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Pharmaceutical Industry Wastewater: Review of the Technologies for Water Treatment and Reuse

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ABSTRACT: Pharmaceutical compounds are typically produced in batch processes leading to the presence of a wide variety of products in wastewaters which are generated in different operations, wherein copious quantities of water are used for washing of solid cake, or extraction, or washing of equipment. The presence of pharmaceutical compounds in drinking water comes from two different sources: production processes of the pharmaceutical industry and common use of pharmaceutical compounds resulting in their presence in urban and farm wastewaters. The wastewaters generated in different processes in the manufacture of pharmaceuticals and drugs contain a wide variety of compounds. Further, reuse of water after removal of contaminants, whether pharmaceuticals or otherwise, is required by industry. In view of the scarcity of water resources, it is necessary to understand and develop methodologies for treatment of pharmaceutical wastewater as part of water management. In this review, the various sources of wastewaters in the pharmaceutical industry are identified and the best available technologies to remove them are critically evaluated. Effluent arising from different sectors of active pharmaceutical ingredients (API), bulk drugs, and related pharmaceutics, which use large quantities of water, is evaluated and strategies are proposed to recover to a large extent the valuable compounds, and finally the treatment of very dilute but detrimental wastewaters is discussed. No single technology can completely remove pharmaceuticals from wastewaters. The use of conventional treatment methods along with membrane reactors and advanced posttreatment methods resulting in a hybrid wastewater treatment technology appear to be the best. The recommendations provided in this analysis will prove useful for treatment of wastewater from the pharmaceutical industry.

1. INTRODUCTION

The global demand for quality water, whether for purposes of drinking, sanitation, irrigation, and industrial use, has been on a continuous rise, and there has been overwhelming concern in recent years about water treatment and reuse requiring the strictest standards (Figure 1).[1] The pharmaceutical industry is beset with high-value, low volume multiproduct plants on one hand which are mostly batch operations wherein the effluent is mixed and treated. There are some dedicated batch, semibatch, and continuous process plants producing bulk drugs. These plants use different types of reactants, (homogeneous) catalysts, solvents, solids, and water, handled in special equipment. In these types of units, the major cost of the drug depends on the type of impurity rather than on the purity of the drug. Thus, separation processes play a very vital role in this industry. The so-called environmental quotient or *E*-factor for the pharmaceutical industry is anywhere between 50 and 100 kg/(kg of desired product) since these processes are multistep operations (anywhere between 5 and 30 steps) with several noncatalytic routes using copious quantities of (volatile organic compound (VOC)) solvents or "crazy" mixtures of close boiling solvents. Further, ultrapure water is used in the pharmaceutical sector to give multiple washings to the solid cake or to use as extractant or as solvent per se. This water is not reused due to strict regulations as defined in drug master file (DMF) etiquettes approved by the authorities. The presence, outcome, and toxicity of pharmaceutical residues in the aquatic environment pose difficulties. Therefore, recovery of high-value API and pharmaceutical drugs from dilute streams, instead of treatment, ought to be considered while dealing with this issue. Many of the frequently used generic drugs such as antibiotics, analgesics, antihistamines, and antituberculosis (anti-TB) drugs, etc., are used on the same scale as pesticides and other organic micropollutants, but they are not subjected to the same level of scrutiny for possible environmental effects. The total spread and repercussions of the presence of these moieties in the environment are therefore mostly unknown and ill-defined. Although these compounds have been detected in a wide variety of environmental samples including sewage, surface waters, groundwater, and potable water, their concentrations generally range from a few parts per trillion to parts per billion levels. It is therefore very often considered unlikely that pharmaceuticals will have a detrimental effect on the environment. However, in the absence of validated analytical methods, proper monitoring information, and associated data about the fate and toxicity of the pharmaceutical compounds and/or their metabolites in the aquatic environment, it is difficult to make a correct risk assessment.

The purpose of the current review is to take stock of effluent arising from different sectors of active pharmaceutical ingredients (API), bulk drugs, and related pharmaceutics, which use large quantities of water, to propose strategies to recover to a large extent the valuable compounds, to demonstrate the economic benefit of recovery, and finally to discuss the treatment of very

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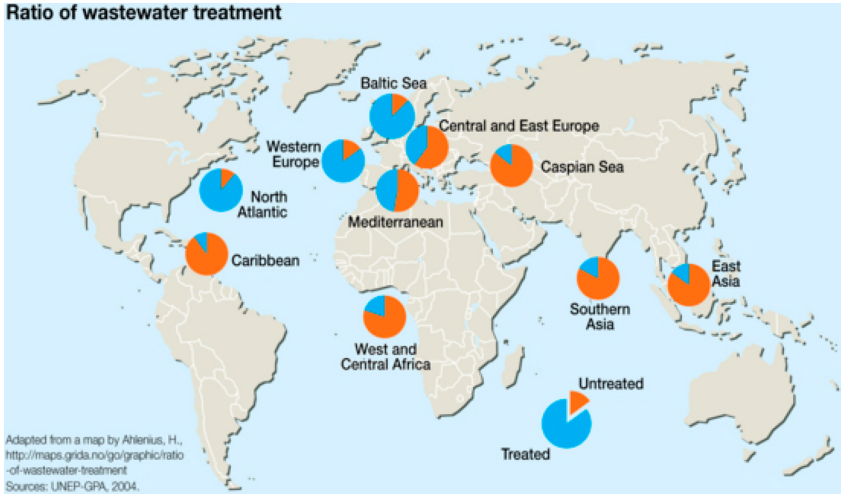

Figure 1. Ratio of treated to untreated wastewater reaching water bodies from 10 regions across the globe. More than 90% of the water is discharged untreated. Reprinted with permission from ref 2. Copyright 2014 GRID-Arendal (T). Adaptation from ref 3. Copyright 2010 UNEP/GRID-Arendal and Hugo Ahlenius.

Table 1. Composition of Pharmaceutical Wastewaters

chemical processes wastewaters			fermentation processes wastewaters		
param	min−max value	av composition	param	min−max value	av composition
COD, mg/L	375−32500[a−c,e−j]	8854	COD, mg/L	180−12380[k−w]	4670
BOD_5, mg/L	200−6000[a−c,f−h,j]	2344	BOD_5, mg/L	25−6000[k−p,r,s,u,v]	2150
BOD_5/COD ratio	0.1−0.6[a−c,f−h,j]	0.32	BOD_5/COD ratio	0.2−0.6[k−p,r,s,u,v]	0.4
TOC, mg/L	860−4940[b,e,j]	2467	TKN, mg/L	190−760[m,o,p]	440
TKN, mg/L	165−770[a−c,h]	383	NH_4^+-N, mg/L	65.5−190[p,u]	128
NH_3−N, mg/L	148−363[a−c]	244	pH	3.3−11[k−u,w]	7
TDS, mg/L	675−9320[d,f,i]	6.9	TDS, mg/L	1300−28000[m,r,s]	12950
pH	3.9−9.2[a−c,e,g,j]		TSS, mg/L	57−7130[m,n,p−t]	1200
			conductivity, μS/cm	1600−44850[n,r,t]	17800
anions[x]			anions[x]		
Cl^-, mg/L	760−4200[a−c,g,i]	2820	Cl^-, mg/L	182−2800[k,l,p,r,t]	1500
SO_4^{2-}, mg/L	890−1500[a−c,i]	1260	SO_4^{2-}, mg/L	160−9000[k−m,o,p,r,t]	2100

[a]Reference 115. [b]Reference 116. [c]Reference 47. [d]Reference 78. [e]Reference 106. [f]Reference 128. [g]Reference 119. [h]Reference 46. [i]Reference 100. [j]Reference 121. [k]Reference 95. [l]Reference 45. [m]Reference 97. [n]Reference 49. [o]Reference 65. [p]Reference 51. [q]Reference 67. [r]Reference 44. [s]Reference 126. [t]Reference 98. [u]Reference 64. [v]Reference 52. [w]Reference 127. [x]Other anions are also likely to be present depending on type of process. Data are scarce to enumerate.

dilute but detrimental wastewaters. Some important drug manufacture flow sheets are included to show how and why the waste is generated and whether some steps could be combined to reduce the cost. There are instances where adequate data are not available or the industry would not share such information for being targeted by pollution control authorities. We also believe that there is tremendous scope to develop new strategies for some of the old problems from the perspective of green chemistry and waste minimization principles.

2. PHARMACEUTICAL PROCESS WASTEWATER

Water is a critical raw material in pharmaceutical and chemical manufacturing operations; consistent and high-quality water supplies are required for a range of operations including production, material processing, and cooling. The various categories of water which need treatments as part of water management are potable water, process water, feedwater for utilities, water recycling, wastewater, water coming from byproduct treatment, water used for odor treatment, water from desalination, and water for irrigation.

We will restrict this review to pharmaceutical water, wherein it is widely used as a raw material, ingredient, and solvent in the processing, formulation, and manufacture of pharmaceutical products, APIs and intermediates, compendia articles, and analytical reagents. Table1 provides the complete compositions of the wastewater generated in pharmaceutical industries. Process water quality management is of great importance in pharmaceuticals manufacturing and is also a mandatory requirement for the sterilization of containers or medical devices in other healthcare applications including water for injection. Process wastewaters are a term used to define wastewater in any industry coming from the processes occurring in the industry. Process wastewaters thus cover any water which at the time of manufacturing or processing comes in contact with the raw materials, products, intermediates, byproducts, or waste products, which are handled in different unit operations or processes.

In fact, the wastewater coming out of pharmaceutical units varies in content and concentration, and thus a unique treatment is not attempted since the volumes are small and different products are manufactured from the same battery of reactors and separators. Water reuse provides savings through the reduction of waste disposal costs and feedwater requirements,

offsetting operational costs associated with the waste reuse process.

2.1. Fate of APIs, Pharmaceuticals, and Drugs in the Environment. A wide variety of sources can deliver pharmaceutical chemicals, APIs, and drugs to streams, groundwater storage, and aquifers. During dry weather, such sources might include failing septic tanks or other on-site waste-treatment systems, leaking sewer lines, permitted and accidental discharges, illicit and unpermitted dumping, sanitary-sewer/storm-sewer cross-connections, and unmanaged or poorly managed pet and livestock wastes. Chemicals, used every day in homes, industry, and agriculture, can enter the environment in wastewater. These chemicals include human and veterinary drugs (including antibiotics), hormones, detergents, disinfectants, plasticizers, fire retardants, insecticides, and antioxidants.[1]

2.2. Health Hazard of Discharged Pharmaceuticals. Pharmaceutically active compounds, APIs, are of emerging concern because of their intrinsic biological activity, which can lead to fatal consequences.[4−7] It is estimated that approximately half of the pharmaceutical wastewaters produced worldwide are discarded without specific treatment.[8,9] The presence of the so-called endocrine disrupting compounds (EDCs) in aquatic systems has caused considerable fear since they are known to disrupt the human endocrine system.[10] The presence of pharmaceutical products in the environment has effects such as development of antibiotic resistant microbes in the aquatic environment,[11] retardation of nitrite oxidation and methagenosis, and the potential increased toxicity of chemical combinations and metabolites.[12] Recent studies have found that pharmaceutical products (PhPs) in water streams can cause adverse effects such as feminization in fish[13] and alligators.[14] PhPs can also affect the behavior and migratory patterns of salmon. The pharmaceutical diclofenac was found to be the direct cause of near-extinction of the vulture population in India.[15]

Pharmaceuticals end up into the environment from humans or animals via urine or faeces, through the sewage system, and into the influent of wastewater treatment plants as partially active metabolites or in unmetabolized form.[7,16] In addition to human consumption waste, disposal of pharmaceuticals which are being used in agriculture, industry, and medical treatment also contribute to the entry of pharmaceuticals into fresh water bodies.[17] Veterinary pharmaceuticals on the other hand contaminate directly soil via manure and surface and ground waters by runoff from fields.[18] But, recently it has been documented that various pharmaceutical production facilities were found to be sources of much higher concentrations of pharmaceuticals to the environment than those caused by the usage of drugs.[19] The major pathway for PhPs to enter the environment is through discharges of pharmaceutical industries wastewater to the wastewater treatment plants (WWTP) and then from municipal effluent, but the extent to which pharmaceuticals and personnel care products (PPCPs) are removed by treatment processes is not well understood, and many of the compounds released are nonbiodegradable and therefore are not efficiently removed by conventional (primary, secondary, and tertiary) treatment technologies, leading to an unfavorable accumulation in the aquatic environment.[20] Pharmaceutical manufacturing processes are batch and multistage processes thus leading to generation of a huge quantity of effluent wastewater.[1] Also, the investigations show that PhP production and administration will continue to increase with the development and advancement of lifestyle and longevity globally.[21−23]

2.3. Wastewater Treatment Options. A lot of research papers have been published on the treatment of PhPs, EDCs, and pharmaceuticals and household consumer products (PHCPs) in the past decade mainly dealing with the effluent from tertiary WWTPs. Table 2 lists the costs of various wastewater treatment technologies. However, treatment options at the source not only could reduce costs and environmental impact but also provide potential recovery of compounds. Although much research has been done in this context and many reviews have been published in recent years, they lack a complete scenario of the pharmaceutical wastewater composition and treatment technologies.[17,24−28]

The pharmaceutical industry requires consistent, high-quality water for production and wastewater treatment to meet the demands of ever-stricter regulatory discharge limits. To meet these challenges, companies must question conventional thinking and typical approaches and explore new technologies and solutions to remain competitive. Thus, in the current review, attempts have been made to (1) understand the nature of the pharmaceutical waste originating at the industry site, (2) categorize the different industrial processes to classify their waste, and (3) access the effectiveness of advanced processes and hybrid technologies for the removal of pharmaceuticals from the aqueous systems.

