

Pharmaceutical compounds in drinking water

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Abstract

Pharmaceutical products and their wastes play a major role in the degradation of environment. These drugs have positive as well as negative consequences on different environmental components including biota in different ways. Many types of pharmaceutical substances have been detected with significant concentrations through various advanced instrumental techniques in surface water, sub-surface water, ground water, domestic waste water, municipal waste water and industrial effluents. The central as well as state governments in India are providing supports by creating excise duty free zones to promote the pharmaceutical manufacturers for their production. As a result, pharmaceutical companies are producing different types of pharmaceutical products at large scale and also producing complex non-biodegradable toxic wastes by-products and releasing untreated or partially treated wastes in the environment in absence of strong regulations. These waste pollutants are contaminating all types of drinking water sources. The present paper focuses on water quality pollution by pharmaceutical pollutants, their occurrences, nature, metabolites and their fate in the environment.

Introduction

The utilization of pharmaceutical drugs keeps rising due to improvement in health care system and expectations of people for longer life. The global utilization of different pharmaceutical drugs by human beings is

about 1 lakh ton/year. This data reveals the worldwide average consumption of 15 gm/capita/annum.^{1,2} The large diversity of the human pharmaceuticals may be noticed by 12,000 approved (authorized) human pharmaceuticals. From environmental consideration, there are 850 active compounds in human pharmaceuticals.³ India has now emerged as one of the top five pharmaceutical markets of the world. As pharmaceutical industry is the leading science based industry in India, thus it contributes 1% of the country's total gross domestic product.⁴ Due to regularly increasing international demand, pharmaceutical industries are rapidly growing. This development of the pharmaceutical industries supplies over 65 countries and earns more than 50% revenue through exports.⁵ United States of America is the largest customer of Indian made drugs, which procured drugs worth Rs. 1.4 billion US dollar during the year 2007.⁶ The pharmaceutical industries consist of approximately 300 large scale and 8000 small scale organizations, producing thousands of formulations containing 350 different bulks of drug.⁴ Many pharmaceutical manufacturing units are rapidly increasing in India,⁷ which dispose-off their effluents into the stream either directly or after partial treatment. Therefore, proper management along with complete and effective treatment of pharmaceutical industrial wastes as well as of expired drugs is required to be undertaken with latest tools and techniques. The pharmaceutical drugs get excreted with urine and faeces as parental compound and as a number of its metabolites. The waste water of toilet is subsequently flushed with clean water, which is known as black water. This black water enters to the municipal sewer and ultimately enters the adjoining water bodies and may affect the water quality and aquatic life.⁸ The water pollution due to pharmaceutical wastes in Andhra Pradesh (India) has been reported to be about 150 times more than the highest level of pharmaceutical pollution in USA.^{5,9-14} However, very few studies on pharmaceutical based water pollution have been carried out in India. The present paper highlights and reviews the impact of pharmaceutical pollutants on quality of water sources.

Global pharmaceuticals market status

Globally, the developed countries are main producers of pharmaceutical drugs. The five major countries in the world namely USA, Japan, Germany, United Kingdom and France are collectively two-third global pharmaceuticals manufacturers, while China and India are main global low cost producers of pharmaceuticals. Approximately 20,000 and 7500 pharma-

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ceutical units are running in India and China, respectively.¹⁵ However, the production of pharmaceuticals at global level as per continent wise is shown in Figure 1. India has progressively producing and consuming the pharmaceutical drugs.¹⁶ According to a recent Indian report, the Indian pharmaceutical market is expected to be US \$ 55 billion by the year 2020 among all third world countries.¹⁷ The European Federation of Pharmaceutical Industries and Associations (EFPIA)¹⁸ shows that Switzerland is the largest producer of pharmaceutical drugs in European continent. It produces pharmaceutical drugs worth 32,380 million €. Whereas, Latvia has the lowest production of these drugs worth only 108 million €. The Cyprus has market value and export of only 203 million € and 223 million €, respectively. While, Germany has highest market value and export of 26,122 million € and 50,818 million €, respectively. Similarly, the Belgium has imported pharmaceutical drugs of 26,757 million €. While, Cyprus has imported drugs of 237 million €. The statistical graph as depicted in Figure 2 represents country wise position in terms of production, market value, import and export respectively.¹⁸ In 1947, the turnover of registered Indian pharmaceutical industries was Rs. 10 Crore. Now, it has increased up to US \$ 5.5 billion in 2004 with 17% annual growth rate.¹⁹

