromatography (HPLC) or gas chromatography (GC) combined with tandem mass spectrometry (MS/MS) are usually used for the identification and quantification of these compounds.

Recently, the immunoassay techniques have also attracted attention for the detection and the monitorization of the pharmaceuticals compounds into the aqueous solutions. The recent progress in the development of analytical methods enables to detect and identify these compounds and their transformation products in environmental samples, contributing to a more effective monitoring of environmental contamination by pharmaceutical compounds (Buchberger 2007; Nikolaou and Lofrano 2012; Bottoni and Caroli 2015).

This chapter will be specifically focused on the following subjects: chromatographic and immunoassay techniques used to identify the psychiatric pharmaceuticals as emergent pollutants and to determine their occurrence in environmental matrices.

4.2 Chromatographic Techniques

The complexity of the environmental samples containing pharmaceutical compounds requires analytical techniques with very high resolution and extremely low quantification limits. The chromatographic techniques are the key for achieving these results. Gas chromatography (GC) or high performance liquid chromatography (HPLC) coupled to tandem mass spectrometry (GC-MS/MS or LC-MS/MS) are the adequate analytical methods, due to their versatility, specificity and selectivity (Nikolaou and Lofrano 2012). These MS techniques enable the analysis of large number of pharmaceuticals in aqueous matrices (Ternes 2001). The same analytical methods used for the determination of the pharmaceutical compounds can be also employed for the identification and quantification of their transformation products. The transformation products of fluoxetine and norfluoxetine, analyzed by MS techniques should be mentioned as an example (Farré et al. 2008).

These analytical methods are successfully used to identify and quantify the psychiatric pharmaceutical compounds present in aqueous matrices. Table 4.1 summarizes the analytical methods optimized for the detection of the main psychiatric pharmaceuticals.

The chromatographic analyses are dependent of the physicochemical properties of the pharmaceutical compounds and the sample preparation for the analysis (Ramirez et al. 2007). Concerning the sample preparation, the extraction of all target analytes from the environmental aqueous matrices involves usually Solid Phase Extraction (SPE) and Liquid-Liquid Extraction (LLE) procedures with appropriate solvents. SPE extraction procedures have become more important in modern organic trace compounds analysis (Nikolaou and Lofrano 2012).

In the application of the extraction procedures, the nature of the stationary phase, solvents and pH are very important in order to extract all analytes. The cartridges Oasis HLB or C18 are the most commonly used for SPE. Also, Lichrolut ENV+, Oasis MCX and StrataX are examples of other cartridges employed in this technique (Kostopoulou and Nikolaou 2008). The elution is achieved with pure organic solvents, generally methanol or acetonitrile, and water-organic solvents mixtures

Table 4.1 Methods of analysis of the main psychiatric pharmaceuticals detected in environment (adapted from Calisto and Esteves 2009)

Therapeutically class	Pharmaceutical	Concentration found in the environment	Matrix/Country	Methods of analysis	References
Antidepressants	Fluoxetine	0.012 µg/L	Surface water/USA, Canada	LC-(ESI+)-MS	Kolpin et al. (2002)
		ND-0.099 µg/L	STP effluents/Canada	GC-MS	Metcalfe et al. (2003)
		17 ± 3 ng/L	Psychiatric hospitals influents/China	LC-MS/MS	Yuan et al. (2013)
	Paroxetine	0.1–10 ng/g	Tissues of fish residing in a municipal effluent-dominated stream/USA	GC-MS	Brooks et al. (2005)
		0.055–0.19 µg/L; 0.010–0.063 µg/L	WWTP influents and effluents/Italy	HPLC and QqLIT-MS	Verlicchi et al. (2012)
		0.14–1.02 µg/kg	Fish tissues/Canada	LC-(APCI)-MS/MS	Chu and Metcalfe (2007)
		2.1 ± 0.4 ng/L; 3 ± 1 ng/L; 2.2 ± 0.2 ng/L	Pecan Creek Water Reclamation Plant/USA	LC-(ESI)-MS/MS	Schultz and Furlong (2008)
	Citalopram	0.48–0.58 µg/kg	Fish tissues/Canada	LC-(APCI)-MS/MS	Chu and Metcalfe (2007)
		0.056–0.076 µg/L	Hospital effluents/Italy	HPLC with QqLIT-MS	Verlicchi et al. (2012)
	Duloxetine	90 ± 20 ng/L; 40 ± 30 ng/L; 80 ± 30 ng/L	Pecan Creek Water Reclamation Plant/USA	LC-(ESI)-MS/MS	Schultz and Furlong (2008)
		67 ± 5 ng/L; 261 ± 14 ng/L	Psychiatric hospitals influents/China	LC-MS/MS	Yuan et al. (2013)
	Sertraline	1.5 ± 0.2 ng/L; 2 ± 2 ng/L; 1.2 ± 0.9 ng/L	Pecan Creek Water Reclamation Plant/USA	LC-(ESI)-MS/MS	Schultz and Furlong (2008)
		0.1–10 ng/g	Tissues of fish residing in a municipal effluent-dominated stream/USA	GC-MS	Brooks et al. (2005)
	Venlafaxine	36 ± 5 ng/L; 49 ± 9 ng/L; 33 ± 8 ng/L	Pecan Creek Water Reclamation Plant/USA	LC-(ESI)-MS/MS	Schultz and Furlong (2008)
		600 ± 200 µg/L; 1000 ± 400 ng/L; 900 ± 300 ng/L	Pecan Creek Water Reclamation Plant/USA	LC-(ESI)-MS/MS	Schultz and Furlong (2008)