3. OVERVIEW OF PHARMACEUTICAL MANUFACTURING PROCESSES AND WASTEWATER COMPOSITIONS

3.1. Profile of the Pharmaceutical Industry. The pharmaceutical manufacturing industry encapsulates the manufacture, extraction, processing, purification, and packaging of chemical and biological materials, as solids and liquids to be used as medication of humans and animals. Wastewaters in a pharmaceutical manufacturing industry usually originate from the synthesis and formulation of the drugs. Most of the APIs distributed worldwide are manufactured by chemical synthesis using organic, inorganic, and biological reactions. Since the reactors and separators used in a multiproduct pharmaceutical industry are not designed per the capacity but typically oversized or used inefficiently, the quantity of wastewaters generated is increased. There are a number of subprocesses occurring in a pharmaceutical industry, and it is a difficult task to characterize each and every product waste. A more elaborated classification based on raw materials, final products, and uniqueness of plants has been attempted. The classification is done on the basis of the similarities of chemical processes and treatments as well as certain classes of products. Based on the processes involved in manufacturing, pharmaceutical industries can be subdivided into the following five major subcategories:[29] (1) fermentation plants; (2) synthesized organic chemicals plants; (3) fermentation/synthesized organic chemicals plants (generally moderate to large plants); (4) natural/biological product extractions (antibiotics/vitamins/enzymes, etc.); (5) drug mixing, formulation, and preparation plants (tablets, capsules, and solutions, etc.).

Table 3 summarizes the different pharmaceutical processes and the classification based on it.

The pharmaceutical industry uses an array of complex batch-type processes and technologies for the manufacture of its products. Figures 2−6 are schematic diagrams of the different stages in the manufacture of a drug. The present section will deal with the brief outline of all of the stages mentioned.

Table 2. Summary of Wastewater Treatment Technologies and Cost Comparison[a]

name of the technology	treatment method	treatment capacity	capital cost ($/KLD)	O & M ($/(KLD/year))	reuse of treated wastewater
DWWT[b]	sedimentation, anaerobic digestion, filtration and phyto-remediation	1000 KLD[c]	$580–$1200	$15–$25	horticulture biogas generation
soil biotechnology	sedimentation, filtration, biochemical process	5 KLD to tens of MLD[c]	$160–$250	$15–$25	horticulture cooling systems
biosanitizer/ecochip	biocatalyst: breaking the toxic/organic contents	100 mg/KLD	chip cost $160 excluding construction cost	not available	in situ treatment of water bodies, horticulture
soil scape filter	filtration through biologically activated medium	1–250 KLD	$300–$500	$30–$35$	horticulture
ecosanitation zero discharge toilets	separation of fecal matter and urine	individual to community level	$650–$850 (excluding the cost of toilet construction)	not available	flushing horticulture composting
Nualgi technology	phyco-remediation (use of micro-/macroalgae): fix CO_2, remove nutrients, and increase DO in water	1 kg treats up to ML	$6/MLD[c]	$150–$160/MLD[c]	in situ treatment of lakes/ponds, increase in fish yield
bioremediation	decomposition of organic matter using Pernickety 713 (biological product)	1 billion CFU/mL	$3750–$5000/MLD[c]	$3000–$5000/MLD[c]	in situ treatment of lakes/ponds
green bridge technology	filtration, sedimentation, biodigestion, and biosorption by microbes and plants	50–200 KLD/m^2	$4–$8	$1	in situ treatment of water bodies

[a]Costs have been estimated on the basis of the year of implementation of listed case studies. The current cost involved may vary. (Adapted from ref 129.) KLD = kiloliters per day. MLD = megaliters per day. [b]DWWT = decentralised wastewater treatment. [c]Cost of the technologies for lakes and water bodies remediation have been indicated in per MLD per year.

3.2. Pharmaceutical Manufacturing Processes.

3.2.1. Chemical Synthesis Process. Chemical synthesis processes use organic and inorganic chemicals in batch operations to produce drugs with defined pharmacological action or intermediates. A schematic diagram of the chemical synthesis process is shown in Figure 2. Mainly, a series of chemical reactions are carried out in multipurpose reactors. The products are isolated by using different separation processes such as liquid–liquid extraction, leaching (solid–liquid extraction), crystallization, and filtration. The product is then usually dried, milled, and sent for further processing to the formulation unit. The chemical synthesis process is usually a multistep process with a lot of intermediates and byproducts. Because of a large number of steps, the atom economy in chemical synthesis is compromised including generation of a lot of waste of material and energy. Apart from the reactors, there are heat exchangers and other process vessels continuously operating. The product usually in the mother liquor is transferred internally using process vessels and pipelines and thus the process becomes more complex leading to a widespread use of raw water at every step. Very rarely, the process water is used to minimize impurities except in a few cases where the filtrate could be and has been reused. The water washing of cakes of crystallized or precipitated solids from organic solvents leads to considerable release of volatile solvents into water and also into the air.

Wastewaters from chemical synthesis operations are diverse due to many operations and reactions taking place in the reactor as well as at different stages. Almost every stage produces mother liquor that contains unreacted reactants, products, coproducts/byproducts, and residual products in the organic solvent base. Acids, bases, halides, nitrates, sulfates, cyanides, and metals may also be generated. Usually, the spent solvent recovery leads to solvent wastewater at the scrubber stage after evaporation. Wastewater is generated at the purification steps comprising solvents, finished products, cleaning water, and spills. This sewage has a high toxicity level; thus, it requires immediate treatment rather than release into WWTP. Wastewaters from synthesis processes typically have high biological oxygen demand (BOD), chemical oxygen demand (COD), and total suspended solids (TSS) levels and pH ranging from 1 to 11.[29]

A typical synthetic organic medicinal chemical production process can be summarized as shown in Figure 3, which shows the production of oxyphenonium bromide with the different waste streams resulting from the process.

3.2.2. Fermentation Process. Fermentation is a biochemical process involving the use of Baker's yeast, lactic acid bacillus, bacillus sp., and various other microorganisms to produce a chemical product. A batch fermentation process involves three steps: seed inoculum and preparation, fermentation, and product recovery. Inoculum preparation is done with necessary conditions and the required microorganism, and then the whole mixture is transferred to the steam sterilized fermenter. Nutrients, inorganic salts, and other materials are added to the fermentation tank. The process is usually a batch step. The temperature is controlled by heat exchangers and coolers. The fermentation broth then undergoes a series of steps such as filtration, solvent extraction, precipitation by metal salts, ion exchange, and addition of disinfectants such as phenolic compounds.

The fermentation process generates a large amount of waste such as spent aqueous fermentation broth and dead cell waste. As in most of the aqueous-phase fermentations the bacteria do

Table 3. Classification of Different Processes Based on Routes of Bulk Pharmaceutical Manufacture

chemical synthesis	fermentation	natural product extraction
antibiotics ; antihistamines; cardiovascular agents; central nervous system (CNS) stimulants; CNS depressants, hormones vitamins	antibiotics; antineoplastic agents; therapeutic nutrients; vitamins; steroids	antineoplastic agents (chlorambucil, daunomycin, melphalan, mitomycinc); enzymes and digestive aids; CNS depressants; hematological agents; insulin; vaccines
Mixing or Compounding/Formulation Stage		
This process is common to all the bulk processes having some API waste along with solvents and packaging waste materials.		

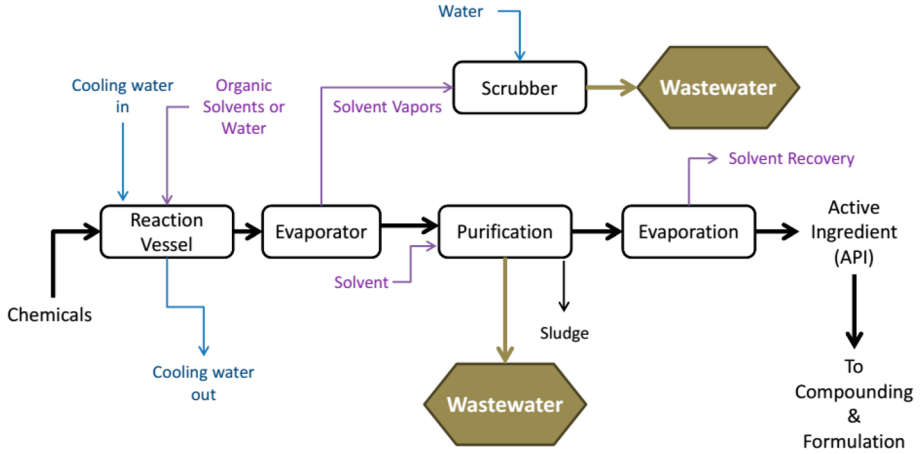

Figure 2. Process flow sheet diagram for the chemical synthesis process. Adapted from ref 29. Copyright 1998 U.S. EPA.

not survive at higher concentrations of the product because of inhibition of the bacteria due to accumulation of the product. The waste stream has a large quantity of unconsumed raw materials such as the nutrient broth, metal salts, starch, nitrates, and phosphates with high COD, BOD, and TSS with pH values ranging from 4 to 8. Steam and small amounts of industrial chemicals (phenols, detergents, and disinfectants) maintain the sterility in the process plant and thus their leftovers also add to the aqueous waste stream. A considerable quantity of metal and halogen impurities is also found due to usage for the precipitation of the product from the mother liquor. Large amounts of solvents are also used for the purification of the desired product, and during the recycling of the solvents aqueous waste having miscible organic solvents is generated.

A good example of the fermentation process in the pharmaceutical industry is antibiotic production of penicillin (Figure 4). The process gives a clear outline of the wastewater streams generated at the various outlets and the prospective of applying recovery and treatment technologies at the site of the generation of wastewater.

3.2.3. Natural/Biological Extraction Process. Large amounts of natural (plant and animal) materials are processed to extract the active pharmaceutical ingredient from the source. In each step, a large volume of water input is required and the product recovery decreases until the final product is reached. Solvents are used on a large scale to remove the lipophilic matter and to extract the desired product. The pH adjustment of the extract solutions makes use of substantial amounts of acids and bases. Also, metal addition for precipitation and phenolic compounds for disinfection add to the number of components in the process leading to further treatment problems. Thus, the final yield of the product is low. Typically hexane is used as solvent for natural product or herbal extraction, which is released into the air and also the water. These days processes based on supercritical carbon dioxide ($scCO_2$) are developed to contain organic impurities in the final product as well as to reduce effluent. Spent raw material and solvents, wash water, and spills are the primary sources of wastewater. Organic and inorganic chemicals may be present as residues in these waste streams. Also, the usage of a variety of low-boiling organic solvents generates wastewater with solvents. Usually, wastewaters have low BOD, COD, and TSS, with relatively neutral pH values ranging from 6 to 8 (Figure 5).

3.2.4. Compounding/Formulation Process. Drug products obtained from the three processes mentioned before are then processed to usable forms such as tablets, ointments, syrups, and other dosage forms. The process uses steps such as milling, mixing, grinding, compression, and packaging (Figure 6). Many types of fillers, binders, flavoring agents, preservatives, and antioxidants are added during the compounding process. The process plant is common to almost all drug manufacturing processes. Very hygienic conditions are required during the process thus making rampant use of steam sterilization and phenolic compounds.

After the production, APIs produced by batch processes must be converted to dosage forms and this part is carried out in a separate batch of mixing/compounding and formulations processes. Thus, various methods such as filler addition, dilution of APIs, binding, and tablet operation machines are involved. Also, various physical operations such as grinding, sieving, filtration, washing, drying, encapsulation, and finally packing are a common practice. All of the mentioned steps add to the wastewater sources in the pharmaceutical industry.

On the contrary, these manufacturing processes may be discrete batch, continuous, or a combination thereof depending on the volume of production and the value of the product. Antibiotics, steroids, and vitamins are produced by fermentation, whereas many other common pharmaceuticals are prepared by chemical synthesis process. Many drugs were derived from natural materials, but due to low recovery and cost efficiency this process is less observed.