Route of entry of pharmaceutical compounds into water system

Pharmaceutical substances are widely used for human and veterinary related health problems. More than hundreds of tonnes of pharmaceutical compounds are used in Austria, England and Germany collectively.²⁰ According

to an investigation, the consumption of pharmaceuticals *i.e.*, 836 ton of acetylsalicylic acid [non-steroidal anti-inflammatory drugs (NSAIDs)], 622 ton of paracetamol (NSAIDs), 517 ton of metformin (antidiabetic), 345 ton of ibuprofen (NSAIDs), 88 ton of carbamazepine (antiepileptic) was found in Germany, where as 35 ton of naproxen (NSAIDs) was observed in England in year 2001.²¹ But due to incomplete metabolism these drugs excrete through defecation and urinary systems as unchanged form and still remain in sufficient concentration level. The discharge of treated, partially treated and untreated effluents of pharmaceutical industries in open areas as well as into the streams²² and unacceptable dispose of unused (*i.e.*, expired drugs) ultimately contaminate various compartments of environment.^{23,24} These pharmaceutical residues may enter: i) in water supplies and soil through the excretion of animals and human beings; ii) in surface water through sewage treatment plants and agricultural runoff; and iii) in ground water through soil.²⁵ In the world, United States of America and Europe have the most advanced and comprehensive waste treatment directives.²⁶ In India, pharmaceutical industries discharge their treated and untreated effluents in open area and into streams.²² Due to change in the pharmaceutical production and effluents input characteristics, the treatment techniques are either inappropriate or inefficient.²⁷ Pharmaceutical compounds have been found to enter the environment by different sources such as discharge of treated or untreated or partial treated industrial wastewater and improper disposal of expired or unused drugs *etc.*^{23,24}

Fate and occurrence of pharmaceuticals in environment

The distribution of pharmaceutical products in the environment is mainly by aquatic medium followed by food-chain dispersal due to their low volatility.²⁰ Although pharmaceuticals persist low in environment, they are ubiquitous in environment due to their higher rate of release as compared to the rate of transformation.³⁰ Composition of sewage, weather conditions, design and operation of treatment plants determine the transformation of various active pharmaceutical products.³¹ The pharmaceutical products contaminated sludge, when used as an agricultural fertilizer can reach to the terrestrial environment and through chain it may enter into surface as well as ground water.³² Pharmaceutical compounds can be

efficiently removed from aqueous phase of waste water in a water treatment plant through several processes namely bio-degradation, sorption, stripping to air and abiotic transformation (photolytic degradation). Complete biodegradation, which results into carbon dioxide (CO₂) and water (H₂O) is called mineralization. Incomplete or partial biodegradation includes the conjugation of the pharmaceutical and the degradation of a compound to a metabolite (also occurs in the human body). Conjugations of pharmaceuticals occur usually before excretion from human body. Due to this, compound becomes more polar and might excrete more easily from body.⁸ Ibuprofen, reached in the aquatic environment through metabolic process, has been studied by many researchers. The metabolism of ibuprofen leads to the formation of hydroxyl-ibuprofen (OH-Ibuprofen), carboxy ibuprofen (CA-Ibuprofen) and carboxy-hydratropic acid (CA-

