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Evaluating toxicological effects, pollution control and wastewater management in pharmaceutical industry

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A B S T R A C T

Pharmaceutical industry represents a range of industries with operation and processes as diverse as its product. Hence effluents coming from pharma industries vary from industry to industry. Thus it is almost impossible to describe a typical pharmaceutical effluent because of such diversity. Waste water is generally evaluated in terms of temp, pH, Total suspended solid (TSS), BOD, COD, Oil & grease, chlorides and sulphates. This paper reviews various treatment methods for treating pharmaceutical waste water. These methods are broadly categorized into physico-chemical, biological and advanced oxidation processes. The paper also discusses briefly about waste generation in pharmaceutical industries.

Introduction

The pharmaceutical industry manufactures biological products. medicinal chemicals, botanical products, and the pharmaceutical products covered by Standard Industrial Classification Code Numbers 2831, 2833 and 2834. As well as other commodities, The industry is characterized by a diversity of products. Processes, plant sizes. As well as wastewater quantity and quality in fact, the pharmaceutical industry represents a range of industries with operations and processes as diverse as its products. Hence, it is almost impossible to describe a "typical" pharmaceutical effluent because of such diversity. Industrialization in the last few decades has given rise to the discharge of liquid. solid. and gaseous emissions into natural systems and consequent degradation of the environment Mehta, G. et al., (1995). This in turn has led to an increase in various kinds of diseases, which has necessitated the production of a wide array of pharmaceuticals in many countries. Wastewater treatment and disposal problems have also increased as a result.

In pharmaceutical industries wastewater is mainly generated through the washing activities of the equipment. Though the wastewater discharged is small in volume. is highly polluted because of presence of substantial amounts of organic pollutants. Solid waste usually comprises of expired or rejected medicines. spent solvents. packaging material and damaged bottles. Level of wastewater pollution varies from industry to industry depending on the type of process and the size of the industry Kavitha, V and Palanivelu, K. (2004).

During the manufacturing process of drugs. varied effluents and contaminants are produced such as organics. debris. dirt. grit. pollution. toxic. non toxic materials. polymers etc. Characterization of wastewater was evaluated in terms of temperature. pH. total suspended solids (TSS). total dissolved solids (TDS). Biochemical oxygen demand (BOD). Chemical oxygen demand (COD). oil & grease. chlorides & sulphates for the influent & effluent from the selected plants Kavitha, V and Palanivelu, K. (2004).

Waste generation

The pharmaceutical manufacturing industry produces a wide range of products to be used as human and animal medications. Manufacturing can be characterized by five main processes; fermentation. extraction. chemical synthesis. formulation and packaging. Each of these steps may generate air emissions. liquid effluents and solid wastes Chelliapan, S and Sallis, J,P. (2011).

I) Gaseous Emissions

Emissions from pharmaceutical industries include gases like Sulphur dioxide hydrogen chloride from the process stacks. Solvent vapours of acetone. chloroform. and toluene are also emitted from the extraction stage of basic drugs.

Particulate emissions are predominant in the material handling section and formulation units when the product is in the form of dry powder.

II) Liquid

The water consumption in pharmaceutical industry depends on process of manufacture. the nature of products. raw materials used and purification process of the final product (Bhatia S.C. Environmental pollution and control) Liquid effluents resulting from equipment cleaning after batch operation contain toxic organic residues. Their composition varies. depending on the product manufactured. the materials used in the process. and other process details. Typically. pharmaceutical wastewater is characterized by high COD concentration. and some pharmaceutical wastewaters can have COD as high as 80.000 mg/L.

III) Solids

Solid wastes are generated from various processing units in the industry. These include spent fermentation media. extracted tissue from animals. extracted bark material from plants. residues from distillation. and packing materials made of cardboard. plastic. glass and metal (Bhatia S.C. Environmental pollution and control). A General flow diagrams for the treatment of wastewaters from various types of pharmaceutical products are presented in the following Fig 1. (Bhatia S.C. Environmental pollution and control).

Treatment methods

The presence of Pharmaceuticals and personal care products (PPCPs) was first identified in surface and wastewaters in the United States and Europe in 1960s Deegan, M.A et al., (2011). A study showed that

organic wastewater contaminants. including PPCPs. were present in 80 % of 139 U.S. streams Kolpin, D H et al., (2002). Although the concentration levels of PPCPs found in the environment are at trace concentrations. their chemical persistence. microbial resistance and synergistic effects are still unknown. Which is a cause for concern. Moreover. low concentrations can elicit adverse effects on aquatic life Miège, C et al., (2008).