3.3. Water Consumption in Pharmaceutical Bulk Manufacturing Process. A wide variety of products are made in the chemical and pharmaceutical manufacturing

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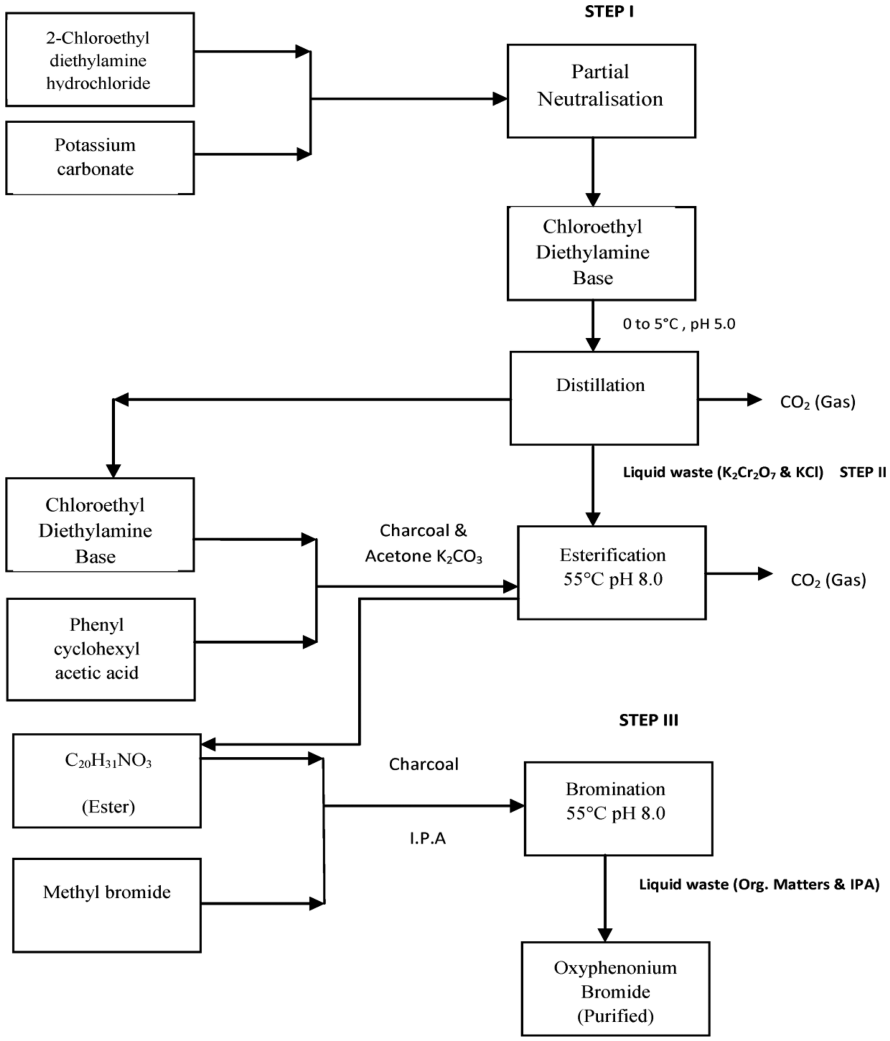

Figure 3. Process flow diagram for synthesis of oxyphenonium bromide (antrenyl). Adapted from ref 30. Copyright 1988−1989 CPCB.

industries, typically requiring large volumes of chemicals, materials, and substances that are used throughout process operations. The mixtures of pharmaceuticals, hormones, and other wastewater contaminants can occur at low concentrations in streams that are susceptible to various wastewater sources, and the volumes will vary from industry to industry or site to site for the same compound. Waste streams generated in these industries can be heavily laden with contaminants, toxins, nutrients, and organics, presenting unique challenges in terms of treatment in view of stringent regulations. It is important that for reuse in both validated and nonvalidated systems the treated wastewater quality must exceed the feedwater quality for high operational efficiency, water quality, and product safety. Thus, it may be possible to expand production capacity without exceeding water discharge limits, drastically reduce raw water requirements and waste disposal cost of operation, and reduce specific organics while leaving other inorganic species intact (Figures 7 and 8).

Figures 7 and 8 highlight the water consumption pattern in a chemical and a fermentation process manufacturing unit. If observed clearly, it can be seen that approximately 50% of the water input is going out as waste. Also, deep analysis of the water balance shows that the fermentation process consumes more process water as compared to the synthetic route. Thus, the need to devise methods of reclaiming and reuse of water is mandatory. There is an ample scope for water reuse by usage of advanced treatment technologies at the site of generation of wastewater rather than treatment at the effluent treatment plant (ETP) and disposal site.

3.4. Solvent Use and Water Requirement. Several solvents are employed as vehicles in the pharmaceutical manufacturing process to dissolve gaseous, solid, or viscous reactants, products, and impurities. They are used in the chemical synthesis process to dissolve reactants in a homogeneous phase to overcome mass and heat transfer effects. Some solvents are also used to control the reaction temperature. A variety of pollutants released during the manufacture of pharmaceutical products are the reaction and purification solvents.[32,33] These include benzene, phenol, toluene, halogenated solvents, and cyanide. Although EPA has banned or put restriction on use of some 23 solvents including some VOCs and chlorinated solvents, some are still used by the pharmaceutical industry since the relevant drugs cannot be manufactured by using other solvents; for instance, methylene chloride (Table 3). The major nonconventional solvents used in industry are methanol, ethanol, isopropanol, acetone, and ethyl acetate. Also, many heteroaromatics such as pyridine or piperidine contribute to this list as they are inert in the reaction process.

Many industries have their solvents recovery systems for purification of contaminated solvents consisting of distillation columns and solvent−solvent evaporation systems in which a

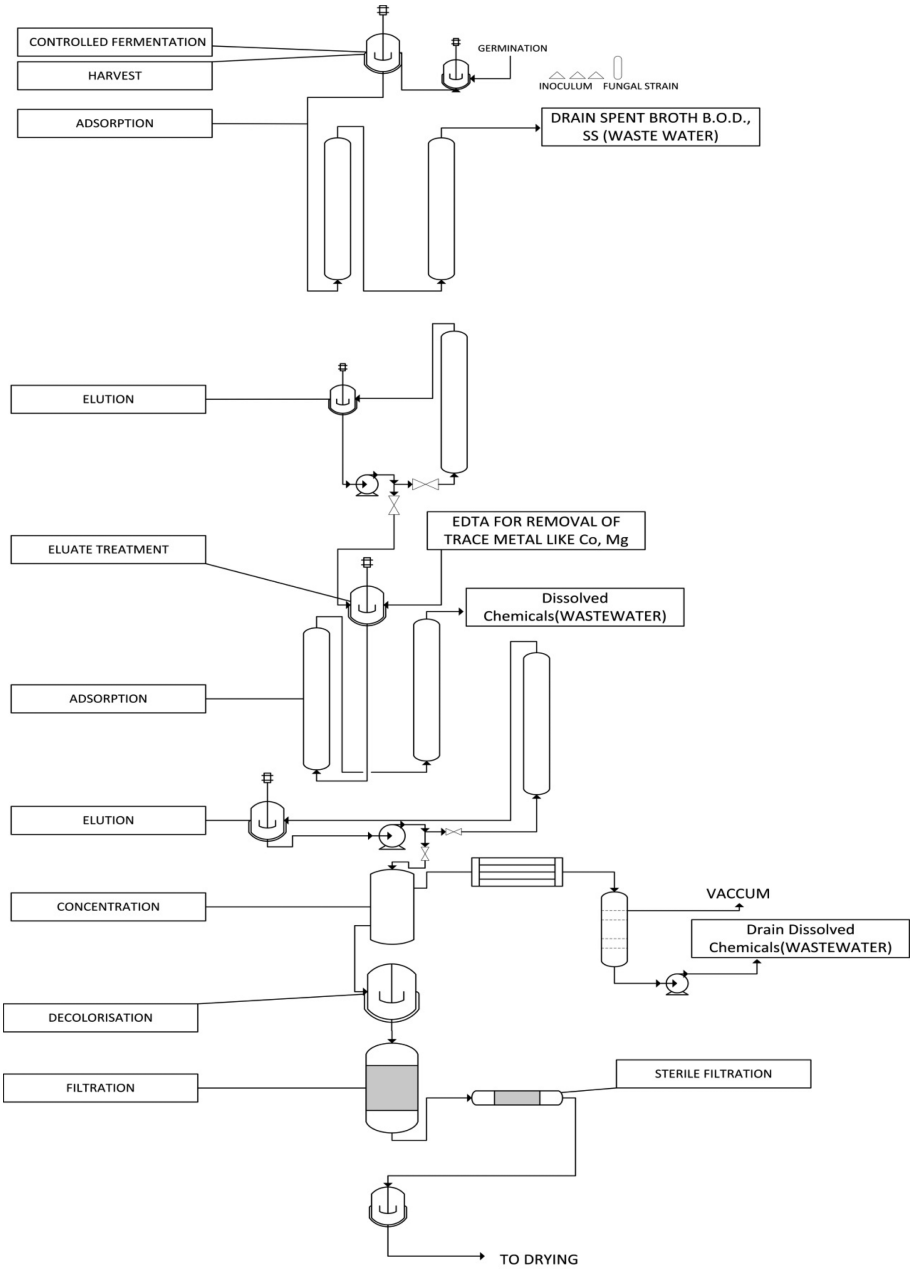

Figure 4. Streptomycin production and its recovery and purification from the fermentation broth. Adapted from ref 30. Copyright 1988−1989 CPCB.

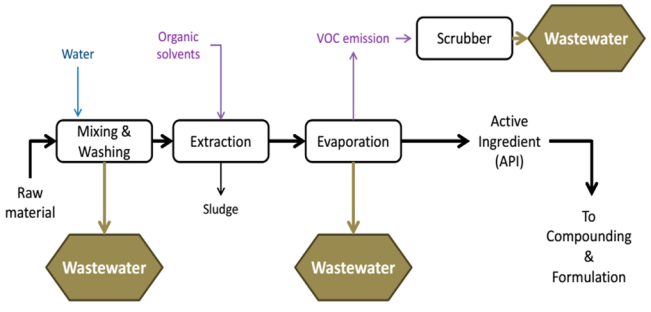

Figure 5. Process flow sheet diagram for natural/biological extraction process. Adapted from ref 29. Copyright 1998 U.S. EPA.

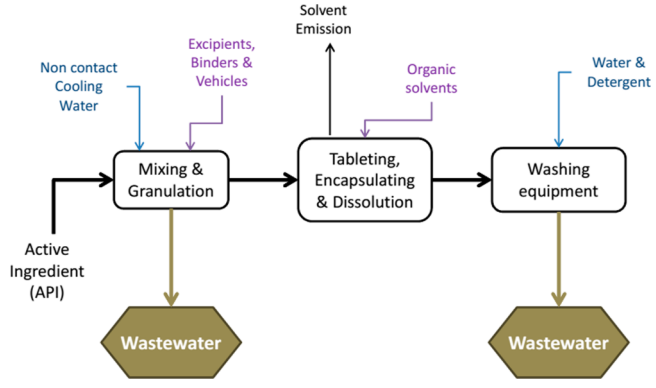

Figure 6. Process flow sheet diagram for the compounding/formulation process. Adapted from ref 29. Copyright 1998 U.S. EPA.

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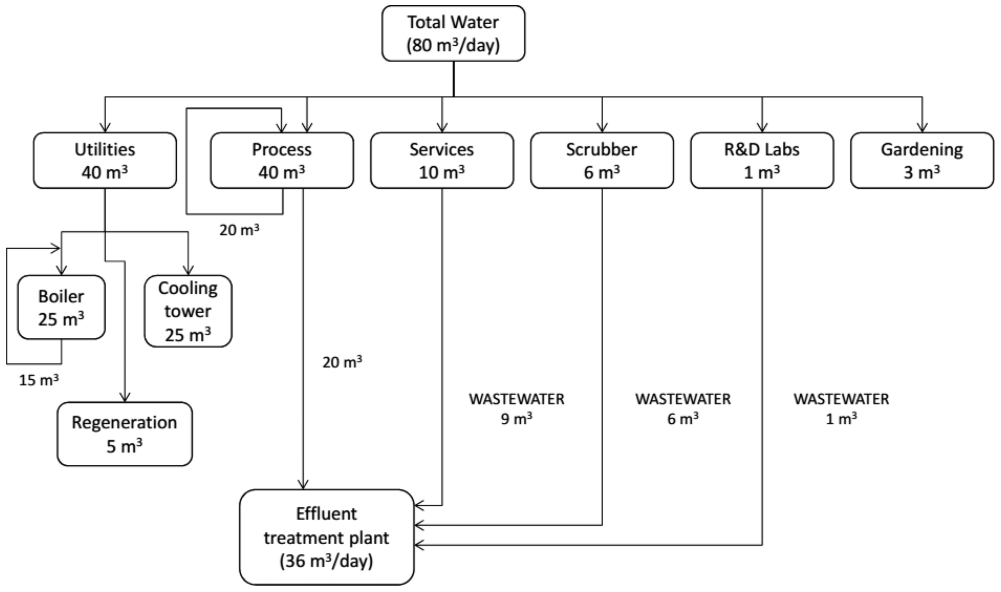

Figure 7. Water balance for a chemical synthesis process manufacturing plant producing paracetamol (ratio of consumption of process water to total water = 0.5). Adapted from ref 31. Copyright 2007 CPCB.