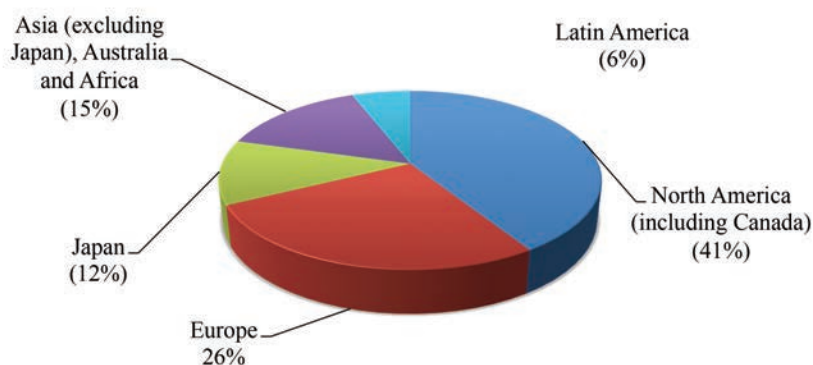


Figure 1. Status of global pharmaceuticals production continent wise.

Regulations for monitoring the presence of drugs in environment

The regulating authorities of pharmaceutical industries must require regular monitoring and enforcement of laws for proper disposal of pharmaceutical wastes for preventing environmental degradation. Central Pollution Control Board (CPCB) and State Pollution Control Boards (SPCBs) established by Water Act, 1974 and Water Cess Act, 1977 provided the option to tax water users violating regulations.²⁸ The CPCB has issued Minimum National Acceptable Standards (MINAS), according to which, SPCBs are required to enforce the laws for pharmaceutical industries. If the industry fails to comply with the Water Act, the SPCBs have authority to cut power supply, water supply, close the firm or even pursue public interest litigation before the Supreme Court.²⁹

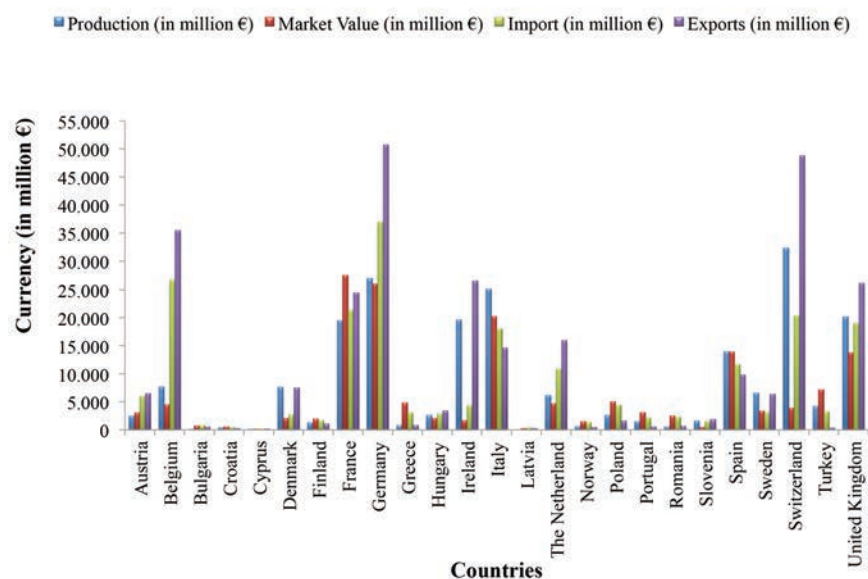


Figure 2. Statistical representation of pharmaceutical's market situation.

AH) as 3 degraded products of ibuprofen.³³ These metabolites are also formed during metabolism of ibuprofen in human body. The degradation process of ibuprofen^{34,35} is given in Figure 3.

The adsorption and complexation of pharmaceutical drugs in water or soil are still largely unidentified. Among studied anti-inflammatories and anti-blockers, most of them were removed less than 5%, while some antibiotics can be even removed upto 90% by sorption technique onto sludge.³⁶ Pharmaceutical compounds, particularly tetracyclines, have the propensity to sorb the soil particles or to form complexes with ions, which are present in the terrestrial ecosystem.³⁷ Numerous pharmaceutical substances might have great impact on their behaviour in spite of being weak acids, weak bases, or zwitterions and site-specific water, soil, or sediment conditions *viz.* pH, cation exchange capacity, *etc.*³⁸ The sixty nine pharmaceutical drugs belonging to fifteen different therapeutic classes have been detected in more than effective concentration ($>0.1 \mu\text{g/L}$) in urban wastewater $0.10 \mu\text{g/L}$ - $38.00 \mu\text{g/L}$ corresponding to salbutamol and acetaminophen, respectively.³⁹