The pharmaceutical industry employs a wide array of wastewater treatment and disposal methods . Wastes generated from these industries vary not only in composition but also in magnitude (volume) by plant. season. and even time. depending on the raw materials and the processes used in manufacturing of various pharmaceuticals. 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 Gupta. S K et al., (2006). Various treatment methods employed for treating pharmaceutical waste fall into one of the following category:

I) Physico-Chemical Treatment Method

II) Biological Tretment Method

III) Advanced Oxidation Process(AOP)

I) Physio-chemical treatment options

These technologies include membrane separation. chemical removal. activated carbon. chlorination. and other novel approaches. The efficiency of these methods for the treatment of pharmaceutical wastewater varies significantly and is described below Deegan, M.A et al., (2011).

a) Membrane processes

Several membrane types and applications were evaluated for the removal of APIs at pilot and fullscale. including microfiltration. ultra filtration. nanofiltration. reverse osmosis. electro dialysis reversal. membrane bioreactors and combinations of membranes in series Bellona, C et al., (2004). Snyder, S et al., (2007).Microfiltration and ultra filtration are generally not fully effective in removing organic contaminants as pore sizes vary from 100-1000 times larger than the micro pollutants which can slip through the membranes. The pressure-driven membrane processes Nanofiltration (NF) and Reverse osmosis (RO) have been the focus of attention of many researchers for the treatment of drinking water Watkinson, A et al., (2007). However, the studies on the use of RO/NF for pharmaceutical removal is limited and most of the studies employed NF and RO membranes for tertiary treatment in wastewater recycling plant or for treating saline groundwater. Snyder, S et al., (2007). Nghiem, L et al., (2005). Yoon. Y et al., (2006). RO in different configurations showed efficient removal of thirty-six personal care products and endocrine disrupting chemicals including antibiotics. lipid regulators. hormones and oral contraceptives. antiepileptics and analgesics Snyder, S et al., (2007).. Yoon, Y et al., (2006).

Pharmaceuticals can be rejected on NF and RO membranes by one or a combination of three basic mechanisms: size exclusion (sieving. steric effect). charge exclusion (electrical) and physico-chemical interactions between solute. solvent and membrane. In laboratory-scale cross-flow tests with NF-90 membranes rejections of

ketoprofen and diclofenac were reported to be greater than 90% (3 .53). In another study with RO membranes the retention of negatively charged diclofenac was 95 % (26). Some studies reported higher removal efficiencies of polar and charged compounds in NF/RO processes due to interactions with membrane surfaces Bellona, C et al., (2004). Amy, G et al., (2005).

c) Chlorination

Chlorination has been shown to be effective for the removal of pharmaceuticals including 17α- ethinylestradiol and 17 β-estradiol Alum, A et al., (2004). and sulfonamides Qiang, Z et al., (2006). Chlorine dioxide is also effective for the removal of sulfamethoxazole. roxithromycin. 17α-ethinylestradiol and diclofenac [26], Chlorination and ozonation when compared for the removal of bisphenol A. 17β- estradiol. and 17α-ethinylestradiol and byproduct estrogenicity from distilled water showed comparable results with ozonation resulting in 75-99 % removal Alum, A et al., (2004). Residual chlorine and ozone was found to be low with > 99 % loss of the parent compound Gharbani, P et al., (2010).

Lee and Von Gunten (2009)[38] achieved 90 % conversion of estrogen. 17α-Ethinylestradiol with chlorine and increased the rate of 17β-Ethinylestradiol transformation by a factor of 3 with the addition of 0.25 mm Br-. The accelerating effect of Br- diminishes in the presence of dissolved organic matter as it consumes bromine faster than estrogens Flores, A and Hill, E. (2008). Acetaminophen. diclofenac. sulfamethoxazole and fluoroquinlone all become oxidised during chlorination. By-products of acetaminophen include the toxic byproducts *N*-acetyl-*p*-benzoquinine imine and 1.4-benzoquinone. Both metoprolol and sulfamethoxazole form carcinogens such as chloramines as one of their oxidation products and this may be due to the fact that ammonia chlorination was about one thousand times faster than phenol chlorination Pinkston, K and Sedlak, D. (2004).