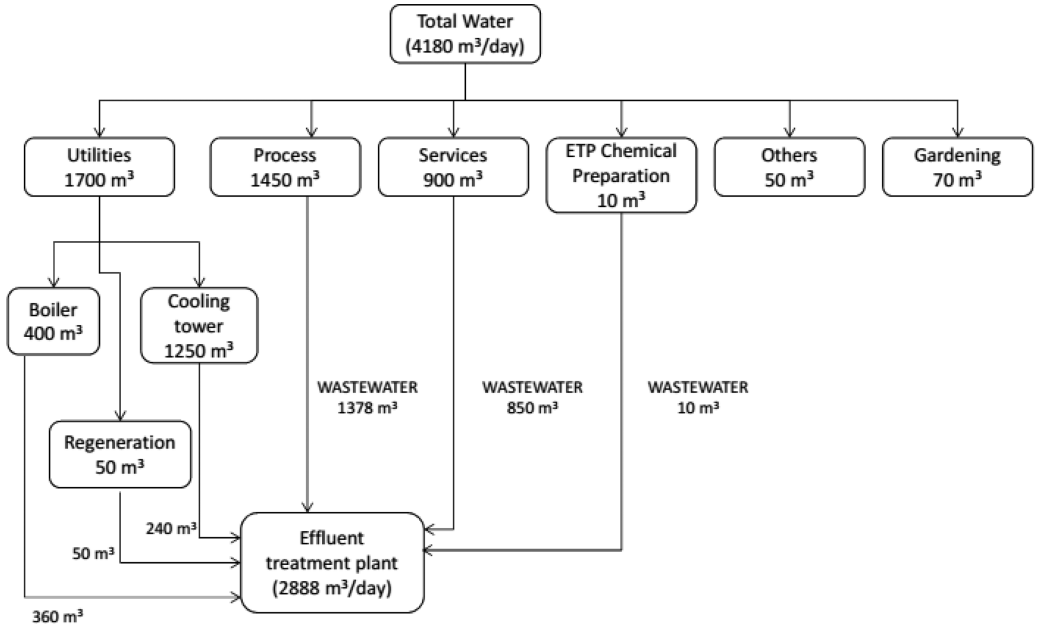

Figure 8. Water balance for a fermentation process manufacturing plant producing penicillin (ratio of consumption of process water to total water = 0.08). Adapted from ref 31. Copyright 2007 CPCB.

second solvent is used to separate impurities.[36] These operations result in aqueous wastewaters being fully or partially saturated with residual solvents. For instance, in 2007, 119000 tons of Ireland's hazardous waste generation was organic solvent and of this, 55400 tons was exported for recovery or disposal. This waste arose primarily from the pharmaceutical sector (Table 4).

A thorough review of published literature suggested that chemical synthesis and fermentation processes are among the pharmaceutical sectors with larger water consumption and wastewater generation, and thus, this work is focused on the wastewater treatment dealing with these two processes exclusively. Tables 5 and 6 give an outline of the composition of the actual wastewater from the chemical synthesis process and fermentation process pharmaceutical manufacturing industries.

4. TREATMENT OF PHARMACEUTICAL WASTEWATER

The pharmaceutical industry employs a wide array of wastewater treatment and disposal methods.[34] Wastewaters generated from these industries vary not only in composition but also in quantity, by plant, season, and even time, depending on the raw materials and the processes used in the manufacturing of various pharmaceuticals. Plant location also brings in a variable related to the quality of available water. Hence it is very difficult to specify a particular treatment system for such a diversified pharmaceutical industry. Many alternative treatment processes are available to deal with the wide array of waste produced from this industry, but they are specific to the type of industry and associated wastes. However, the analysis of published information in the public domain shows that six

Table 4. Solvents Used in Pharmaceutical Manufacturing Process

chemicals	priority pollutant under the clean water act	chemicals	priority pollutant under the clean water act
acetone		ethylene glycol	
acetonitrile		formaldehyde	
ammonia (aq.)		formamide	
n-amyl acetate		furfural	
amyl alcohol		*n*-heptane	
aniline		*n*-hexane	
benzene	×	isobutyraldehyde	
2-butanone (MEK)		isopropyl ether	
n-butyl acetate		methanol	
n-butyl alcohol		methyl amine	
chlorobenzene	×	methyl cellulose	
chloroform	×	methylene chloride	×
chloromethane	×	methyl isobutyl ketone	
cyanide	×	*N*-methylpyridine	
cyclohexane		petroleum naptha	
o-dichlorobenzene	×	phenol	×
diethyl amine		PEG-600	
diethyl ether		*n*-propanol	
dimethyl sulfoxide		pyridine	×
N,*N*-dimethylformamide		tetrahydrofuran	
1,4-dioxane		toluene	×
ethyl acetate		triethylamine	
ethanol		xylene	

general approaches are employed to treat pharmaceutical wastewaters which are (i) recovery of individual APIs or drugs which are likely to be present in wash waters and solvents, (ii) physical−chemical treatment by sedimentation or floatation, (iii) aerobic/anaerobic biological treatment in membrane bioreactors or bioaeration, (iv) inactivation of active substances by UV oxidation in conjunction with O_3 or H_2O_2, (v) sterilization and decontamination of infectious and bioactive substances from biotechnology, and (vi) new hybrid technologies specific to the pharmaceutical industry. An attempt is made here to discuss some of these issues with reference to general methodology and specific examples.

4.1. Recovery Processes. Pretreatment and recovery of various useful byproducts, such as solvents, acids, heavy metals, and various important API's, which find their way into the waste streams comprise a very important waste control strategy for pharmaceutical plants. In the fermentation plants, the fermentation broth contains large amounts of solvent and mycelia. The solvents exhibit very high BOD strength, and also some of the solvents are not biologically degradable.

Recovery of the pharmaceutical product can reduce or even eliminate waste disposal costs of the primary unit process and raw water requirements of the secondary unit process, quickly offsetting waste-treatment operational costs and improving the economics of the process. The recovered waste stream can be used elsewhere in the process, and the water could be used for boiler feed or cooling towers and other operations thereby reducing consumption of precious raw water and drastically reducing operating costs. In fact, hot waste streams after processing can be used for other heat exchangers (heat pinching) or as boiler feed thereby reducing water and energy costs.

In general, pharmaceuticals have molecular weights higher than 250 Da and can be recovered by using effective membrane technologies provided that the product is alone in the stream. Indeed, a lot of economic benefit can be realized by using reverse osmosis, nanofiltration, and ultrafiltration. The filtrate can then be subjected to further processing as given in what follows.

Nanofiltration is the most recent developed pressure driven membrane separation process, and its applications have been increasing rapidly in the past decade. It has been widely used in aqueous systems such as the concentration of antibiotic aqueous solutions.[35,36] As an example, recovery of amoxicillin based on its physical characteristics and release in the environment is important. Amoxicillin (MW = 365.40 Da) is a widely used antibiotic in human and veterinary medicine for the treatment and prevention of respiratory, gastrointestinal, urinary, and skin bacterial infections due to its pharmacological and pharmacokinetic properties. In human medicine amoxicillin is commonly used in combination with clavulanic acid, a penicillinase inhibitor in veterinary use. It is used in many domestic and food animals, including cats, dogs, pigeons, horses, broiler chickens, pigs, goats, sheep, preruminating calves (including veal calves), and cattle. In dogs and cats, amoxicillin is used in respiratory and urinary infections and in soft tissue wounds caused by Gram-positive and Gram-negative pathogenic bacteria.[38] So the quantity of amoxicillin released into the atmosphere and in sewage, wastewater, and potable waters could be quite high. Nanofiltration (NF) can be used to separate and recover amoxicillin from pharmaceutical wastewater in order to palliate the amoxicillin's harm to the environment and also improve economics. Separation of amoxicillin from pharmaceutical wastewater by NF membrane has also been investigated by Shahtalebi et al.[39] The rejection of the amoxicillin by the selected NF membrane was adequate and in most cases exceeded 97% whereas COD reached a maximum of 40% rejection and permeation flux was over 1.5 L/(min·m^2). The stable permeation flux and high rejection of amoxicillin indicated the potential of NF for the recovery of amoxicillin from pharmaceutical wastewater.

Nanofiltration can be useful in recovering more than 80% of the complex waste stream with a quality better than feedwater quality for high operational efficiency and product safety. This is a sort of process intensification which permits increased production capacity without exceeding water discharge limits, drastically reducing raw water requirements and waste disposal cost while reducing specific organics and, at the same time, leaving other inorganic species intact.

The assessment of pollution due to toxic heavy metals in the industrial wastewater effluents collected from the Taloja industrial belt of Mumbai revealed that dye, paint, pharmaceutical, and textile industries are some of the major industries contributing to the heavy metal pollutants in the surrounding aquatic environment. For instance, the concentration of Cd and Ni was found maximum in effluent samples collected from pharmaceutical industries amounting to 35.8 and 33.6 mg/L, respectively.[40]

Studies at the University of Alicante showed development of electrochemical processes for the recycling and recovery of metals (Pb, Zn, Ni, ...) from their secondary process. The use of electrochemical processes allows obtaining metals of a higher purity, and it supposes a much less polluting alternative than the classic pyrometallurgy, since it avoids the emission of gases, sulfur, and metal particles.[41]