Characteristics of pharmaceutical drugs

Many endocrine disrupting chemicals (EDCs) as synthetic organic chemicals like surfactants, pesticides, poly aromatic hydrocarbons, pharmaceuticals, brominated flame retardants, polychlorinated biphenyls and phthalates are being released in the environment through human induced activities.²⁰ Generally, some pharmaceutical compounds have hydrophilic nature, whereas some have hydrophobic nature. But, the nature of some pharmaceuticals even varies as per environmental conditions. Besides, the nature of a pharmaceutical compound depends upon its chemical composition. Some of the pharmaceutical compounds with their nature have been provided in Table 1.⁸

Detection of pharmaceutical compounds in fresh water and wastewater samples

In the past decade, the numbers of papers on the analysis of pharmaceuticals in drinking water samples have increased considerably.^{23,24,40} After 8 years period, a follow-up study has reconfirmed that pharmaceutical residues were still present in the water of adjoining areas.⁴¹ Several researchers have

identified different types of pharmaceutical compounds in various types of water samples with specific extraction methods using high-performance liquid chromatography (HPLC), high-performance liquid chromatography coupled with mass spectrometry (HPLC-MS), high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS) *etc.* from $\mu\text{g/L}$ to ng/L concentration ranges.⁴²⁻⁴⁵

Pharmaceuticals in Indian drinking water

Larsson and his group⁴⁶ have reported the concentration (90 - $31,000 \mu\text{g/L}$) of various drugs like metoprolol, enoxacin, enrofloxacin, citalopram, norfloxacin, lomefloxacin, ciprofloxacin, losartan, cetirizine, ofloxacin and ranitidine in the effluent of sewage treatment plant in Patancheru Enviro Tech Ltd. (PETL) of Patancheru, in Hyderabad.

The pharmaceutical compounds with detected concentrations in ground and surface water have been summarized in Table 2.⁴²⁻⁴⁴ In another study, the average total concentration of detected pharmaceutical compounds was found 24 ng/L in each studied sample. While, antipyrine (analgesic) and sulfamethizole (antibiotic) were detected for first time in drinking water sources of USA.⁴⁷ Fick *et al.* have reported the presence of drugs in the samples of wells, lakes and rivers of nearby areas of Hyderabad in India (Table 3).⁴¹ The authors found that all the wells were contaminated with drugs like Ciprofloxacin, enoxacin,

cetirizine, terbinafine and citalopram in more than $1 \mu\text{g/L}$ concentration whereas higher concentration of ciprofloxacin (6.5 mg/L), norfloxacin (0.52 mg/L), enoxacin (0.16 mg/L) and cetirizine (1.2 mg/L) drugs were investigated in two lakes of the area using C 18 column in HPLC instrument.

Impact of pharmaceutical pollutants on water quality

The effluents released from pharmaceutical industries consist of different chemical and biological compounds. Due to such nature, these effluents may lead changes in water quality. Out of all drinking water quality parameters, some characteristics *viz.* pH, temperature, total solids, total dissolved solid (TDS), total suspended solid, chloride, oil and grease, biochemical oxygen demand (BOD) and chemical oxygen demand (COD) indicated higher pollution level in effluents of Taloja industrial area, Mumbai, India.^{48,49} In Patancheru industrial area, Medak (India), the concentrations of TDS, BOD, COD, copper, arsenic, selenium, fluoride and iron were recorded 5 to 10 times higher than maximum permissible limit^{50,51} in waste water of inlet and outlet of a septic tank in pharmaceutical industrial area of Bangalore in India. However, several researches have focused on physico-chemical characteristics and heavy metals analysis of pharmaceutical effluents in various parts of India and are summarized in Tables 4^{48,52-54} and 5.^{49,52,55,56}

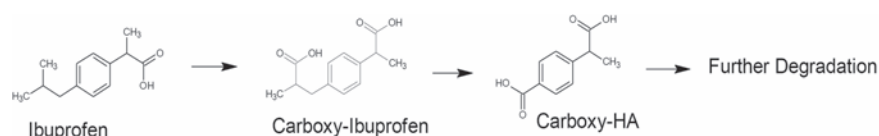


Figure 3. Oxidative metabolism of ibuprofen.