(continued)

Table 4.1 (continued)

Therapeutically class	Pharmaceutical	Concentration found in the environment	Matrix/Country	Methods of analysis	References
Antipsychotics Anxiolytics/Hypnotics	Chlorpromazine	217 ± 21 ng/L	Psychiatric hospitals	LC-MS/MS	Yuan et al. (2013)
		0.053 µg/L	Municipal STP effluents/China	LC-ES-MS/MS	Ternes et al. (2001)
	Diazepam	0.88 µg/L	Surface water/Germany	HPLC-MS/MS	Ternes (2001)
		3–62 ng/L	Lake Mead/USA	GC-MS	Snyder et al. (2001)
		>0.01 µg/L; 0.66 µg/L	STP influent/Belgium	LC-ES-MS/MS	Van Der Ven et al. (2004)
		0.39 ± 0.24 ng/g	Sediments collect in the Todos os Santos Bay/Brazil	LC-MS/MS	Beretta et al. (2014)
		8.3 ng/L	WWTP effluent/France	GC-MS	Togola and Budzinski (2008)
	Nordiazepam	2.4 ng/L	Surface waters/France	GC-MS	Togola and Budzinski (2008)
	Oxazepam	0.25 µg/L	STP effluents/Germany	GC-MS	Heberer (2002)

(Petrovic et al. 2006). Considering the presence of groups susceptible to receive positive or negative charges in these molecules, the control of the pH is very important during the extraction. For the Oasis HLB, neutral pH is advisable, while for C18 the pH must be adjusted prior to extraction depending on the acidic, neutral or basic nature of the analytes (Nikolaou and Lofrano 2012). For environmental samples which, considering their complexity, are more susceptible to be affected from matrix effect, a purification step is necessary after the extraction. Purification is generally performed passing through the same cartridge, eluents with higher water content, in order to avoid losses of target compounds during SPE.

In general, the pharmaceutical compounds are polar and present low volatility which increases the probability of these compounds to be transported to surface water (Brausch et al. 2012; Kümmerer 2009). For the nonpolar and volatile pharmaceutical compounds GC-MS can be applied. However, for the non-volatile or thermally instable compounds a derivatization step is necessary although there are risks of analyte losses due to the different steps involved in derivatization procedure (Kolpin et al. 2002; Weigel et al. 2004). Pentafluorobenzylbromide, methyl chloromethanoate, methanol/BF₃ or tetrabutylammonium salts are typical derivatization reagents used for acidic pharmaceutical compounds (Buchberger 2007). The usual ionization procedures like electron impact (EI) or chemical ionization (CI) in GC-MS are generally less affected by the matrix of the sample than ionization modes used in HPLC-MS (Buchberger 2007). However, in order to achieve the complete HPLC separation of target analytes and consequently improve the sensitivity of MS detection, mobile phase modifiers, buffers and acids are widely recommended (Petrovic et al. 2006).

For HPLC-MS/MS based methods the major disadvantages of this technique is its susceptibility to matrix interferences, in particular when associated with the electrospray ionization mode (ESI), leading to the suppression of the analyte signals (Kot-Wasik et al. 2007). HPLC-(ESI)-MS method with a two-step sample purification procedure, including SPE and LLE, was developed to overcome this handicap providing limits of quantification in the pg/L range (Vasskog et al. 2006). Recently, Yuan et al. (2013) successfully quantified 22 common psychiatric pharmaceuticals using high performance liquid chromatography-electrospray ionization-tandem mass spectrometer (HPLC-MS/MS) coupled with solid-phase extraction (SPE). The analyzed samples were collected from two psychiatric hospital wastewater treatment plants (P-WWTP) and three municipal wastewater treatment plants (M-WWTP) with different biological treatment processes in Beijing, China. In these 22 psychiatric pharmaceuticals, six antidepressants were detected in P-WWTP influents with a concentration range of ~89 ng/L for chlorimipramine, 67–261 ng/L for citalopram, 0–17 ng/L for fluoxetine, 29–106 ng/L for sertraline, and ~435 ng/L for fluvoxamine. The authors compared the occurrence of these antidepressants pharmaceuticals with that found in western countries and concluded that the concentrations found in M-WWTP influent of Beijing are lower than those observed in Canada and USA. In a Montreal WWTP influent, the concentrations of paroxetine, citalopram, fluoxetine and sertraline were detected ranging from values inferior to MQL (method quantitation limit) up to 53 ng/L,

using solid phase extraction and liquid chromatography-tandem mass spectrometry (Lajeunesse et al. 2008). Vanderford and Snyder (2006) quantified the fluoxetine in Las Vegas WWTP influent with a concentration of 177 ng/L by isotope dilution liquid chromatography/tandem mass spectrometry.