II) Biological Treatment Methods

The biological treatment of pharmaceutical wastewater includes both aerobic and anaerobic treatment systems. Aerobic treatment systems have traditionally been employed. including the activated sludge process. extended aeration activated sludge process. activated sludge process with granular activated carbon. or natural or genetically engineered microorganisms and aerobic fixed growth system. such as trickling filters and rotating biological contactors. Anaerobic treatment includes membrane reactors. continuously stirred tank reactors (anaerobic digestion). upflow filters (anaerobic filters). fluidized bed reactors. and upflow anaerobic sludge blanket reactors. Anaerobic hybrid reactors. which are a combination of suspended growth and attached growth systems. have recently become popular. Pharmaceutical/fine chemical wastewater presents difficult substrates for biological treatment due to their varying content of a wide range of organic chemicals. both natural and xenobiotic. which may not be readily metabolized by the microbial associations present in the bioreactors. Various processes dealing with the biological treatment of pharmaceutical wastewater are summarized in subsequent sections Gupta, S K et al., (2006).

a) Activated Sludge Process

Conventional activated sludge with a long hydraulic retention time (HRT) has

historically been the method of choice for the treatment of pharmaceutical industry wastewater Deegan, M.A et al., (2011), Oz, N et al., (2004) It has a lower capital cost than more advanced treatment methods and a limited operational requirement; it is generally more environmentally friendly than chlorination. However. high energy consumption. the production of large amounts of sludge Sreekanth, D et al., (2009)and operational problems including colour. foaming and bulking in secondary clarifiers are associated with activated sludge plants (41). Factors which affect the efficiency of activated sludge facilities for the treatment of pharmaceutical wastewater include HRT. temperature. pH. dissolved oxygen (DO). organic load. microbial community. presence of toxic or recalcitrant substances and the batch operation of pharmaceutical production facilities Deegan, M.A et al., (2011). These variables require modification for adaptation to pharmaceutical industry wastewater.

Temperature is a key factor in the efficiency of activated sludge facilities. It has an important role in selecting individual microbial species and overall microbial diversity in the activated sludge. This is where industrial wastewater can be very different from municipal wastewater. COD removal and examination of 16hr RNA of the bacterial community in aerobic biological systems at 5 °C intervals between 30 and 70 °C showed that high temperatures were limiting factors to COD removal La Para, T et al., (2001b).The number of bacterial species decline with temperature between 30-60 °C. with the activated sludge process failing at temperatures above 60-65 °C La Para, T et al., (2001a). A two stage operation at 55 °C followed by 30 °C produced a lower quality effluent than operation at 30 °C alone. Therefore, water from high temperature processes must be cooled prior to treatment by AS. which increases the time and cost of treatment.

c) Extended Aeration

The performance of the ASP has been found to be more efficient when operating on an extended aeration basis. The design parameters of the process were evaluated for the treatment of combined wastewater from a pharmaceutical and chemical company in North Cairo that produced drugs. diuretics. laboratory chemicals. and so on El-Gohary, F, A et al., (1995). The study revealed that at an extended aeration period of 20 hours. COD and BOD removal efficiency ranges of 89–95% and 88–98%. respectively. can be achieved. The COD and BOD values of the treated effluent were found to be 74 mg/L and 43 mg/L. respectively. In contrast. the performance of an extended aeration system for the treatment of pharmaceutical wastewater at Lincoln. Nebraska. was poor. At an organic loading of 30 kg BOD/day and a detention period of 25 hours. the percentage BOD reduction ranged from 30 to 70%. The degree of treatment provided was quite variable and insufficient to produce a satisfactory effluent. The pilot plant study performed at various feeding rates of 1.5. 2.4. 3.0. 3.6. and 4.8 L/12 hours indicated that at feeding rate of 4.8 L/12 hours. the sludge volume index was 645 and suspended solids were being carried over in the effluent Gupta, S K et al., (2006).

d) Trickling Filter

The performance of a trickling filter has been studied by many researchers [50] and it was found that a high-rate trickling filter was capable of treating wastewater containing diversified fine chemicals and pharmaceutical intermediates to a level of effluent BOD less than 100 mg/L. A similar conclusion was made in the performance

study of a trickling filter for the treatment of wastewater from chemical and pharmaceutical units Gupta, S K et al., (2006).It has also been reported that wastewater from a pharmaceutical plant manufacturing antibiotics. vitamins. and sulfa drugs can be treated by using a trickling filter . One study evaluated the efficiency of a sand bed filter for the treatment of acidic waste streams from a synthetic organic pharmaceutical plant at Hyderabad. The acidic waste stream was neutralized to a pH of 7.0 and treated separately through a sand bed filter. The sand bed filter was efficient in treating the acidic waste stream to a level proposed for its discharge to municipal sewer Gupta, S K et al., (2006).