Table 1. Different classes and nature of pharmaceutical drugs.

Pharmaceutical classes	Pharmaceutical drugs	Nature of pharmaceutical drug
Anti-inflammatory	Aspirin	Hydrophilic
	Diclofenac	Varies
	Ibuprofen	Moderate hydrophobic
Lipid regulators	Clofibrac acid	Moderate hydrophobic
	Bezafibrate	Hydrophobic
	Fenofibrac acid	Hydrophobic
Antiepileptics	Carbamazepine	Moderate hydrophobic
β -blockers	Metoprolol	Hydrophilic
Antibiotics	Ciprofloxacin	Hydrophilic

Health impacts due to pharmaceutical drugs present in fresh water and waste water

Pharmaceutical compounds present in water bodies directly affect the user's health through respiratory disorders, cancers, reproductive problems, chronic depression and congenital problems including mental retardation and physical abnormalities, whereas indirectly by lowering productivity of agricultural land, altering agricultural infrastructure and leads to massive death of livestock and fishes.⁵⁷⁻⁵⁹ Trace amount of pharmaceuticals in drinking water may cause considerable adverse effects to human health after long term exposure. The concentrations of pharmaceuticals detected in drinking water samples have numerous disorders.⁶⁰ The release of EDCs into the environment may lead endocrine related diseases in the health of users, which are increasing in the wildlife and also changing the reproductive health of human beings includes declining male fertility, birth defects, breast and testicular cancer.²⁰ EDCs also affect different hormones of the organisms. 17 β -ethinylestradiol

compounds are used as steroid estrogen analogue in the feminine pill and subsequently released in the environment through waste water treatment plant in the form of effluent. The predicted no-effect concentrations of the natural feminine hormones *i.e.*, estrone, 17 β -estradiol, estriol were determined upto 6 ng/L, 2 ng/L and 60 ng/L respectively, which is 20 to 600 times greater than the prescribed limit. The antineoplastics and immune modulating agents are responsible for genotoxic effects *i.e.*, damage of DNA, cause cancer, *etc.*^{61,62}

Pharmaceutical substances *i.e.*, tamoxifen and cyclophosphamide used against breast cancer and ifosfamide, used for a large variety of cancer have already been detected in surface water.^{31,61} It was also observed that all eukaryotic organisms are found to be susceptible to the pharmaceutical drug namely cytostatic.⁶² Caffeine works as metabolic stimulant and increase its effectiveness, when combined with medicines.²⁰ However, Chiral pharmaceutical compounds can be a better option to reduce the load of pharmaceutical dosages to the patients and to protect the drinking water resources from unnecessary impact of pharmaceutical drugs.^{63,64}

Conclusions

The pharmaceutical drugs and their metabolites are being found with increasing concentrations in aquatic as well as in terrestrial ecosystems. Due to continuous release of pharmaceutical compounds through different anthropogenic ways in significant amount, the impacts of drugs are increasing and affecting the environment. In recent years, the development of advanced and sophisticated analytical instruments has enabled scientists to detect the concentrations of these drugs upto ppm and ppb levels and even lower. Present study focuses on global production, occurrences, fate, properties, toxicity, chemical compositions, behaviour patterns and health hazards of these drugs on environmental components and other living beings. The study highlights the need of development of new techniques to safeguard the society from adverse health related acute and chronic effects of drugs. Pharmaceutical based environmental pollution has become an international issue, which requires due attention and changes in policies and regulations. Thus, detailed studies and

Table 2. Pharmaceutical compounds with detected concentrations in different water bodies with their extraction methods.