Bottoni and Caroli (2015) describe the recent advances in analytical techniques to determine the residues and metabolites of medicinal products in aquatic matrices with special focus on the new advances in gas chromatography (GC) and high performance liquid chromatography (HPLC) instruments. For the detection of the pharmaceuticals compounds at the ng/L range, the instruments with triple quadrupole (QqQ) and ion trap (IT) mass analyzers are more commonly used (Nikolaou and Lofrano 2012). New generation of triple quadrupoles and hybrid instruments, such as quadrupole–time of flight (QqTOF) and quadrupole–linear ion trap (QqLIT) were developed for LC-MS/MS analysis (Pérez and Barceló 2007; Petrovic et al. 2007). The transformation products from pharmaceutical compounds have been also quantified using QqTOF instruments (Eichhorn et al. 2005; Gómez et al. 2007; Stolker et al. 2004). The improvement of selectivity achieved by TOF is due to its mass accuracy provided by mass measurements with an error typically lower than 2 mDa (Buchberger 2007). QqTOF analyzer was successfully used to determine 29 pharmaceuticals of different classes in samples from waste water treatment plants (Petrovic et al. 2006). For the determination of β -blockers in wastewater (Nikolai et al. 2006) and the identification of diclofenac, carbamazepine and iodinated X-ray contrast media (Seitz et al. 2006), the QqLIT methods have also been applied. MS-based methods, namely electrospray ionization tandem mass spectrometry (HPLC-ESI-MS/MS) were used for the determination of four acidic pharmaceuticals (acetaminophen, gemfibrozil, ibuprofen, naproxen), three neutral compounds (cotinine, fluoxetine, carbamazepine), one sulfonamide antimicrobial (sulfamethoxazole), a β -blocker drug (atenolol), and two antimicrobials (triclosan, triclocarban) widely used in personal care products including soaps and toothpastes, in tile water and in the raw DMB (dewatered municipal biosolids) with limits of detection and quantification in the ranges of 1–11 ng/L and 3–35 ng/L, respectively (Edwards et al. 2009). In this work, a Quattro LC triple quadrupole mass spectrometer which includes an electrospray interface (ESI) was used to analyze acidic pharmaceuticals. The neutral pharmaceuticals and the sulfonamides were analyzed with a QTrap mass spectrometer equipped with an atmospheric pressure chemical ionization (APCI) ion source.

The results obtained from these analytical techniques are important in order to establish the methodologies used for the development of an internationally standardized analytical protocol, which is essential to ensure both quality and comparability of data. The Strategic Approach to International Chemicals Management (SAICM 2007) from United Nations Environment Programme is a policy framework to adopt the rigorous management of chemicals in ways that minimize significant adverse impacts on the environment and human health (SAICM 2007).

4.3 Immunoassay Techniques

Immunoassays can be described as biochemical analytical methods that rely on the specific interactions between antibodies and antigens to measure a variety of substances, ranging from complex viruses and microorganisms to simple pesticide molecules and industrial pollutants (Plaza et al. 2000). Mainly, these methods are based on a competitive binding reaction between a fixed amount of labelled form of an analyte, and a variable amount of unlabeled sample analyte for a limited amount of binding sites on a highly specific anti-analyte antibody. An immune complex is created when the analyte binds to the antibody after the mixture and incubation of all reagents. Later, physical or chemical separation methods are used for the separation of the immune complex from the unbound reagent fraction. The immunoassays analysis is accomplished by measuring the label activity (enzyme, radiation or fluorescence for example) in either bound or free fraction. Immunoassays methods can be classified into heterogeneous and homogenous assays and can be performed in either competitive or non-competitive designs (Figs. 4.1 and 4.2). The nature of the analyte, the labelling chemistry available and the analytical parameters needed for testing will affect the choice of these designs (Darwish 2006).