Table 5. Chemical Synthesis Based Pharmaceutical Wastewater Treatment Technology

no.	technology and its features	matrix	comments	ref
1	sulfate anion radical oxidation (Fe and Co sulfate salts used with hydrogen peroxide and ozone)	simulated aniline-based pharmaceutical product waste: diclofenac and sulfomethaxazole, both 1000 mg/L	DCF and SMX followed second-order kinetic degradation, with N-centered radical mechanism: very efficient method as sulfate radicals is more selective than hydroxyl radicals	Ahmed et al.[117]
2	dissolved air precipitation with solvent sublation	simulated water: mineral oil layer with organic solvents (toluene, methylene chloride, benzene, chlorobenzene, hexane, butyl acetate)	Removal efficiencies for a mixture of contaminants can differ from a case of single contaminants due to differences in their physical properties such as Henry's constant and interfacial partitioning coefficient. A higher removal of toluene was observed.	Bayati et al.[118]
3	electrocoagulation (EC) followed by heterogeneous photocatalysis (TiO_2; iron electrodes were used as cathode and anode)	BOD:COD, 0.11, caused by the high COD value (such alow index indicates the presence of refractory substances, probably stable organic compounds, which can hardly undergo biological degradation): COD, 1753 mg/L; BOD, 200 mg/L; sulfate, 893.7 mg/L; phosphate, 17.0 mg/L; *N*-ammonical, 220.4 mg/L; organic nitrogen, 344.0 mg/L; nitrite, 383.9 mg/L	This allowed the removal efficiency of 86% COD and 90% turbidity; the initial removal with EC is 70% which is enhanced to 76% by the use of UV/H_2O_2. Combination works best for wastewater with a high concentration of refractory chemicals.	Boroski et al.[115]
4	up-flow anaerobic sludge blanket (UASB) + micro-aerobic hydrolysis acidification reactor (NHAR) + two-stage aerobic process, cyclic activated sludge system (CASS) and biological contact oxidation tank (BCOT)	amoxillin (69.2−105.4 mg/L) manufacture wastewater from different stages of the plant: COD, 4016−13093 mg/L; total N, 156.4−650.2 mg/L	The combined process leads to total reduction in COD levels at every stage of the process and above 90% COD removal efficiency and is best suited for chemical synthesis based wastewater effluents.	Chen et al.[47]
5	two-phase anaerobic digestion (TPAD) system and a subsequential membrane bioreactor (MBR) TPAD system comprised of a continuous stirred tank reactor (CSTR) and an up-flow anaerobic sludge blanket-anaerobic filter (UASBAF), working as the acidogenic and methanogenic phases	product manufacture and wash water waste comprised of organic compounds such as the GCLE intermediate, cefdinir, pingyangmycin, riboflavin sodium phosphate, and glibenclamide: COD, 5000−60000 mg/L; BOD5, 750−10800 mg/L; TN, 560−980 mg/L; TP, 51.41−120.4 mg/L; TOC, 3593−6287 mg/L; NH_3−N, 36.31−260.6 mg/L; suspended solids, 600−2000 mg of COD/L; many solvents and sulfate, 1128−1627 mg/L; chloride ion, 2324−3570 mg/L; pH, 6.0−7.0	The combined pilot plant removed 99% COD, and the MBR reduced the pH in the neutral range. The combination of TPAD-MBR can be successfully applied to chemical synthesis based wastewater.	Chen et al.[116]
6	adsorption: granular activated carbon (a series of columns of GAC were used)	major impurity mercury and organomercury compounds: TDS, 675 mg/L; pH, 8.9	Removal efficiency was 99% of total mercury and 90% of copper. The treatment system was also effective for removal of turbidity (99%), color (99%), and phenols (96%) from the wastewater.	Cyr et al.[78]
7	electrochemical treatment (boron doped diamond BDD anode for corrosion stability)	organics (aromatic and aliphatic compounds), solvents (methanol and ethanol), and high concentration of chloride ions: COD, 12000 mg/L; TOC:COD, 0.27; pH, 8.5; TSS, 5000 mg/L; TOC, 1600 mg/L	The process was capable of achieving satisfactory levels of TOC removal at short treatment times. With adequate combinations of both variables (current density and flow rate), almost 100% of TOC content can be removed.	Domínguez et al.[106]
8	continuous heterogeneous catalytic wet peroxide oxidation (CWPO) process using a Fe_2O_3/SBA-15 nanocomposite catalyst	pH, 5.6; COD, 1901 mg of O_2/L; TOC, 860 mg/L; BOD, 38 mg of O_2/L; HCO_3, 112 mg/L; NO_3, 500 mg/L; NH_4, 4.8 mg/L; Cl^{1-}, 3380 mg/L; suspended solids, 40.6 mg/L; BOD/COD, 0.20; av oxidation state (AOS), 0.70	Fe_2O_3/SBA-15 extruded catalyst exhibits high efficiency, TOC removal of 50−60%, and efficient COD degradation. After initial treatment water can be treated biologically.	Melero et al.[119]
9	acidogenic reactor (USAB sludge from an alcohol industry was used with high glucose as initial feed and then varying pharmaceutical wastewater)	COD, 40000−60000 mg/L; TKN, 800−900 mg/L; phosphate, 3−6 mg/L; volatile SS/TSS, 0.6−0.7 mg/L; alkalinity (as $CaCO_3$), 900−1000; pH, 7−8; also traces of bacampicilline and sultampicilline tosylate	efficient acidification method for chemical synthesis based waste; COD removal 10−25% throughout; acidification conversion of 44% of the influent waste	Otkem et al.[120]
10	hybrid up-flow anaerobic sludge blanket reactor	COD, 40000−60000 mg/L; TKN, 800−900 mg/L; phosphate, 3−6 mg/L; volatile SS/TSS, 0.6−0.7 mg/L; alkalinity (as $CaCO_3$), 900−1000; pH, 7−8; also traces of bacampicilline and sultampicilline tosylate	This allowed 60−65% removal efficiency for chemical synthesis wastewater having organic content. SMA test showed no inhibitory action. Biomass was economical. USAB reactor showed stability for high organic contaminants	Otkem et al.[66]
11	conventional treatment: activated sludge reactor using sequencing batch reactor	COD, 250−500 mg/L; BOD, 130−280 mg/L; ammonia as N, 80−200 mg/L; total N, 90−240 mg/L; total phosphorus, 1−2 mg/L; pH, 8.8−9.6	Nitrogen removal efficiency of 99% was achieved at 23 °C. The nitrite reduction efficiency of the reactor can be used for wastewater with high ammonia content. Nitrogen removal can be controlled and cost reduction can be achieved.	Peng et al.[46]
12	hybrid up-flow anaerobic sludge blanket reactor	wastewater conditions: TDS, 8500−9000 mg/L; TSS, 2800−3000 mg/L; COD, 13000−15000 mg/L; BOD, 7000−7500 mg/L; volatile fatty acids, 600−750 mg/L; alkalinity (as $CaCO_3$), 2500−3000; chlorides, 200−250 mg/L; nitrates, 120−170 mg/L; sulfates, 300−450 mg/L; phosphates, 100−120 mg/L; phenol, 25−30 mg/L; 2-methoxy phenol, 20−25 mg/L; 2,4,6-trichlorophenol, 20−25 mg/L; dibutyl phthalate, 30−40 mg/L; 1-bromonaphthalene, 5−10 mg/L; antipyrene, 5−10 mg/L; carbamazepine, 10−15 mg/L; pH, 7.0−7.5; BOD:COD, 0.45−0.6 (amenable to biological treatment)	Best option for high organic wastewater. Removal efficiency: COD, 65−75%; BOD, 80−90%. The bio gas production rate is high, thus an economically feasible process	Sreekanth et al.[70]

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no.	technology and its features	matrix	comments	ref
13	catalytic wet air oxidation: homogeneous catalyst, Cu salt; heterogeneous catalyst, Mn–Fe composite; temperature variation study	pH, 2.6–5.2 (organic matter content); COD, 7–12 g/L; BOD, 5–7 g/L	With the increase in the temperature and catalyst loading (Cu salt), higher COD removal was achieved within a 1 h interval.	Zheng[121]
14	multistage loop membrane bioreactor	COD, 1200–9600 mg/L; BOD5, 500–2500 mg/L; NH_4–N, 50–200 mg/L; TN. 105–400 mg/L; intermediates (6-APA, 7-ACA, GCLE), cefazolin, cefoperazone sodium, cephalosporins ampicillin, penicillin G sylvite, amoxicillin, ampicillin sodium, and poly(ethylene oxide); ethylene; glycerin	The removal rate was constant at 90% with pH constant. The technology is not suitable for wastewater having a lot of organic contaminants.	Chen et al.[47]
15	photofenton followed by lime or NaOH coagulation	wash waters from the production plant and mixture of spent chemicals from ointment production already treated by adsorption, flocculation, and filtration: COD, 4–13 mg/L	86–96% COD removal and biodegradability increase after 120 min oxidation at H_2O_2:Fe^{2+} molar ratio, 10:1; lime coagulation, 0.5 g/L	Kulik et al.[96]

The ultrafiltration process has also been effectively used for the recovery of organic compounds from several synthetic media resulting from fermentation process wastewater. Bezawada et al.[42] used ultrafiltration for recovery of alkaline protease from spent fermentation broth. Alkaline protease accounts for 60% of the total enzymes sales and is a very important material for the fermentation industry. The recovery of alkaline protease using ultrafiltration process with an optimum transmembrane pressure of 90 kPa and feed flux of 714 L/(h/m^2) showed a recovery of 83% of the protease activity.

4.2. Wastewater Treatment of Dilute Streams. The dilute streams from the manufacturing units are mainly treated by biological treatment methods as they convert most of the waste into gases and sludge can be disposed off harmlessly. Available treatments include the activated sludge process, trickling filtration, the powdered-carbon-fed activated sludge process, and the anaerobic hybrid reactor. Apart from the foregoing conventional treatment processes there are several other oxidation processes, membrane techniques, and advanced oxidation processes.[43] Based upon an extensive literature survey of the research carried out on actual pharmaceutical waste treatment, a listing has been made of the treatment technologies available in Table 2.

To have a clear understanding of the various techniques used in the treatment and disposal of various types of wastes produced in the pharmaceutical industry, the treatment processes can be divided into the following four categories and subcategories:

(1) biological treatment process;
  (a) aerobic treatment
  (b) anaerobic treatment
(2) advanced treatments;
  (a) membrane technology
  (b) activated carbon
  (c) membrane distillation
(3) advanced oxidation processes
  (a) ozone/hydrogen peroxide treatment
  (b) Fenton oxidation
  (c) photocatalysis
  (d) electrochemical oxidation/degradation
  (e) ultrasound irradiation
  (f) wet air oxidation
(4) hybrid technologies

4.2.1. Biological Treatment. Biological treatment methods have been traditionally employed for dealing with pharmaceutical wastewater.[44] The biological treatment of pharmaceutical wastewater includes both aerobic and anaerobic treatment systems. Apart from the previously mentioned two processes, Afzal et al.[45] investigated an efficient degradation by using *Pseudomonas aeruginosa* (*P. aeruginosa*) and *P. pseudomallei* where the former showed a higher degradation rate and COD and BOD removal which indicated that the strains work well for phenolic wastewaters from fermentation processes.

4.2.1.1. Aerobic Treatment. Aerobic treatment is one of the common technologies applied which include the activated sludge (AS) process, extended aeration activated sludge process, AS with granular activated carbon, and membrane bioreactors.[46−50]

Activated Sludge Process. The activated sludge process is the most common aerobic treatment which has been found to be efficient for various categories of pharmaceutical wastewaters.[51] The conventional activated sludge (CAS) treatment is a low-cost method which depends mainly on two parameters, the temperature and the hydraulic retention time (HRT). Apart

Table 6. Fermentation Process Based Pharmaceutical Wastewater Treatment Technology