The efficiency of the biological filter (trickling filter) for treatment of combined wastewater from a pharmaceutical and chemical company in North Cairo has been evaluated. The treatment system consisted of a biological filter followed by sedimentation. The degree of treatment was found quite variable. The COD and BOD removal efficiencies of the trickling filter at an average OLR (organic loading rate) of 26.8 g BOD/m2 day were found to be 43–88% and 58–87%. respectively. The study revealed that a biological filter alone was unable to produce effluents to a level complying with the national standards regulating wastewater disposal into the surface water El-Gohary, F, A et al., (1995).

III) Advanced oxidation processes

AOPs 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. Over the past 30 years. research and development concerning AOPs has been immense particularly for two reasons. namely (a) the diversity of technologies involved and (b) the areas of potential application. Key AOPs include heterogeneous and homogeneous photocatalysis based on near ultraviolet (UV) or solar visible irradiation. electrolysis. ozonation. the Fenton's reagent. ultrasound and wet air oxidation. while less conventional but evolving processes include ionizing radiation. microwaves. pulsed plasma and the ferrate reagent. Although water and wastewater treatment is by far the most common area for research and development. AOPs have also found applications as diverse as groundwater treatment. soil remediation. municipalwastewater sludge conditioning. production of ultrapure water and volatile organic compounds treatment and odor control.

a) Photolysis

It involves the interaction of artificial or natural light with the target molecule and the induction of photochemical reactions which can lead to its direct degradation to intermediate products whose further decomposition eventually yields mineral end-products Doll, T, E and Frimmel, F, H. (2007), Saritha, P et al., (2007). UV treatment (and in particular UVC irradiation) has traditionally been employed for the disinfection of drinking water with the advantage. compared to chlorination. of minimizing the formation of any regulated disinfection by-products Pereira, V, J et al., (2007). However. recent studies Bartels, P and Tumpling, W. (2007), Canonica S et al., (2008) have been undertaken in order to understand the aquatic photochemistry of pharmaceutical compounds which still remains a largely unexplored field. The efficiency of direct photolysis is usually enhanced when irradiation is combined with

hydrogen peroxide. a strong oxidant whose photolytic dissociation yields hydroxyl radicals. thus facilitating the degradation process.

The beneficial role of hydrogen peroxidepromoted photolysis (also referred to as indirect photolysis) has been demonstrated in recent studies Pereira, V, J et al., (2007b), Pereira, V, J et al., (2007). where bench scale experiments with artificial light were performed. The efficiency of photolytic degradation depends on several factors such as the absorbance spectrum of the pharmaceutical. the quantum yield of photolysis. the concentration of hydrogen peroxide employed and the water matrix. The latter appears to play an important role as the presence of natural organic matter (NOM) in waters may induce radicals scavenging. thus decreasing degradation Pereira, V, J et al., (2007b), Pereira, V, J et al., (2007). Nonetheless. it has been reported Doll, T, E and Frimmel, F, H. (2007). That NOM acts as a precursor of reactive species (i.e. superoxide anion. hydroxyl radicals etc) and so its presence leads to a faster degradation due to the production of photochemically induced reactive species.

b) Ozonation

Ozone has been applied to the treatment of waters primarily due to its strong disinfection and sterilization properties Araña, J et al., (2002).The main mode of action in the ozonation process is the formation of OH- radicals due to ozone decay in the water. but there are also ozone molecules present for chemical attack. This increases the oxidation capacity Ozonation has been implemented as the principle treatment method or to enhance the biodegradability and efficiency of subsequent treatment Cokgor. E et al., (2006).

Ozone production is an energy intensive process. making it costly to implement. An ozone treatment system may increase the energy demand over a conventional wastewater treatment plant by 40-50 %. The use of ozone as a means of breaking down pharmaceuticals in water has been the subject of numerous studies over the last ten years including However the reported removal rate for lipid regulators is less at about 50 % and about 60-80 % for β-blockers and below 50 % for some Antiphlogistics although the degree of removal and mineralization of pharmaceuticals in water or synthetic industrial effluent has been reported. little or no literature exists on the ozonation of pharmaceuticals in actual pharmaceutical wastewater Cokgor, E et al., (2006).