Immunoassays techniques have become extremely popular for environmental analysis, particularly for organic trace analysis (1) because they require little sample pre-treatment, making the procedure inexpensive in comparison with the chromatographic instrumental analysis (Buchberger 2007) and (2) because to their inherent specificity, high-throughput, high sensitivity for the analysis of wide variety of analytes in biological samples, even if they might be extremely complex. In the

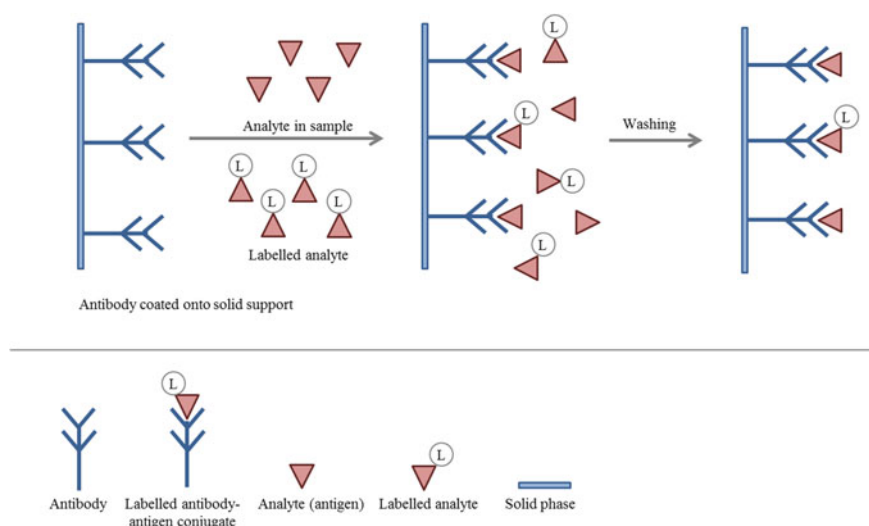


Fig. 4.1 Schematic diagram for the competitive immunoassay (adapted from Darwish 2006)

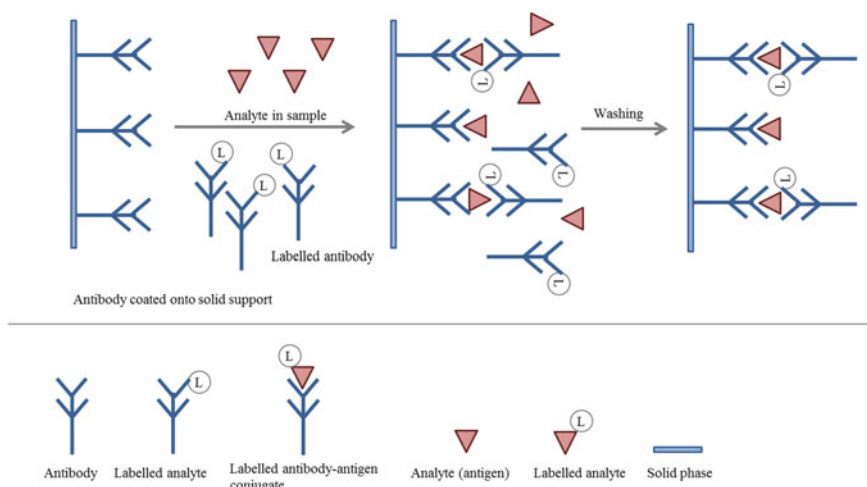


Fig. 4.2 Schematic diagram for the non-competitive immunoassay (adapted from Darwish 2006)

field of pharmaceutical analyses, clear improvements were obtained in the immunoassay techniques which include the preparation of a unique reagent, analysis of new categories of compounds, methodology and instrumentation (Darwish 2006).

Among the immunoassays methods, the Radioimmunoassay (RIA), the Enzyme Immunoassay (EIA), the Fluoroimmunoassay (FIA), the Chemiluminescence Immunoassay (CLIA) and the Liposome Immunoassay (LIA) have been used for the analysis of psychiatric pharmaceuticals in different matrices such as plasma, serum, blood and urine. The RIA, EIA, FIA, CLIA and LIA methods use respectively a radio-isotope, an enzyme, a fluorophore, a chemiluminescent substance and a liposome-encapsulating marker as a label. ELISA, an enzyme-linked immuno-sorbent assay, is the most commonly used enzymatic immunoassay method for environmental analysis (Lesnik 2000). A detailed list regarding the analyses of several psychiatric drugs using immunoassays techniques is presented in Table 4.2.

Since the immunoassays methods were employed primarily as quantitative screening methods, the conventional analytical methods are also used to support and confirm the immunoassay data. For example, OSW (Office of Solid Waste) from USA recommends that approximately 5–10 % of the immunoassay samples, which generate negative results, have to be confirmed by conventional laboratory techniques (Lesnik 2000). Several studies using immunoassay techniques were compared with the conventional chromatographic techniques.

Huo et al. (2007) studied the detection of the pharmaceutical indomethacin in water samples using the immunochemical techniques, especially ELISA and compared with the conventional HPLC. The authors found a good correlation between the results obtained from ELISA and those from HPLC, with a correlation coefficient of 0.988.