no.	technology and its features	matrix	comments	ref
1	photocatalysis (TiO_2) + H_2O_2; a single baffled reactor for the process.	pH, 8.2; phenol, 380 mg/L; chlorides, 182 mg/L; sulfates, 160 mg/L; COD, 1082 mg/L; BOD, 170 mg/L; BOD:COD, 0.15	Addition of H_2O_2 to the system increases degradation rate from 75 to 95%. Also, phenol removal rate enhanced from 40% to 45%. The combination of H_2O_2 to the photo catalytic system enhanced the effluent removal rate.	Adishkumar and Kanmani[95]
2	biodegradation using bacterial strains (*Pseudomonas aeruginosa* and *Pseudomonas pseudomallei*)	aqueous phenol waste, 1053 mg/L; COD, 5097 mg/L; BOD, 1100 mg/L; chloride, 1152 mg/L; sulfate, 2280 mg/L; pH, 4−8	Efficient degradation of phenol by two strains at higher concentration. *P. aeruginosa* showed higher degradation rate and COD and BOD removal and can be used for phenolic treatment.	Afzal et al.[45]
3	photocatalysis (Fenton + photo-Fenton + ozonation)	penicillin formulation effluent: av COD, 1395 mg/L; TOC, 920 mg/L	10−20% COD removal after 60 min. Poor improvement in biodegradability	Arslan-alaton and Dogruel[90]
4	ozonation (pretreatment) + biological activated sludge reactor combination in series	penicillin formulation effluent: av filtered COD, 830 mg/L; soluble COD, 615 mg/L; pH, 6.9; amoxicillin trihydrate; lactamase inhibitor; potassium clavulanate	Preozonation enhanced the biodegradability of the effluent. Efficiency of the process for COD, around 90% removal with the organic content. The combination of preozonation and biodegradation is the best option for pharma effluent.	Alaton et al.[93]
5	Fenton−biological process: first Fenton coagulation and then biological treatment by activated sludge	COD, 4100−13023; TSS, 20−330 mg/L; oil grease, 17.4−600 mg/L; traces of salicylic acid, chlorompenicol, and paracetamol; TOC, 4679.4 mg/L; sulfate, 788 mg/L	More than 95% COD removal was observed. Fenton pretreatment reduced the COD and toxicity level thus making it suitable for biological treatment. Also, many organic compounds were degraded.	Badawy and Wahaab[97]
6	chemical oxidation ozonation and ozonation coupled with treatment with hydrogen peroxide	antibiotic formulation waste was made synthetically by characterizing the actual industrial waste: antibiotic I (ceftriaxone sodium, cephalosporine group); human antibiotic II (penicillin VK and penicillin group; contain only active substances); veterinary antibiotic enrofloxacin, quinolone group are prime constituents. COD up to 1400 mg/L	Preozonation helps to reduce the COD level to a great extent and H_2O_2 enhances the process to the maximum. Also, the biodegradability characteristic of the waste also increases. Thus, ozonation can be successfully applied as a pretreatment.	Balcıoğlu and Otker[91]
7	membrane bioreactor technology (hollow fiber membrane)	pH, 6.6−9.4; SS, 60−360 mg/L; COD, 800−11800 mg/L; BOD, 100−6350 mg/L	MBR system is capable of removing 95% and 99% of COD and BOD, respectively.	Chang and Chang[49]
8	up-flow anaerobic stage reactor (UASR)	soluble COD, 7000 ± 800 mg/L; soluble BOD5, 3500 ± 500 mg/L; sulfates, 2500 ± 500 mg/L; total Kjeldahl nitrogen (TKN), 364 ± 50 m/L; pH, 5.2−6.8; tylosin concentration, 10−220 mg/L	75% of soluble COD removal with 95% reduction in tylosin concentration was observed. The anaerobic biological reactor can be efficiently applied to such antibiotic wastewater.	Chelliapan and Sallis[65]
9	up-flow anaerobic stage reactor (UASR)	tylosin and avilamycin; soluble COD, 7000−7800 mg/L; soluble BOD 3500−7500 mg/L; sulfates:2500−7500 mg/L; total Kjeldahl nitrogen (TKN): 364−750 mg/L; pH: 5.2−6.8; and tylosin concentration, 20−200 mg/L	UASR can be used effectively as an option for pretreatment of pharmaceutical wastewaters that contain Tylosin and Avilamycin macrolide antibiotics. COD reduction of 70−75%; Tylosin can be degraded efficiently in anaerobic environments	Chelliapan[69]
10	ozonation (pretreatment) + biological activated sludge treatment by synthetic biomass with 30% COD	penicillin formulation waste with wash waters: COD, 710 mg/L; soluble COD, 690 mg/L; TOC, 200 mg/L; BOD, 15 mg/L; pH, 6.85; with chlorides and sulfates	ozonation removed 34% COD and 24% TOC and then the water showed efficient COD removal by biodegradability using activated sludge.	Cokgor et al.[94]
11	activated sludge reactor in batch and continuous flow	process waste: COD, 1488−6818 mg/L; BOD, 950−4050 mg/L; TSS, 56−656 mg/L; TDS, 1371−7314 mg/L; chloride, 100−5000 mg/L; iron, 1−4 mg/L; phenol, 116.7−210 mg/L; pH, 1.87−4.4	More than 95% efficiency was obtained by biologically activated sludge reactor, films reactor, and trickling filter reactor. Biological treatment is best suited for such waste.	El-Gohary et al.[51]
12	anaerobic biological treatment using activated sludge reactor	solvent containing wastewater from an API producing industry having propanol, methanol, and acetone in water	A good COD removal efficiency with production of biogas was observed.	Enright et al.[68]
13	hybrid treatment technology (aerobic biological pretreatment + ozonation + MBR), the biological treatment for reducing the ozone demands. Ozonation reduces almost all of the organic compounds.	API formulation waste comprised of estrogens, many small steroids, and oral contraceptives; no specific physiochemical characteristics	Aerobic biological treatment reduces most of the organics, and then ozonation eliminated the bulk organic load and API's. More than 90% COD and TSS removal was obtained, and the MBR led to complete treatment of wastewater.	Helmig et al.[50]
14	anaerobic granulation batch/column reactor	COD, 4000−5000 mg/L; ammonical N, 20−300 mg/L; TSS, 150−300 mg/L; pH, 4−7	Nitrate and phosphate removal by precipitation was observed, as well as 95% removal of COD.	Inizan et al.[67]
15	catalytic wet air oxidation coupled with anaerobic biological oxidation	wastewater from a vitamins manufacturing company: COD, 70000−120000 mg/L; BOD, 5000−7000 mg/L; TSS, 50−80 mg/L; pH, 3−5; N−NH_4, 8−150 mg/L	CWAO removed COD and BOD to the maximum and enhanced the biodegradability of the wastewater; 94.66% removal of COD was obtained.	Kang et al.[71]
16	aerobic biological treatment with variable temperature study	effluent: soluble COD, 8150−7170 mg/L; soluble BOD, 3800−7900 mg/L; total ammonia, 220−750 mg/L	Soluble COD removal in a given batch reactor declined as temperature increased by an average of 60 (mg/L)/°C.	La Para et al.[122]
17	biological treatment by activated sludge: in seven stages, a pilot plant study	effluent: high COD, more than 500 mg/L; BOD, more than 50 mg/L; total ammonia, more than 5 mg/L	This is a table microbial reactor for a long time operation.	LaPara et al.[48]
18	suspended growth photo-bioreactor: nonsulfur photosynthetic bacterium isolated from the soil and fluorescent light reactor	wastewater: COD, 9450 mg/L; BOD, 197 mg/L; pH, 6.6	COD was reduced 80%, and there is the potential to improve the treatment process without any considerable increase in cost. The biomass produced could be economical.	Madukasi et al.[123]

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Table 6. continued

no.	technology and its features	matrix	comments	ref
19	membrane bioreactor (GE ZeeWeed membrane bioreactor technology)	pharmaceutical wastewater (typical ranges): COD, 2000−40000 mg/L; MLSS, 10000−20000 mg/L; total Kjeldahl nitrogen (TKN), up to 1000 mg/L	The following results were achieved: COD and BOD, >90% (>98% for BOD) removal; with permeate of , typically BOD < 5 mg/L, TSS > 99% removal; with permeate typically TSS < 5 mg/L, TKN > 90% removal; with permeate typically ammonia < 1 mg/L, phosphorus > 90% removal, using appropriate chemical dosing	Noble[124]
20	semiconductor photocatalysis Ti/TiO_2: RuO_2−IrO_2 as anode, graphite as cathode, and chloride as electrolyte	phenolic compounds: COD, 8880 mg/L from a bulk manufacturing process	This allowed 95% COD removal with first-order kinetics and was energy efficient with consumption of 17 kWh/(kg of COD).	Rajkumar and Palanivelu[100]
21	pervaporation through water-selective membranes	wastewater (having solvents such as ethanol, ethyl acetate, acetic acid, and methanol along with sodium chloride and other organic impurities): TOC, 145000 mg/L; COD, 70000 mg/L	This allowed 45−80% removal of COD, and TOC was observed in two different compositions of waste. But, pervaporation cannot be applied to dilute aqueous waste.	Shah et al.[125]
22	sequencing batch reactor: an activated sludge reactor	simulated wastewater with high COD and BOD levels: TDS, 1000−1500 mg/L; COD, 1500−7000 mg/L; BOD, 1000−3000 mg/L; pH, 7.0−8.5	The removal efficiencies of COD and BOD are 93.34% and 98.98%, respectively. The biosludge generated is nontoxic and can be used as a manure for horticulture.	Shivaprasad et al.[126]
23	solar photo-Fenton and biological treatment	main effluent in water is 45 mg/L nalidixic acid with 775 mg of dissolved organic carbon/L: COD, 3420 mg/L; pH, 3.98	COD elimination was 95%, of which 33% was accomplished by the solar photo-Fenton treatment and 62% by the biological treatment. Wastewater can be successfully treated by photo-Fenton treatment with peroxide usage and low toxicity removal efficiency.	Sirtori et al.[98]
24	anaerobic multichamber bed reactor (AMCBR) + AMCBR with continuous stirred tank reactor (CSTR)	simulated antibiotic wastewater having oxytetracycline (155.56 and 177.78 (g of OTC/m^3)/day with the organic loading rate (OLR) being 2.65 and 2.22 (g of COD/m^3)/day, respectively	The combination anaerobic AMCBR and aerobic CSTR treatment system was effective in removing OTC from synthetic wastewater with high yields (>95%).	Sponza and Çelebi[63]
25	ANAMMOX (anaerobic ammonium oxidation) process with sequential biocatalyst (ANAMMOX granules) addition (SBA-ANAMMOX process)	colistin sulfate and kitasamycin manufacturing wastewater: pH, 6.8−7.8; NH_4−N, 123−257 mg/L; NO_2−N, 133−264 mg/L; NO_2−N/NH_4−N, 1.0−1.4 mg/L; COD, 415−843 mg/L; BOD, 0−51mg/L	This method was unsuccessful in removing the toxic organic content but efficient in removal of COD and BOD and ammonical nitrogen.	Tang et al.[64]
26	Fenton oxidation (pretreatment) by oxidation and coagulation stage followed by aerobic biological degradation in sequencing batch reactor	from the manufacturing process and wash waters: traces of organic compounds, iodine, and metal salts; COD, 900−6800 mg/L; BOD, 85−3600 mg/L	Fenton treatment removed 45−50% of COD, and the biological treatment reduced the COD by 98%.	Tekin et al.[52]
27	catalytic wet air oxidation (CWAO) mixtures of waste streams used in autoclave to form polyoxometalates (POMs) as a cocatalyst system	wash waters from the antibiotic industry: traces of fosfomycine (COD, 188108 mg/L; TOC, 46000 mg/L; phosphate, 3000 mg/L; pH, 11); berberine (COD, 3201 mg/L; TOC, 1470 mg/L; Cu^{2+}, 12790 mg/L; pH, 1); other toxic intermediates	40% of COD and TOC removal can be easily realized in 1 h of WAO oxidation at 523 K, 1.4 MPa; CWAO by Cu^{2+} and $[P_xW_mO_y]^{q-}$ cocatalysis was found to be an effective method for treating the real pharmaceutical wastewater.	Wang et al.[127]

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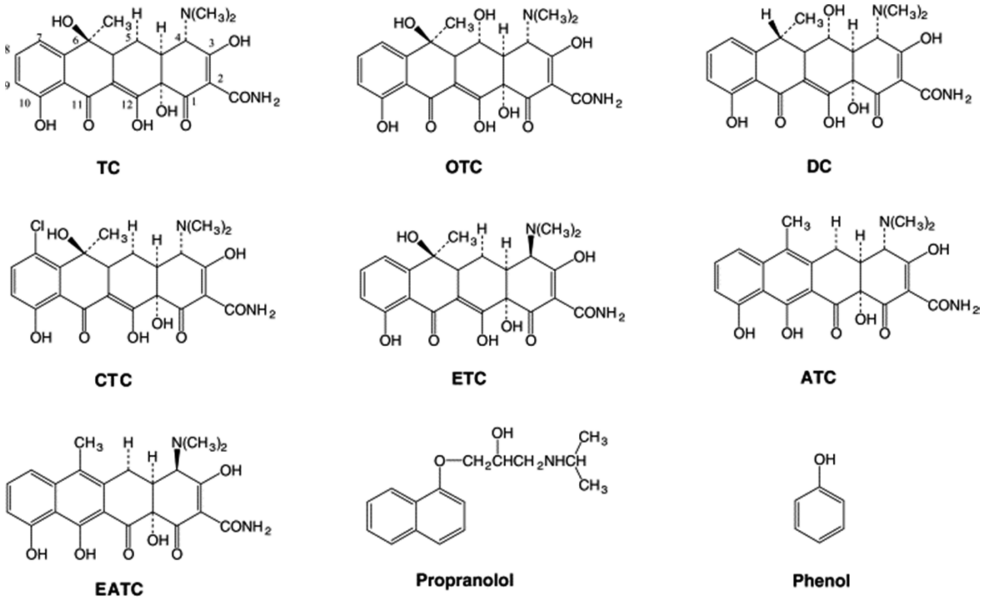
Scheme 1. Use of Molecularly Imprinted Polymers from a Mixture of Tetracycline and Its Degradation Products To Produce Affinity Membranes for the Removal of Tetracycline from Water[64]



from these the presence of organic matter, COD, BOD, pH, presence of non-biodegradable matter are other factors which affect the efficiency of AS method. Peng[46] achieved 99% nitrogen removal efficiency at 23 °C. The nitrite reduction efficiency was suitable for high ammonia content wastewater and in a reduced cost. Tekin[52] obtained 98% COD removal for a Fenton pretreated manufacturing process wastewater using an aerobic sequential batch reactor. Ibuprofen, naproxen, bezafibrate, ethynilestradiol and several other estrogens show a high degree of removal efficiency but sulfa drugs like sulfomethaxazole, carbamezapine and diclofenac showed limited removal.[43,53]

Membrane Bioreactors. In the past decade, use of membrane bioreactors (MBRs) for pharmaceutical wastewater treatment has gained much attention as it is a technically and economically feasible alternative for water and wastewater treatment, especially because of high sludge retention time (SRT) achieved within compact reactor volumes. In the MBR the concentration of microorganisms can be increased to up to 20 mg/L.[54] This high concentration of biomass increases the degradation capacity of larger organic molecules. Another advantage of membrane treatment is separation of suspended solids by membranes, so they are not limited by the settling characteristics of the sludge.[55] Removal efficiencies of 98.7% for TSS and 90.4% for total COD were achieved for a MBR coupled with conventional activated sludge reactor in a study carried out[54] for wastewaters comprised of analgesics and anti-inflammatory drugs (ibuprofen, diclofenac, indomethacin, and acetaminophen), antibiotics (ofloxacin, sulfamethoxazole, and erythromycin), and β-blockers (atenolol and metoprolol).[54] Noble[56] used a hollow fiber submerged MBR, for fermentation process wastewater having a very high COD of around 40000 mg/L. More than 90% COD and 98% BOD removal was achieved. Apart from that 90% phosphorus removal was also obtained by proper treatment measures. Comparative studies of MBR AS[54] and CAS[57] showed that the elimination of this drug is enhanced in the MBR treatment, probably due to better adaptation of microorganisms. The poor removal of erythromycin has been reported for CAS,[54,58] whereas laboratory-scale MBR was capable of 67% elimination.[54] However, complete removal of all pharmaceuticals by MBR or any single operation is very rare.[50] MBR removed more than 10 estrogens such as 17-α-estradiol, 17-β-estradiol (E2), 17-α-dihydroequilin, trimegestone, estriol (E3), medrogestone, norgestrel, and estradiol valerate and several others, to near and below analytical detection levels in a study that was carried out,[50] but the system was resistant to a specific serotonin re-uptake inhibitor venlafaxine. Thus, it becomes inevitable to use a combination of various pre- and posttreatment methods for complete removal of diverse pharmaceutical effluents.