Pharmaceutical compound	Concentration	Extraction method	Instrument used	Country	References				
Ground water									
Acetaminophen	1.89 $\mu\text{g/L}$	Solid phase extraction	HPLC-MS	USA	42				
Caffeine	0.29 $\mu\text{g/L}$								
Carbamazepine	0.42 $\mu\text{g/L}$								
Codeine	0.214 $\mu\text{g/L}$								
P-xanthine	0.12 $\mu\text{g/L}$								
Sulfamethoxazole	0.17 $\mu\text{g/L}$								
Trimethoprim	0.018 $\mu\text{g/L}$								
Surface water									
Ibuprofen	414 ng/L	Solid phase extraction using high performance extraction disks (SBD-XD)	HPLC with tandem MS	South Korea	43				
Carbamazepine	595 ng/L								
Atenolol	690 ng/L								
Clarithromycin	443 ng/L								
Mefenamic acid	326 ng/L								
Erythromycin	137 ng/L								
Fluconazole	111 ng/L								
Levofloxacin	87.4 ng/L								
Indomethacin	33.5 ng/L								
Propranolol	40.1 ng/L								
Ifenprodil	35.4 ng/L								
Finofibric acid	3.20 $\mu\text{g/L}$					Oasis HLB solid phase extraction	Reverse Phase HPLC through diode array detector with C18 column	Douro River Estuary	44
Carbamazepine	0.60 $\mu\text{g/L}$								
Diazepam	1.60 $\mu\text{g/L}$								
Fluoxetine	32.00 $\mu\text{g/L}$								
Propranolol	0.80 $\mu\text{g/L}$								
Sulfamethoxazole	1.40 $\mu\text{g/L}$								
Trimethoprim	8.00 $\mu\text{g/L}$								

HPLC-MS, high-performance liquid chromatography coupled with mass spectrometry;

Table 3. Detection of pharmaceuticals in fresh water samples in Hyderabad area, India.

Drug	Lakes (03 sampling sites of 02 lakes)	River (06 sampling points)	Wells (06 wells)
Norfloxacin	60,000-520,000	ND-4700	ND-31
Ciprofloxacin	ND-6,500,000	10,000-2,500,000	44-14,000
Ofloxacin	ND-11,000	180-10,000	ND-480
Enoxacin	14,000-160,000	ND-66,000	ND-1900
Enrofloxacin	ND-25,000	ND-30,000	ND-67
Metoprolol	7000-ND	ND-240	ND-90
Cetirizine	5000-1,200,000	5,400-530,000	550-28,000
Citalopram	2000-8000	ND-76,000	ND-1400

ND, not detected.

Table 4. Physico-chemical characteristics in pharmaceutical industrial effluents.

S. No.	Characteristics	Unit	Ref. 48	Ref. 52	Ref. 53	Ref. 54
1.	pH	-	5.1	12.54	10.34	8.00
2.	Temperature	°C	29.8	-	36.34	28.87
3.	Conductivity	µS/cm	-	27,400	1534.21	1733.13
4.	TSS	mg/L	654	2980	2673.22	348.75
5.	TDS	mg/L	3412.5	8741	2655.43	873.81
6.	DO	mg/L	-	3.50-4.70	8.43	5.78
7.	BOD	mg/L	1083.5	546	341.11	52.13
8.	COD	mg/L	2797.3	1271	698.11	218.42

TSS, total suspended solid; TDS, total dissolved solid; DO, dissolved oxygen; BOD, biochemical oxygen demand; COD, chemical oxygen demand.

Table 5. Concentrations of heavy metals in pharmaceutical industrial effluents.

S. No.	Characteristics	Unit	Ref. 49	Ref. 52	Ref. 55	Ref. 56
1.	Chromium	mg/L	30.6	0.57	2.34	0.31
2.	Cadmium	mg/L	35.8	-	ND	0.55
3.	Nickel	mg/L	33.6	0.43	-	0.12
4.	Zinc	mg/L	26.8	3.31	-	1.3
5.	Copper	mg/L	17.6	14.06	2.30	0.38
6.	Lead	mg/L	21.7	0.42	ND	0.263
7.	Iron	mg/L	10.4	18.93	19.38	19.38

ND, not detected.

investigations are required to develop the sustainable and long term effective solutions in order to save the health of mankind, other living organisms and environment from any type of pharmaceutical related pollution.

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