Table 4.2 List of psychiatric compounds analyzed by several immunoassays techniques (adapted from Darwish 2006)

Pharmaceutical	Biological sample	Immunoassays techniques	Sensitivity	References
Oxazepam	Urine	EIA	0.3 µg/mL	Laurie et al. (1996)
Nordizepam	Serum, urine	FIA	na	Schwenzer et al. (2000)
Iorazepam	Serum, urine	FIA	na	Agbuya et al. (1996)
Adinazolam	Serum	FIA	na	Fraser and Bryan (1995)
Phenytoin	Serum	FIA	na	Chetty and Wilson (1999)
		CLIA	0.45 µg/L	Frank et al. (2002)
		LIA	5 µg/L	Kubotsu et al. (1992)
Carbamazepine	Serum	CLIA	0.13 µg/L	Frank et al. (2002)
		LIA	4 ng/L	Kubotsu et al. (1992)
Phenobarbital	Serum	CLIA	0.3 µg/L	Frank et al. (2002)
		LIA	15 µg/mL	Kubotsu et al. (1992)
Chlorpromazine	Serum	FIA	10 ng/L	Kimura et al. (2000)

na—not available

There are few studies with these techniques for the analysis of psychiatric pharmaceuticals due to the lack of knowledge on the metabolites coming from these compounds (Calisto and Esteves 2009). The study of the impact of the fluoxetine concentrations in native fish species, including reproduction, feeding and predator avoidance was conducted by Weinberger Li and Klaper (2014) using enzyme immunoassays (EIA). Carvalho et al. (2010) developed a new immunoassay based on a commercially available anti-caffeine monoclonal antibody and a new synthesized tracer, using a horseradish peroxidase and UV-visible detection. In this study, caffeine was quantified in several matrices such as Coca-Cola, Red Bull, Earl Grey tea, espresso coffee, shampoo, caffeine tablets and tap water. A limit of detection of 0.001 µg/L was experimentally verified and concentrations higher than 0.025 µg/L (limit of quantification) presented a relative error lower than 20 %.

Although the immunoassays techniques present several advantages (wide applicability, sensitivity and specificity, easy to use, rapid and cost-effective for small-volume samples, suitable for laboratory and field use, accurate and reliable results) and disadvantages (development costs, not suited for small sample loads or multi-analyte analysis of compounds with different chemical structures, vulnerability to cross reacting compounds and non-specific interferences and the necessity

of an independent test) (Lesnik 2000; Aga and Thurman 1996; Plaza et al. 2000) over the conventional analytical techniques, its full potential has not been properly and extensively explored for the determination of pharmaceuticals, in particularly the determination of psychiatric pharmaceuticals. According to Buchberger (2007) the immunoassays methods may be an excellent tool to a quick and inexpensive screening. It is therefore important to perform more research work in order to bring out the best of immunoassay technology.

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Chapter 5

Green Pharmaceuticals

Abstract The contextualization of the general issue of environmental contamination with psychiatric pharmaceuticals, their metabolites and transformation products and the recognition of the huge effort, the spent energy and the investment needed to remediate the contaminated sites and systems, make us wonder why not avoid it in the first place? Green technology, clean products and processes may be a first step to make the present world needs as sustainable as possible. This chapter presents the way to sustainability through green procedures applied to the pharmaceutical industry.

Keywords Amidations • Catalytic reactions • Enzymatic reactions • Fluorinations • Green chemistry • Hydrogenations • Oxidations • Reductions • Solvents

5.1 The Green Strand

The conceptualization of the so called green chemistry appeared in the last decade of the XXth century and it embraces different technological sectors that have or may have relevant impact in environment and sustainability (Richards 1997). This concept is defined through twelve principles that demonstrate the breath of such a definition. Those principles include waste prevention or reduction, through innovative or adapted chemical syntheses design, as waste is increasingly expensive to dispose of. Any synthesis should consider that the final product have to contain the maximum proportion of starting materials, wasting few or no atoms, maximizing atom economy eventually through process intensification. Chemical syntheses ought to generate substances with little or no toxicity to either humans or environment, by substitution of hazardous substances under the light of inherently safe design of reactions and processes. Avoiding the usage of solvents, separation agents, derivatives to temporary block or protect specific groups or other auxiliary chemicals is also evaluated in this item. The pursuit of energy efficiency indicates

that chemical reactions should be run at room temperatures and pressures, whenever possible. For that purpose, catalytic reactions are preferable to homogeneous ones as they allow more efficient reactional mechanisms. Renewable feedstocks are preferable to depletable materials and reaction products must be designed to degrade after use, by breaking down to innocuous substances so they will not accumulate in environment. A relevant tool in green chemistry is the in-process, real-time monitoring and control during synthesis to reduce any by-products formation and minimize the potential for accidents (Lancaster 2002).

The consciousness of the unsustainable industrial activity, in terms of resources depletion of the planet as well as in terms of xenobiotic wastes accumulation defines an opportunity window to develop cost effective products and processes, transforming them into competitive and environmentally benign solutions to our urge of development benefits. Chemistry and chemical engineering are the main protagonists in this green chemistry process, but other activities will be directly and indirectly involved. That is the case of pharmaceuticals.