d) Fenton oxidation

Homogeneous oxidation with the Fenton reagent occurs in the presence of ferrous or ferric ions with hydrogen peroxide via a free radical chain reactionwhich produces hydroxyl radicals. It is considered to be a metal-catalyzed oxidation reaction. in which iron acts as the catalyst Tekin, H et al., (2006), Saritha, P et al., (2007). Ultraviolet light enhances the generation of free radicals by the photo reduction of Fe (III) to Fe (II). Since iron is abundant and non-toxic. Fenton reactions are a viable option for wastewater treatment. Photo- Fenton reactions have been used for the degradation of diclofenac Ravina, M et al., (2002). Pérez-Estrada, L et al., (2005b). Complete mineralisation of diclofenac and its intermediates via photo-Fenton reactions in a concentric photo reactor took approximately 50 min Pérez-Estrada, L et al., (2005b). Compound parabolic collectors have also been used to

mineralise diclofenac in approximately 60 min. Another advantage of Fenton reactions is that mineralisation is possible in sunlight avoiding the use of UV light Pérez-Estrada, L et al., (2005a). Fenton (Fe^{2+}/ H_2O_2) and Fenton-like ($Fe^{3+/}H_2O_2$) reactions were compared for both dark and photo-assisted reactions [6]. Penicillin was completely removed after 40 min of advanced oxidation with Fe^{2+}/ H_2O_2at pH 3. Higher COD and Total organic carbon (TOC) removals were obtained with dark $Fe^{2+/}H_2O_2$at pH 3 compared with dark Fenton-like $Fe^{3+/}H_2O_2$. Arslan-Alaton. I, Dogruel. S. (2004). Photo-assisted reactions using UV-C provided only slightly higher removal efficiencies. TOC removal was higher with photo-Fenton reaction and COD removal was slightly higher with photo-Fenton-like reactions.

Since Fenton reactions operate at room temperature normal pressure and without the highly complicated apparatus. there should be a smooth transition from laboratory scale to large scale Kavitha, V and Palanivelu, K. (2004). On the other hand. the strong dependence on the aqueous solution pH (optimum pH 2-4 for the production of OH. radicals) and on the concentrations of hydrogen peroxide and ferric / ferrous ions and the disposal of the iron sludge are factors which need to be taken into consideration Shemer, H et al., (2006). One possibility is the partial use of Fenton reactions to produce a non-toxic and biodegradable intermediate which could then be treated in an inexpensive biological step to achieve complete mineralisation Munoz, I et al., (2006).

e) TiO_2 photocatalysis

Photocatalysis is the acceleration of a photochemical transformation by the action of a catalyst such as TiO2 or Fenton's reagent Chatterjee, D and Dasgupta, S. (2005, Dalrymple, O et al., (2007). Most photocatalysts are semiconductor metal oxides which characteristically possess a narrow band gap. Radicals formed degrade impurities in the water relatively unselectively. reacting with impurities in the wastewater as well as the target pharmaceuticals Lhomme, L et al., (2008). Since the degradation of chlorobipenyls and biphenyls from aqueous media using TiO_2 photocatalysis was first reported Deegan, M.A et al., (2011). the number of publications on the removal of micropollutants from aqueous media using TiO_2 has grown considerably Deegan, M.A et al., (2011). Pérez-Estrada, L et al., (2005a). Titania is the most widely investigated of the heterogeneous photocatalyst due to its cost effectiveness. iner t nature and photostability Gaya. U, Abdullah. A. (2008). Investigations into the removal of the pharmaceuticals using TiO_2. include but are not limited to work on antibiotics. lipid regulators. x-ray contrast media. antiepileptics and antiphlogistics Deegan, M.A et al., (2011). Pérez-Estrada, L et al., (2005a). Removal rates have been reported at 98 % for antibiotics when used in combination with UV. Addamo. M et al., (2005).

However. removal rates for carbamazepine are under 10 % . TiO_2 is available at a relatively modest price and would be recyclable in an industrial application when fixed on films or beads. reducing the quantities of TiO_2 required . Furthermore. solar studies have proved effective for a wide range of pharmaceuticals replacing the expense of generating UV light. There are difficulties in implementation on a commercial scale due to the number of operating parameters e.g. type and geometry of reactor. the photocatalyst. optimum energy use and wavelength of radiation. Moreover. it is difficult to assess the true

success of the photocatalytic process in the absence of identified intermediate compounds and end Deegan, M.A et al., (2011).

Conclusions

The occurrence and fate of pharmaceuticals in the environment, and in aquatic media in particular, have received considerable attention by the scientific community during the last two decades. There are various conventional treatment processes available for treating pharmaceuticals in waste water. In addition There are a number of promising new treatments including AOPs such as oxidation, ozonation, perozonation, direct photolysis, TiO_2 photocatalysis, solar photocatalysis, Fenton reactions and ultrasonic irradiation. These significantly enhance the removal rate of pharmaceuticals from wastewaters. Comparisons among these technologies are problematic since most researchers used synthetic water rather than actual wastewater samples. Research is required in this area to improve treatment efficiencies, identify degradation compounds and to determine the cost and feasibility of full-scale applications.

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