METHODS OF PURIFICATION OF WASTE WATERS OF PHARMACEUTICAL ENTERPRISES

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Abstract. The process of the pharmaceutical industry include is the manufacturing, extraction, supply, alteration, processing, purification, and packaging, release and storage of chemical and biological materials, as solids, semi-solids and liquids to be used as drugs for humans and animals. Waste waters in the pharmaceutical and biotechnology industries usually originate from the synthesis, fermentation and formulation operations of the drugs. Most of the APIs, FDF and drug excipients which distributed worldwide are manufactured by chemical synthesis using organic, inorganic, and biological reactions. In most times the reactors and separators which are used in a large scale product pharmaceutical industry are not designed with the demanded capacity although it is oversized but less efficient. The quantity of wastewaters that produced is frequently increased. There are a number of processes occurring in a pharmaceutical industry, and it is difficult to characterize each and every product waste. Many classifications based on raw materials, final products, and herbal plants. The classification is depend on the basis of the chemical processes and treatments as well as certain classes of products. Based on the processes involved in manufacturing, pharmaceutical industries can be divided into five categories: (1) fermentation of plants; (2) synthesized organic chemicals plants; (3) fermentation, synthesized organic chemicals plants (generally moderate to large herbal plants); (4) natural, biological product extractions (antibiotics/vitamins/enzymes, etc.); (5) drug milling and mixing, compounding, formulation, and preparation plants (tablets, capsules, and syrups, drops, etc.) Keywords: waste water, pharmaceutical manufacturing, treatment process, chemical synthesis, environment standards.

Pharmaceutical manufacturing process.

Chemical substances synthesis processes use organic and inorganic chemicals in several operations to produce drugs with unique physical and pharmacological properties. A diagram of the chemical synthesis process is shown in Figure 2. Mainly, a series of chemical reactions are processing in multipurpose reactors. The products are isolated by using different separation processes such as liquid–liquid extraction, solid–liquid extraction, crystallization, and filtration. The final product is then dried, milled, and mixed then processing to the formulation unit. The chemical synthesis process becomes complex with a multiple steps process of bulk chemicals, intermediates and the finished byproducts. Because of this many steps, the atoms in chemical synthesis are generating a lot of waste toxic materials and energy. From the process of the reactors, there are heat exchangers equipment and process of pressure vessels, bulk chemical supplies and temperature and other processes continuously operating. The product usually in the mother liquor is transferred by vessels and temporary or permanent pipelines pressured by pump gas or vacuum and this leading to a widespread use of raw water at every step. Very rarely, the process of water is used to minimize impurities except in a few cases where the filtrate could be 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 produced due to many operations and reactions taking place in the reactors at different stages. Almost every stage produces mother liquor that contains unsoluble reactants, products, coproducts, byproducts, and residual products in the organic solvent base. Acids, bases, halides, nitrates, sulfates, cyanides, and metals may be released. Usually, the solvent recovery process leads to small portions of solvents wastewaters after evaporation stage. Wastewaters which produced at the purification stage of solvents, finished products, cleaning water, and spillage. All This precipitation has a high hazards of toxicity level for workers and people health and it requires immediate treatment. 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.
Synthetic organic chemical drug production process can be summarized as shown in Figure 1, which shows the production of oxyphenonium bromide with different waste water sewers resulting from the process.

**Table 2. Summary of Wastewater Treatment Technologies and Cost Comparison**

| treatment method | treatment capacity | capital cost ($/KLD) | O & M ($/KLD/year) | reuse of treated wastewater |
|------------------|--------------------|----------------------|-------------------|---------------------------|
| DWWT* | pretreatment | 1000 KLD | $100–$120 | $15–$25 | horticultural biomass generation |
| soil biotechnology | pretreatment | 5 KLD to tons of MLD | $100–$200 | $15–$25 | horticultural cooling system |
| bioaerobic/anaerobic | biocatalytic; breaking the toxic/organic contents | 100 mg KLD | chip cost only excluding construction cost | not available | in situ treatment of water bodies, horticultural |
| soil scale | fermentation | 1–250 KLD | $300–$500 | $50–$150 | horticulture |
| biogas technology | biogasification (use of microorganisms); for CO2, removal treatments, and increased O2 in water | 1 kg treats up to ML | $40–$50/MLD | not available | horticultural composting |
| bioremediation | biodegradation of organic matter using Pseudomonas 713 (biological product) | 1 Billion CFU/ml | $200–$500/MLD | $4–$9 | in situ treatment of water bodies |
| green biogas technology | fermentation | 80–200 KLD/m³ | $84–$88 | $1 | in situ treatment of water bodies |

*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. **DWWT = decentralised wastewater treatment. *Cost of the technologies for lakes and water bodies remediation have been indicated in per MLD per year.