5.2 The Economic Perspective

The generalized idea that green products are more expensive and entail some sort of extra taxes do not apply to industry where greener is cheaper. In past decades new and renewable feedstock have been developed, produced through biological, chemical or thermal processes applied to cellulosic materials like agricultural wastes or switch grass, more competitive than petroleum derived feedstock, with reduced toxicity and lower greenhouse gases emission. Green chemicals and chemistry are growing very fast and considering the size of the chemical and pharmaceutical industry, small improvements will mean significant direct and indirect costs savings. Noticeable advances in biotech and bioengineering allow the manipulation of microorganisms to produce valuable compounds with reduced waste and increased efficiency. The volatile price of petroleum also enhances the search for alternatives for chemicals and energy production. The evolution of these green practices is established by a combination of economic factors technical, regulatory and consumer preference. Overall, green processes represent a market opportunity that will grow from €2.2 billion in 2011 to €86.5 billion by 2020.

Several organizations are working towards the sustainability of chemical, biochemical and pharmaceutical industries. In 2005, the American Chemical Society's (ACS) Green Chemistry Institute (GCI) Pharmaceutical Roundtable (PR) was founded to implement the integration of green chemistry and green engineering principles into the pharmaceutical industry and the major strategic priority of such organizations was assumed to be the enhancement and influence of the worldwide research agenda (Constable et al. 2007).

5.3 General Green Approaches Applied to Pharmaceuticals

The use of green chemistry metrics for the synthesis of the drug candidate (S,S)-reboxetine succinate was published by Assaf et al. (2012) and Jimenez-Gonzalez et al. (2012), who also evaluated some other chemical processes at GSK by the use of green metrics. Some examples of how a greener reaction design may increase overall efficiency are presented by Sheldon (2012) and also by Dunn (2012). The approach to green methodologies used by 21 pharmaceutical companies and one fine chemical company is reviewed by Watson (2012). Another approach to greener methodologies consists in processes intensification and in continuous processing, avoiding the batch philosophy of the earlier years of pharmacology. Continuous processing is indicated for extreme reactional conditions as high pressure and a publication from Genzyme (Cooper et al. 2012) describes the amination of an aldehyde at 150 °C and 100 bar in a kilo-lab reactor, with fast kinetics, high catalyst loadings and low material handling. Another example of green continuous processing, an asymmetric hydrogenation catalyzed by rhodium in a plug-flow reactor at high pressure followed by solvent swap and crystallization, is presented by Johnson et al. (2012). Some other approaches to greener and more sustainable pharmaceutical processes include process systems engineering methods and process analytical techniques (Gernaey et al. 2012).

5.3.1 Green Reactions in Pharmaceuticals

Reducing wastes is about environment saving and protection, but it also makes good business sense. In this perspective, there is room for a lot of improvements in pharmaceutical industry as most drugs to be used by humans go through many reaction and purification stages driving companies to look for more efficient and less polluting processes. Tools like life-cycle analysis may be used to assess the mass balance between the amount of substances that are really entrapped in the users' bodies and the amount that gets flushed down the toilet. The green chemistry principles may be implemented in pharmaceutical industry mainly by the development of new products, new processes or by atomic economy enhancement, as described in the following examples.

Terrence Collins and co-workers developed a series of tetra-amido macrocyclic ligand (TAML) catalysts modelled on natural peroxidase enzymes, which are able to break down complex molecules like Prozac, the antidepressant sertraline (Zoloft), the blood cholesterol reducer (Lipitor) and the contraceptive pill, Ellis et al. (2009). Those catalysts should be added to wastes at the early stages of the wastewater treatment plant.

Pfizer got an UK Award for Green Chemical Technology, Best Process category, for the sildenafil citrate (commercially known as Viagra) process, published by

Dunn et al. (2004). The added value of this process is not its environmental impact, but the fact that it reduces the amount of solvent, tin chloride and hydrogen peroxide required, as well as it reduces the amount of waste produced by the original process. The achievements reached during the development of this process are a convergent, efficiency synthetic route, with no extractive work-up in any of the seven steps and with implemented solvent recovery. The E-factor for the process is very low with 6 kg of waste per kilogram of product, while the industry average ranges from 25 to 100. Another interesting case is the production of paclitaxel, a chemotherapy drug known as Taxol in USA, usually obtained by solvent extraction of chemicals from yew tree bark but nowadays those chemical principles are produced by growing tree cells in a bioreactor. The utilization of enzymatic procedures to catalyze chemical reactions in aqueous media reduces the need of xenobiotic organic solvents, as it happened in the production process of atorvastatin, which reduces blood cholesterol and is commercialized by Pfizer.

Applying the atom economy principle, BASF substituted the six-step by a three-step process to produce the 2 billion tablets of ibuprofen, a painkiller, by making into the final product 77 % of the reagent atoms instead of the 44 % used in the original process.