Tambosi[59] investigated that compounds acetaminophen and ketoprofen had the highest removal efficiencies, while roxithromycin and sulfamethoxazole exhibited persistence to microbial attack and were removed to a lesser extent in two MBRs studied. However, in general terms, membrane retention using micro- or ultrafiltration membranes can be neglected, whereas biodegradation plays an important role, since higher removal efficiency was obtained for higher SRTs. Nevertheless, the elimination by MBR treatment using ultrafiltration was only partially successful, and therefore, persistent pharmaceuticals in small concentrations and their transformation products were discharged with the wastewater into the environment. This discharge could be reduced with the application of additional treatment steps using advanced treatment techniques, e.g., activated carbon adsorption, ozone oxidation, advanced oxidation processes (AOP), NF, or reverse osmosis (RO).

The molecularly imprinting technology (MIP) possesses several advantages over the conventional immunosorbent (IS) and shows high selectivity and affinity, high stability, and the ease of preparation. The MIPs can be used repeatedly without loss of activity with high mechanical strength and are durable against harsh chemical media, heat, and pressure compared to biological receptors. MIP targeting tetracycline (TC) and oxytetracycline (OTC) was developed by Caro et al.[60] to selectively remove the antibiotics and several tetracycline analogues from pig-kidney tissue. Use of molecularly imprinted polymers from a mixture of tetracycline and its degradation products to produce affinity membranes for the removal of tetracycline from water has been reported by Suedee et al. (Scheme 1).[61] Many of the

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successful applications in various fields, especially in solid-phase extraction (SPE) for sample cleanup, have proved the potential of MIP. There are MIP-based SPE cartridges that have been commercialized by companies, for examples, clenbuterol-selective, triazine-selective and chloramphenicol-selective MISPE.[62]

In the case of membrane processes, a general approach to produce clean water from dirty or polluted water in the pharmaceutical industry will be based on the size of the pollutants in the following order: bacteria particles (microfiltration), macromolecules and viruses (ultrafiltration), divalent ions (nanofiltration), and monovalent ions (reverse osmosis).

4.2.1.2. Anaerobic Treatment. Anaerobic treatment has been done by using continuous stirred tank reactors (anaerobic digestion), fluidized bed reactors, and up-flow anaerobic sludge reactors, etc.[63−68] Anaerobic hybrid reactors, which are a combination of suspended growth and attached growth systems, have recently gained much attention. The significance of anaerobic treatment over aerobic processes is the ability to deal with high concentration wastewater, with lesser energy inputs, low sludge yield, low operation cost, and economical byproduct recovery of biomethane as a valuable energy source.[43] Up-flow anaerobic batch reactor (USAR) has been shown to be very efficient in removal of high concentrations of PhP's from pharmaceutical wastewater.[65,69] A USAR operating at higher temperatures of about 55 °C showed a high COD (65−75%) and BOD (80−94%) removal even at a very high concentration of organic content of 9 kg of COD/(m^3·day).[70] It is shown that 75% COD removal and more than 95% tylosin removal from an antibiotic effluent wastewater is possible thereby making USAR a suitable application for such wastewaters. In a study by Kang et al.,[71] catalytic wet air oxidation was employed with anaerobic biological oxidation to high COD (70000−120000 mg/L) containing vitamin process wastewater. With the combination, more than 94.66% COD removal was obtained with total biodegradability of the organic content. More than 60−65% removal was achieved for chemical synthesis wastewater having a COD of about 40000−60000 mg/L by using a hybrid up-flow anaerobic sludge blank reactor. Specific methanogenic analysis showed no inhibitory action, and the biomass obtained was highly economical.[66]

Recently, Sponza and Çelebi[63] used an anaerobic multichamber bed reactor (AMCBR) coupled with a continuous stirred tank reactor (CSTR) to an oxytetracycline spiked antibiotic wastewater. The combination of anaerobic AMCBR and aerobic CSTR treatment system was effective in removing OTC from synthetic wastewater with high yields (>95%) at OTC loadings < 177.78 g of OTC/(m^3/day), respectively. However, Tang et al.[64] were unsuccessful in removal of colistin sulfate and kitasamycin containing anitibiotic wastewater.

4.2.2. Advanced Treatment Process. Advanced treatment of pharmaceutical wastewater can be considered as the primary treatment or pretreatment processes to accelerate the removal efficiency of pollutants by the secondary treatment. These include membrane technology, membrane distillation, and activated carbon adsorption.

4.2.2.1. Membrane Technology. Implementation of membranes in water treatment is greatly increasing. It is well-known that low-pressure membranes are capable of removing microbial constituents without increasing disinfection byproducts, thereby allowing compliance with the rules promulgated in response to the 1986 Surface Water Treatment Rule Amendments.[72] Whether the purpose is desalination or water reuse, low-pressure membrane systems play an important role as reverse osmosis pretreatment processes. In one of the studies 95% rejection of diclofenac was obtained by RO membranes.[57] Microfiltration/ultrafiltration (MF/UF) systems are strongly recommended when there are space limitations and/or variable feedwater quality.[73] Nanofiltration and ultrafiltration processes have been used in wastewater reclamation and drinking water to remove micropollutants and natural organic matter (NOM). The NF membrane retained EDC/PPCPs greater than the UF membrane, implying that retention is affected by membrane pore size. In addition, the retention of EDC/PCPs appears to be affected by source water chemistry conditions.[74] Therefore, it can be concluded that both RO and NF show better removal of efficiency of certain organic pharmaceuticals but the problem of retentate/concentrate disposal remains the same. Thereby further treatment of the concentrate generated is required.

4.2.2.2. Activated Carbon. Adsorption using activated carbon (AC) is well-suited to remove OCs due to its high surface area (over 1000 m^2/g) and the combination of a well-developed pore structure and surface chemistry properties. Recently Mestre et al.[75] have demonstrated the removal of ibuprofen by using waste derived activated carbon. The AC process thus has an advantage of easy raw material input for the production of carbon. The AC process makes use of powdered activated carbon (PAC) or granular activated carbon (GAC). PAC has an advantage over GAC as it is usually fresh as compared to GAC which is usually recycled in fixed bed columns.[76,77] Although PAC gives higher efficiency, it is not cost effective and regeneration/disposal of saturated GAC columns are also an issue.[72] Cyr et al.[78] found that a series of GAC columns removed 99% of the total mercury (organic + inorganic) and around 90% copper removal from a chemical synthesis based pharmaceutical wastewater. The column was also effective in turbidity as well as 96% phenol removal. Another study on the adsorption of 62 EDCs and PPCPs by PAC in different source waters showed that PAC was capable of partially removing all target compounds, depending on the physicochemical properties of each compound.[79] The major difficulty faced by using PAC is the separation of the adsorbent from the treated water, and thus, it has to be integrated with a filtration unit. Recently many studies have been carried out on using AC along with other treatment technologies where activated carbon can be used as a pretreatment.[80]

4.2.2.3. Membrane Distillation. Membrane distillation is a very important separation technology with interesting properties. Presently membrane distillation is used for the production of demineralized water.[81,82] The membrane distillation process operates at atmospheric conditions, and the heat requirement is also very low.[83] The technology has been used to recover process waters by using the heat generated during the industrial processes and thus making the technology very promising for application.[84] Membrane distillation provides very clean water, but membrane fouling is a major disadvantage of this technique. Membrane distillation has been very successfully applied for recovery of the acids from fermentation broths.[85]

4.3. Advanced Treatment Processes (Advanced Oxidation Processes). Owing to the low biodegradability of many pharmaceuticals, the commonly employed treatment processes are not effective enough for complete removal of such species and the discharge of treated effluents into receiving waters can lead to contamination with these micropollutants.[86] These compounds thus released into the environment have proven to be high enough to cause toxic effects to environmental organisms.[87,88] Advanced oxidation processes

can be broadly defined as aqueous-phase oxidation methods based on the intermediacy of highly reactive species such as (primarily but not exclusively) hydroxyl radicals in the mechanisms leading to the destruction of the target pollutant.[17] The main AOPs are heterogeneous and homogeneous photocatalysis and ultraviolet (UV) or solar irradiation: electrooxidation, Fenton and photo-Fenton process, wet air oxidation, and, recent ones in this category, ultrasound irradiation and microwave treatment, which typically operate around 2450 MHz in either a monomode or multimode type of vessel. Depending upon the nature of the pharmaceutical effluent and the treatment objective of destruction or transformation, AOPs can be employed either alone or coupled with other physiochemical and biological processes.

4.3.1. Ozone/Hydrogen Peroxide Treatment. Ozone is a very strong oxidizing agent that either decomposes in water to form hydroxyl radicals which are stronger oxidizing agents than ozone itself, thus inducing the so-called indirect oxidation, or attacks selectively certain functional groups of organic molecules through an electrophilic mechanism.[17,89] Pharmaceutical wastewater contains various kinds of recalcitrant organics such as toluene, phenols, nitrophenols, nitroaniline, trichloromethylpropanol (TCMP), and other pollutants that exhibit resistance against biodegradation. Since these pollutants cannot be easily removed by biological treatment, biologically treated effluent exhibits a considerable BOD and COD, in the effluent. It has also been reported that activated carbon adsorption may not always be successful in removing such recalcitrant organics.[72] Economic constraints may also prohibit the treatment of pharmaceutical wastewater by activated carbon adsorption. In such cases, ozone/hydrogen peroxide treatment may appear to be a proven technology for treating such pollutants from pharmaceutical wastewater. The removal of high concentrations of penicillin and the enhancement of biodegradability of the fermentation process wastewater have been studied.[90] However, as stated earlier, the best approach should be removing penicillin by ultrafiltration and subjecting the filtrate to oxidation. Ozonation has been largely employed in removal of antibiotics.[50,89,91] But ozonation cannot be employed in all circumstances as compounds with amide linkages are resistant to ozone.[92]

Thus, in such cases a combination of ozone with hydrogen peroxide has been successfully utilized for the degradation of penicillin formulation wastewater.[91,93,94] It was shown that the conjugate base of H_2O_2 at millimolar concentrations could initiate the decomposition of ozone much more rapidly into hydroxyl radicals than with the hydroxide ion and that the COD removal efficiency was greatly enhanced by 76%.[91] Combination of hydrogen peroxide with photocatalysis has also been successfully studied.[95]

4.3.2. Fenton's Oxidation Treatment. Fenton's reagent involves the reaction of hydrogen peroxide with ferrous or ferric ions via a free radical chain reaction which produces hydroxyl radicals. It is a heterogeneous catalytic reaction in which iron acts as a catalyst.[52,93] Since iron is an abundant element, this process is the most viable for wastewater treatment. Recent research has shown the use of Fenton oxidation capable of reducing a load of refractory effluents to being less toxic and more readily amenable to biological posttreatment.[52,96] More than 95% COD removal was observed in a pharmaceutical effluent containing chloramphenicol, paracetamol, and COD of ~12000 mg/L.[97] Penicillin was completely eliminated after 40 min of advanced oxidation with Fenton/UV treatment.[90] However, Fenton processes suffer a major drawback of pH dependency and a lot of iron sludge which is generated. The Fenton process can be best applied as a pretreatment technology to convert the non-biodegradable pharmaceutical effluent into biodegradable and thus make treament of the effluent by biological process more efficient.[93,98]

Enzymatic Water Purification: Fenton Chemistry in Situ. A very interesting case of enzymatic catalysis and Fenton chemistry in situ has been advocated and has a potential for treatment of a variety of wastewaters coming from different industries as has been demonstrated through the integration of nanostructured materials, enzymatic catalysis, and iron-catalyzed free radical reactions within pore-functionalized synthetic membrane platforms without use of toxic oxidants, by Lewis et al.[99] They employed two independently controlled, nanostructured membranes in a stacked configuration for in situ synthesis of the oxidizing species. The upper bioactive membrane contains an electrostatically immobilized enzyme to generate hydrogen peroxide (H_2O_2) from glucose. The bottom membrane contains either immobilized iron ions or ferrihydrite/iron oxide nanoparticles for the decomposition of hydrogen peroxide to form powerful free radical oxidants. By permeating (at low pressure) a solution containing organic contaminant with glucose in oxygen-saturated water through the membrane stack, significant contaminant degradation was realized.