**Figure 1.**

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

| chemical synthesis | fermentation | natural product extraction |
|-------------------|-------------|---------------------------|
| antibiotics; antimetabolites; cardiovascular agents; central nervous system (CNS) stimulants; CNS depressants; hormones; vitamins | antibiotics; antineoplastic agents; therapeutic nutrients; vitamins; steroids | antineoplastic agents (doxorubicin, dexamethasone, melphalan, mitomycin); enzymes and digestive aids; CNS depressants; hematological agents; insulin; vaccines |

**Fermentation Process.**

Fermentation is a biochemical process involving the use of microorganisms and microbiological technologies e.g. yeast, lactic acid and bacillus to produce a desired chemical product. Fermentation process involves several basic steps: seed inoculum and preparation, fermentation, and product recovery and isolation. Inoculum preparation is done with necessary conditions and the required microorganism, and then the whole mixture is exposed to warm steam sterilization. Activated by nutrients, inorganic salts, waters and other materials are added to the fermentation tank. Cells cultured in agar plates under controlled conditions. 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, adsorption and addition of disinfectants such as phenols. The fermentation process generates a large amount of solid waste such as spent aqueous fermentation broth and dead cell waste. Fermented batches may be become infected by a viral attack of microorganisms which can create environmental problems by producing large amounts of waste broth. The waste broth has a large quantity of raw materials such as nutrients, metal salts, starches, nitrates, and phosphates with high COD, BOD, and TSS with pH values ranging from 4 to 8. Small amounts of industrial chemicals (phenols, detergents, and disinfectants) maintain the sterility in the process plant during fermentation and also can be added to the aqueous waste waters. A considerable amount 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 then aqueous waste waters which having organic solvents is produced. An example of the fermentation process in the pharmaceutical industry is antibiotic production of penicillin. The process gives a clear outline of the wastewater streams that produced and how to apply the recovery and the treatment technologies in case of the generation of wastewater.

**Natural and Biological Extraction Process.**

Large amounts of natural (plant and animal) materials are processed to extract the active pharmaceutical ingredient from the drug. In each step, a large volume of water sources is required and the product recovery process reduced until the final product is reached. Solvents are used on a large scale to remove the lipophilic molecules and insoluble fats which can be obtained the final product. The pH adjustment of the extract and waste product can be by the use of amounts of strong acids and bases. Also, metal ions are used for precipitation and phenolic compounds are used for disinfection leading to further treatment problems. The final product is low. Hexane is used as solvent for natural product or herbal extraction, which is released into the air and the water. These days processes based on carbon dioxide...
(scCO2) are developed to contain organic impurities in the final product as well as to reduce effluent. Spent raw materials and solvents, wash waters, and spillages 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 generate wastewaters including solvents. Usually, wastewaters have low BOD, COD, and TSS, with relatively neutral pH values ranging from 6 to 8.

Compounding/Formulation Process.
The Drug products that obtained from the previous three operations that mentioned before are compounded to produce drug usable forms such as tablets, ointments, syrups, and other dosage forms. The process uses many several steps such as milling, mixing, grinding, granulating, drying, compression, sterilization and packaging. Many types of fillers, binders, flavoring agents, preservatives, and antioxidants, buffering agents are used during the compounding process. The herbal plant is common used in all drug manufacturing processes. Use hygienic conditions are required during the manufacturing process e. g prompted use of steam sterilization and phenolic compounds.

After the production, APIs produced by batch processes in shape of dosage forms and this part is carried out in a separate procedure of mixing, compounding and formulations processes of active ingredient substances., various methods such as fillers additions, dilutions, bindings, and tablets, capsules formations machines are involved. Also, many operations like grindings, filtrations, washings, dryings, encapsulations, and finally packaging are common to produce the final formula of drugs. All of this previous steps leading to the resulted waste waters in the pharmaceutical industry.

These manufacturing processes may be formed as batch, continuous, or in a combination depending on the quantity of production and the value of the product. Antibiotics, steroids, and vitamins are produced by fermentation process. Many of common pharmaceutical forms are produced by chemical synthesis process. Many drugs were derived from natural materials, but due to low recovery and cost efficiency this process is rarely observed.

Water Consumption in Pharmaceutical Manufacturing Process.
A wide variety of products are made in the chemical and pharmaceutical manufacturing industries, typically requiring large volumes of chemicals, materials, and substances that are used throughout process operations. Waste streams which discharged from these industries can be heavily loaded with contaminants, toxins, nutrients, and organics. water consumption methods in chemical and fermentation manufacturing process. It can be seen that approximately 50% of the water input is carried out as waste. Also, deep analysis of the water balance shows that the fermentation process consumes more water as compared to the chemical synthetic methods. the need to process methods of manufacturing and reuse of water is mandatory. There is scope for water reuse by usage of modern treatment technologies at the areas of generations of wastewaters rather than treatment at the effluent treatment plant (ETP) and disposal areas (Fig. 3).