5.4 Future Trends

The American Chemical Society's Green Chemistry Institute Pharmaceutical Roundtable identified the following as the main trends to implement greener and more sustainable products and processes within pharmaceutical development and production (Bandichhor et al. 2012).

5.4.1 Solvents

Organic solvents are to be avoided in terms of sustainable chemical processes, even if they are quite efficient in solubilization. Legislation in the European Union is quite restrictive in terms of organic solvents usage, through the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) document. Some other substances are under consideration for the same purpose. The naturally available γ -valerolactone (GVA), obtained from lignocellulosic biomass that is hydrolysed into levulinic acid and its esters, has several physical and chemical characteristics that make it an interesting green solvent. Moreover, it is soluble in water and non-toxic. Galletti et al. (2012) published a catalytic method to obtain yields of GVA over 90 %. The catalysts made of Amberlyst resins with ruthenium are recyclable up to five times. Another work published by Zhang-Qun and Fei (2012) describes some enzymatic biotransformations using GVA as the solvent medium, with competitive yields in comparison to organic solvents. Deep eutectic

slats proved to be useful and Azizi et al. (2012) promoted the reduction of epoxides and carbonyl compounds using choline chloride/urea as solvent.

5.4.2 Amidations

Amidation is one of the most common reactions in pharmaceutical processes so its implementation through catalysis is a main stream in research. Several reports presented recently the direct amidation of acids and amines promoted by acids, boric or boronic. The boiling rate of this reaction is determined by the heat input as well as by the catalyst effect, which demands a careful approach (Grosjean et al. 2012). Allen et al. (2012) evaluated the thermal amidation of carboxylic acids in nonpolar solvents and catalyzed by ZrCl_4 and by ZrCp_2Cl_2 . These catalysts are able to increase the uncatalyzed conversion six fold. Lundberg et al. (2012) also studied the effect of ZrCl_4 in such reactions, using tetrahydrofuran, THF, as the preferred solvent. These amidation reactions become much greener when promoted in mild conditions as defended by Ohshima et al. (2012) who selected sodium methoxide as catalyst with good conversions even at 50 °C, mainly with the addition of 2,2,2-trifluoroethanol or some other phenols. The effect of water-free or oxygen-free conditions on the amidation of esters catalyzed by potassium tert-butoxide was described by Kim et al. (2012). Again the THF was selected as solvent and ethyl esters are the preferred substrates. Isopropylmagnesium chloride also proved to be an interesting catalyst for esters amidation by Bodroux mechanism, with THF as solvent, as presented by Munoz et al. (2012). The authors used two microreactors at room temperature with a reagent ratio of 1:1.5:3 (ester/amine/Grignard reagent) in their assays. Iron sulfate also proved to efficiently catalyze the oxidative amidation of aldehydes with amine salts, at 60 °C, using acetonitrile as solvent and aqueous tertbutyl hydroperoxide as oxidant (Ghosh et al. 2012).

5.4.3 Oxidations and Reductions

Green oxidation processes were reviewed recently, within the perspective of their application in pharmaceutical production. Oxidations with molecular oxygen promoted with transition metals were detailed by Shi et al. (2012b), with specific highlights on free radical reactions and oxidative dehydrogenation. The relevance of gold catalysts in oxidations reactions is thoroughly reviewed by Pina et al. (2012). Other oxidation catalysts as Cu or Pd were evaluated and compared to transition metals and the effect of ligands in selectivity and in reactivity is also discussed in a review presented by Campbell and Stahl (2012). Photooxidation has been considered as an interesting green and competitive technology and Sun et al. (2012), described the usage of iridium complexes in such reactions. Yavorskyy

et al. (2012) also detailed photooxidations with rose Bengal in a bubble column. Some other reactions with pharmaceutical applications may be enhanced by temperature as described by Moriyama et al. (2012), and these authors compare the thermal promotion with the light promotion, as both mechanisms may be relevant in sustainability implementation.

Although oxidations may be promoted by enzymes, this has not been really interesting to synthetic chemistry, but nevertheless biocatalysis is under active research. Kluge et al. (2012), used extracellular *Agrocybe aegerita* peroxygenase in benzylic hydroxylations of alkylbenzenes. Aerobic oxidations of alcohols using different transition metals as catalysts were reviewed by Parmeggiani and Cardona (2012). Solvent free reactions and several types of solvents like supercritical fluids, ionic and fluoruous liquids were also listed. This review indicates that studies with more complex solvents and substrates are needed in order to render these oxidations competitive and useful.

Chemical reductions are part of most mechanisms used in pharmaceutical processes, becoming greener through the usage of new catalysts. The conversion of imides to amines is promoted by zinc triflate in toluene and in the same publication the reductive hydroamination of alkynes is presented (Werkmeister et al. 2012). These reactions demand high pressure and temperature, but the catalysts are not as expensive as some others and they are simple, selective and efficient.