4.3.3. Photocatalysis. Photocatalysis is the acceleration of a photochemical transformation by the action of catalyst such as TiO_2 or Fenton's reagent.[43] The catalyst which is most commonly employed for all pharmaceutical photocatalytic studies is rutile TiO_2. Photocatalysis is the best suited process for effluents having a high COD and for complete transformation of highly refractory organic contaminants to reach biological treatment level. In the context of pharmaceutical treatment, it has also been reported that for the degradation of sulfamethazine and chloramphenicol respectively ZnO_2 showed higher catalytic activity than TiO_2. Photocatalytic reactions usually obey the Langmuir−Hinshelwood kinetic model which is reduced to pseudo-first- or zero-order kinetics depending on the operating conditions.[17]

The use of UV/TiO_2 along with H_2O_2 has shown enhanced removal efficiency of phenols and COD from fermentation effluent.[95] Also, a combination of photocatalysis with ozonation has also shown improvement of COD removal in penicillin formulation effluent.[93] A novel semiconductor photocatalysis by using a combination of TiO_2 with RuO_2−IrO_2 as anode and chloride as an electrolyte has also shown 95% COD removal with first-order kinetics.[100]

From an economic point of view, photocatalysis can be carried out by the usage of solar irradiation and much research has been done in this regard for the treatment of pharmaceutical effluents.[101−103] Photocatalytic process is also found to be highly energy efficient with consumption of 17 kWh/(kg of COD removed).[100]

4.3.4. Electrochemical Oxidation/Degradation. Electrochemical method is based on in situ production of hydroxyl radical ($^{\bullet}OH$) as the main oxidant, which is the second strongest oxidizing agent known after fluorine, having such a high standard reduction potential (E° ($^{\bullet}OH/H_2O$) = 2.8 V vs SHE) that it is able to nonselectively react with most organic contaminants via hydroxylation or dehydrogenation until their total mineralization.[104] The treatment of ethinylestradiol in urine by electrodialysis has led to a 99% removal of toxicity.[105]

Simulated waste having pharmaceutical residues such as diclofenac, carbamezapine, propranolol, ibuprofen, and ethinylestradiol, treated with electrochemical method, has shown complete degradation. Dominguez et al.[106] showed a satisfactory removal of total organic carbon (TOC) by the usage of boron doped diamond (BDD) anode which showed higher corrosion stability. With the adequate combination of current density and flow rate almost 100% TOC removal was observed.

More than 97% TOC removal has been observed in paracetamol and diclofenac spiked wastewater by BDD electrochemical treatment.[107,108] The degradation rate of the antibiotic was also enhanced with an increasing concentration of doping boron and decreasing electrode thickness. Electrocoagulation coupled with photocatalysis has shown 86% COD removal efficiency in chemical synthesis based wastewater. The use of photocatalysis enhances the degradation capability.[109]

The efficiency of electrooxidation may be enhanced by the synergetic action of dissolved iron, i.e., the electro-Fenton process which catalyzes the degradation of H_2O_2 to hydroxyl radicals. It has been very well reported that EF with use of doped BDD electrode reduces the toxicity of the byproduct water which is formed in electrooxidation alone.[109,110]

4.3.5. Ultrasound Irradiation. Ultrasound irradiation is a relatively very recent technique which has been applied for wastewater treatment. Not much literature is available on sonochemical degradation of pharmaceutical compounds. Sonochemical reactions are induced upon high-intensity acoustic irradiation of liquids at frequencies that produce cavitation (25 kHz). Thus, cavitation serves as a means of concentrating the diffused energy of ultrasound into microreactors with the simultaneous release of radicals. Many estrogenic compounds have been removed by ultrasonic irradiation from contaminated waters, with a reduction of 80−90% COD within 40−60 min of treatment.[111] The technique can be best used for treatment of two-phase wastewater having organics of low solubility. Recently a combination of biological treatment and hydrodynamic cavitation was used for the removal of pharmaceutical compounds from wastewaters. Coupling the attached-growth biomass biological treatment, hydrodynamic cavitation/hydrogen peroxide process, and UV treatment resulted in removal efficiencies of >90% for clofibric acid and >98% for carbamazepine and diclofenac, while the remaining compounds were reduced to levels below the level of detection (LOD). For ibuprofen, naproxen, ketoprofen, and diclofenac the highest contribution to overall removal was attributed to biological treatment; for clofibric acid UV treatment was the most efficient, while for carbamazepine hydrodynamic cavitation/hydrogen peroxide process and UV treatment were equally efficient.[112]

4.3.6. Wet Air Oxidation. Wet air oxidation is a thermochemical process where hydroxyl radicals and other active oxygen species are formed at elevated temperatures (200−320 °C) and pressures (2−20 MPa).[113] Recent research has shown the applicability of this process to remove COD to a great extent. Catalytic wet air oxidation of a chemical synthesis wastewater having a COD of 7−12 g/L showed removal of total organic matter and the process enhanced with enhanced loading of heterogeneous copper catalyst and high temperatures.[114] A study conducted by the usage of heterogeneous nanocatalyst Fe_2O_3/SBA15 exhibited high TOC removal and COD degradation capability.[115] This technique can also be applied as a pretreatment process thereby making the wastewater suitable for biological treatment.

4.4. Hybrid Technologies. Hybrid technologies are the combinations of one or more conventional/advanced treatment technologies for the complete eradication of pharmaceutical contaminants. The need for hybrid technologies arises from the fact that none of the single-treatment technologies can remove all compounds.[76] There are a number of hybrid technologies which have been used for the treatment of refractory pollutants as well as to reduce the cost of the treatment process. The technology basically uses the conventional filtration step to remove any solid matrix and the sludge is removed for incineration. The clear wastewater is then treated by the different combination of processes.

4.4.1. Hybrid Technologies for Chemical Synthesis Process Wastewater. Chemical synthesis process wastewater usually contains high concentrations of organic contaminants ranging from the reagents to the intermediates and the final products. Many researchers have used the combination of advanced treatment method along with biological treatment methods to deal with such a matrix. Chen et al.[116] have used a two-phase anaerobic digestion (TPAD) system and a subsequential MBR, TPAD system comprised of an up-flow anaerobic sludge blanket-anaerobic filter (UASBAF) and continuous stirred tank reactor (CSTR), working as the acidogenic and methanogenic phases. The combined pilot plant removed 99% COD; and the MBR reduced the pH in the neutral range. The combination of TPAD-MBR can be successfully applied to chemical synthesis based wastewater.

Boroski at al.[115] employed electrocoagulation (EC) followed by heterogeneous photocatalysis (TiO_2) and obtained removal efficiency of 86% COD and 90% turbidity; initial removal with EC is 70% which is enhanced to 76% by the use of UV/H_2O_2. Combination works best for wastewater with high concentrations of refractory/nonbiodegradable chemicals. Sreekanth et al.[70] investigated a hybrid up-flow anaerobic sludge blanket reactor for wastewater having the following: TDS, 8500−9000 mg/L; TSS, 2800−3000 mg/L; COD, 13000−15000 mg/L; BOD, 7000−7500 mg/L with a BOD:COD ratio of 0.45−0.6. Such wastewater is highly pliable to biological oxidation. Removal efficiencies were as follows: COD, 65−75%; BOD, 80−90%. The process has a high biomass production rate thus making the process economically feasible.

4.4.2. Hybrid Technologies for Fermentation Process Wastewater. Fermentation process wastewaters mainly consist of fermentation broth, mycelia, and the nutrients which are added for the cell cultivation. Also, there are some organic solvents which are added for recovery of the API of interest. Helmig et al.[50] treated API formulation waste comprised of estrogens with a hybrid treatment technology comprised of pretreatment ozonation and the aerobic treatment, i.e., membrane bioreactor technology. More than 90% COD and TSS removal was obtained. And the MBR led to complete treatment of the wastewater.

Cokgor et al.[94] studied the penicillin formulation waste comprised of wash water. They used ozonation (pretreatment) coupled with biological activated sludge treatment by synthetic biomass with 30% COD. Ozonation removed 34% COD and 24% TOC, and then the water showed efficient COD removal with enhanced biodegradability using activated sludge. Penicillin formulation effluents sometimes have pollutants such as tylosin which have refractory action on biological processes and thus use of a hybrid process leads to complete removal. Tylosin and avilamycin containing wastewater were treated by a hybrid up-flow anaerobic stage reactor by

Chelliapan and Sallis.[65] For avilamycin macrolide and tylosin antibiotic waste stream, UASR can be used commendably as an option for pretreatment with a COD reduction of 70−75%; thus in anaerobic conditions tylosin can be degraded effectively. Tekin et al.[52] studied the manufacturing process and wash waters containing traces of organic compounds, iodine, and metal salts with 900−6800 mg/L COD and 85−3600 mg/L BOD. They coupled an AOP with biological treatment to tackle this type of wastewater. The Fenton oxidation (pretreatment) coagulation stage followed by aerobic biological degradation in sequencing batch reactor gave 45−50% COD removal and the biological treatment reduced the COD to 98%.

5. RECOMMENDATIONS AND FUTURE TECHNOLOGIES

The accelerating progress of novel pharmaceutical products is being added exponentially to the already existing vast number of chemical compounds that are introduced to the environment. As mentioned previously, the pharmaceutical waste stream is of a diverse nature and thus treatment of the wastewater is to be achieved for benign disposal of it into the environment. Reduction of the waste stream at the source along with recycling of the water or reclamation of some part of this waste is among the desirable options. Nanofiltration is a very important operation to recover more than 80% of the complex waste stream or single products, and it can impart quality better than the quality of feedwater with high operational efficiency and product safety. It can be used to recover valuable single products from mother liquors which could be reused or further processed. This is a process intensification strategy which permits increased production capacity without exceeding water discharge limits, drastically reducing raw water requirements and waste disposal costs. The waste stream can be further used by other waste-treatment technologies. Membrane processes will be effective to produce clean water in the pharmaceutical industry based on the molecular size of the contaminant such as bacteria particles (microfiltration), macromolecules and viruses (ultrafiltration), divalent ions (nanofiltration), and monovalent ions (reverse osmosis). In some cases, in situ Fenton chemistry as given by the group of Bhattacharyya[99,120] will be of immense potential and needs further work.

On-site reduction can be achieved by deeply understanding the process and analysis of the stages in the process and identifying the pollutants to be released. By deep understanding of this a recovery technology such as membranes can be applied at the source of pollutant generation, the recovered material can be utilized, and the concentrate can be treated with other treatment technologies for safe disposal. In this way a considerable value addition can be provided to the waste generated, thus making the process economical.

Recovering and recycling in pharmaceutical wastewater implies removal of impurities from the waste stream and obtaining relatively pure substances for reuse or secondary purposes. The strict quality control requirements of the pharmaceutical industry often restrict reuse opportunities. Recycling can either be done on-site or off-site. An alternative to recycling of recovered products is waste exchange, which involves the transfer of a waste to another company for use as is or for reuse after treatment.

6. CONCLUSION

Pharmaceutical manufacturers must operate under strict regulations by food and drug agencies in different countries and ought to maintain acceptable water quality standards for use, discharge, or reuse elsewhere in the plant. Huge quantities of ultrapure water are required with regulatory requirements on the limit or even presence of specific waste contaminants. There can also be volume limits on water discharged into municipalities or other waste streams.

Pharmaceuticals reach the environment primarily through usage and inappropriate disposal from the manufacturing units. Various production facilities are found to be the source of pharmaceuticals in the environment out of which chemical synthesis process and fermentation process wastewaters constitute the bulk of it. These plants generate a large amount of waste during manufacturing, purification, cleaning, washing, and maintenance.

Several reports have been produced on the treatment of pharmaceutical compounds and endocrine disrupting chemicals in recent decades. Most of the treatment technologies deal with the treatment of wastewaters from chemical and fermentation processes. Use of hybrid technologies has been made for the treatment of certain compounds which are not completely eradicated by the single-stage treatment. The use of hybrid technologies mainly removes the pollutant almost completely or within safe discharge limits. The most common treatment technology applied to both the wastewater streams is a pretreatment stage comprising of the advanced oxidation processes which is mainly to remove recalcitrant/refractory compounds which are sometimes nonbiodegradable. Then the waste having enhanced biodegradability thus can be treated effectively by the biological treatment methods. Out of the two biological treatment methods of aerobic and anaerobic, a membrane bioreactor provides a promising solution. Also, anaerobic reactors are employed on a wide scale as the byproduct, i.e., biogas from the process, can be economically used, along with the treated sludge, by the agriculture industry.

As it can be seen, most of the technologies mentioned are "removal" technologies; emphasis has been laid on recovery technology. Many researchers have been trying to implement recovery options to recover important and valuable reagents, byproducts, and solvents which can be reused thereon. Extensive analysis on the characteristics of the system to understand its benefits or limitations from an individual and global perspective, and thus leading to overall economic consideration, should be taken into account rather than just publications on the problem. More emphasis should be made on recovery and reuse of the pharmaceutical wastewaters.

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Notes

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