**Fig. 3.** water balance and ratio of consumption for chemical manufacturing process of plant producing paracetamol (ratio of consumption of water to total water =0.5).
Solvent: solvents are used as a vehicle in hundreds of the pharmaceutical manufacturing products e.g. Isopropyl alcohol to dissolve oils, gaseous, resins, solids, or viscous reactants, products, and impurities. They are used active substances in the chemical synthesis process to dissolve reactants in a homogeneous phase at elevated temperature under pressure. Some solvents are also used to control the reaction of temperature. Usually some small amounts of solvents may remain in the final product or released during the manufacture of pharmaceutical products e.g. the reaction, extraction, crystallization and purification of solvents. These may include benzene, phenol, toluene, halogenated solvents, and cyanide. Although US EPA (Environmental protection agency) had restrictions on use of some solvents because of their high toxicity e.g. Volatile organic compounds and chlorinated solvents, but this contaminated solvents are still used by the pharmaceutical industry since the relevant drugs cannot be manufactured by using other kind of less contaminated solvents; for example methylene chloride (Fig. 4.). The major solvents that used in industry are methanol, ethanol, isopropanol, acetone, and ethylene glycol. Also, many heteroaromatics such as pyridine or piperidine they are used in chemical reaction process.

Many pharmaceutical industries have made recovery systems for their solvents this can be done by many operations of purification of contaminated solvents and their impurities consisting of distillation columns and solvent–solvent evaporation systems and filtration. In this systems a second solvent may be used to separate the impurities. 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 was exported for recovery or disposal.

Treatment of pharmaceutical wastewater.

The pharmaceutical industry plays big role of wastewater treatment and its disposal methods. Wastewaters which discharged from these manufacturing process are variable not only in composition but also in quantity, by plant, seasons and times, depending on the raw materials and which process of pharmaceutical manufacturing are used. Plant location is also related to the quality of available water. It is very difficult to use specific treatment system with in those wide scale of manufacturing of pharmaceutical industry. Many alternative treatment processes are available to deal with the wide range of wastes which produced from this industries but they are specified to the type of manufacturing and its associated wastes. However, the analysis showed that there is six general approaches are employed to treat pharmaceutical wastewaters: (1) recovery of individual APIs or drugs which are likely to be present in wash waters and solvents, (2) physical–chemical treatment by sedimentation or floatation, (3) aerobic/anaerobic biological treatment in membrane bioreactors or bioaeration, (4) inactivation of active substances by UV oxidation in conjunction with O3 or H2O2, (5) sterilization and decontamination of infectious and bioactive substances from biotechnology, and (6) new hybrid technologies specific to the pharmaceutical industries.

| Chemicals | Priority pollutant under the Clean Water Act | Chemicals | Priority pollutant under the Clean Water Act |
|-----------|---------------------------------------------|-----------|---------------------------------------------|
| Acetone   | Ethylene glycol                            | Isopropanol | Isopropyl alcohol |
| Acetonitrile | Formamide                          | N-Pentane | N-Pentane |
| Acetic acid | Acetic acid                          | Acetone | Acetone |
| Acrylonitrile | Acrylonitrile                      | Benzene | Benzene |
| Acrylic | Acrylic acid                          | Butane | Butane |
| Acetic acid | Acetic acid                          | Isobutyraldehyde | Isobutyraldehyde |
| Acrylonitrile | Acrylonitrile                      | Isopropyl alcohol | Isopropyl alcohol |
| Acetyl | Acetyl chloride                      | Methanol | Methanol |
| Acrylonitrile | Acrylonitrile                      | Methyl amine | Methyl amine |
| Acetic acid | Acetic acid                          | Methyl cellosol | Methyl cellosol |
| Acrylonitrile | Acrylonitrile                      | Methylene chloride | Methylene chloride |
| Acrylic | Acrylic acid                          | Methyl isobutyl ketone | Methyl isobutyl ketone |
| Acrylic | Acrylic acid                          | N-Methylpyridine | N-Methylpyridine |
| Acrylic | Acrylic acid                          | Phenol | Phenol |
| Acrylic | Acrylic acid                          | Pentane | Pentane |
| Acrylic | Acrylic acid                          | PEG-600 | PEG-600 |
| Acrylic | Acrylic acid                          | n-Propanol | n-Propanol |
| Acrylic | Acrylic acid                          | Pyridine | Pyridine |
| Acrylic | Acrylic acid                          | Tetrahydrofuran | Tetrahydrofuran |
| Acrylic | Acrylic acid                          | Toluene | Toluene |
| Acrylic | Acrylic acid                          | Triethylamine | Triethylamine |
| Acrylic | Acrylic acid                          | Xylene | Xylene |

Fig. 4.
Conclusions. Pharmaceutical industries must work under restrictions of FDA in different countries and able to standardized the quality of water. There is must be volume limits of waste water discharged from industries. Also large amount of waters need in case of presence waste pollutions. pharmaceutical manufacturing waste waters causing contaminated environment through chemical synthesis and fermentation process. Plants generate large amounts of wastes during purification, maintenance and cleaning systems. Use hybrid technology for treatment of waste water not completely remove wastes by single stage treatment. Oxidation process is more effective in biological treatment methods of aerobic and anaerobic.

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