Lindlar's catalysts, Pd/CaCO₃ with Pb(OAc)₂, promote the semireduction of alkynes with some drawbacks but Yabe et al. (2012), proposed a catalyst made of palladium supported on boron nitride, a powder able to over-reduce alkynes in the presence of DETA and methanol. This catalyst may be recovered from reactional medium and reused several times without relevant metal leaching or loss in selectivity and activity. Another catalytic application with promising perspectives is the hydrogen transfer from isopropanol promoted by Rh supported on clays (Sarmah and Dutta 2012), again with the possibility of catalysts recycling as advised by green protocols. A different perspective in the usage of reduction catalysts is presented by Shi et al. (2012a), who described the reduction of aldehydes and ketones by borane-ammonia. As a consequence, these complexes may act as hydrogen storage at room temperature. They also may perform as hydrogen donor, associated to different phosphorous compounds, so avoiding the usage of heavy metals, but this application does not have yet relevant interest in pharmaceutical processing (Dunn et al. 2012).

5.4.4 Hydrogenations and Fluorinations

Every process strategy that may increase reaction control and safety, intrinsic kinetics and atomic economy is considered as green and catalysts became an excellent tool to reach those purposes (Rueping et al. 2012). Chiral products are very relevant to pharmaceuticals and to medicine and they may be obtained through asymmetric hydrogenations, combining catalytic metals with chiral ligands, which

gives catalysts some green characteristics. Such is the case of ruthenium that catalyzes the production of chiral β -aryloxy cycloalkanols (Chen et al. 2012), and like the chiral ruthenium catalysts some others will allow the synthesis of alkaloids relevant to medicine applications. The same relevance presents Ir as catalyst for asymmetric hydrogenations of dihydroisoquinoline derivatives. BenzaPhos analogues are quite promising chiral supramolecular ligands that associated with Rh define efficient hydrogenation catalysts (Pignataro et al. 2012).

The very selective fluorination of acetoacetamides was thoroughly evaluated by Bi et al. (2012), without the need of a base or metallic catalyst. The downstream isolation seems to be easily performed by crystallization or evaporation. The whole process is presented as simple, intense and sustainable, very much in accordance with the green approach. The fluorination of carboxylic acids catalyzed by silver was described by Yin et al. (2012). As carboxylic acids present distinct reactivity, the manuscript presents the practical interest of this chemoselective fluorination considering the low cost of fluorine, of the catalysts and the mild reactional conditions needed for the purpose. The fluorine transfer from N-fluorobenzenesulfonimide onto peroxides by decarboxylative radical fluorination was described in first hand by Rueda-Becerril et al. (2012). The procedure is presented as very promising, to be applied to different alkyl radicals in different contexts and with different objectives. In another publication by Liu et al. (2012), sulfuric acid is presented as an effective catalyst to the fluorination of enols. The selected solvents for these reactions may be acetonitrile, methanol or sulfuric acid and the reactions occur with high catalytic activity and selectivity for the monofluorinated products.

The high exothermicity of direct fluorination, as well as the difficult handling of fluorine have been two relevant drawbacks in the fluorination processes, but McPake and Sandford (2012) defend the continuous processing as an efficient and inexpensive approach that may overcome those limitations.

5.4.5 *Enzymatic Reactions*

The green approach towards sustainability suggests the selection of catalytic processes and these include enzymatic reaction. Dehydrogenases are used with isopropyl alcohol to be oxidized to acetone, defining a thermodynamic equilibrium that establishes the maximum conversion of the reaction to be promoted. Acetone may be removed by distillation, implementing overall conversion (Calvin et al. 2012). Similar problem emerges from the chiral amine synthesis by transaminases, with the presence of a ketone in the reactional system that prevents higher conversions to be achieved. As an alternative to classical procedures, an amine dehydrogenase, AmDH, obtained by protein engineering presents an inverted specificity (Abrahamson et al. 2012). Monoamination of diketones by transaminases for the production of chiral dihydropiperidines is described by Simon et al. (2012). A recent publication from Agudo et al. (2012), describes the hydroxylation

of cyclohexene and pentene substrates using a cytochrome from *Bacillus magate-rum*, obtained by synthetic organic chemistry. These results incorporate a major achievement in enzymatic technology, the selective C–H activation, and the same happens with reverse epoxide opening with halogens promoted by dehalogenases obtained from *Arthrobacter* sp. strain AD2 (Tang et al. 2012). Some other synthetic tools are being developed with the perspective of C–C bonds formation, as it is the case of amide oxidations to imines catalyzed by a mutant monoamine oxidase, MAO. This technique was successfully applied to the production of an intermediate for boceprevir production, a protease inhibitor for the hepatitis C treatment (Li et al. 2012). This antiviral implements the success of some other drugs treatment. An exhaustive listing of Baeyer–Villiger monooxygenases (BVMO), their engineering and applications has been presented by Balke et al. (2012).

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