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Value-added Waste Potential of Wastewater Sludge from Pharmaceutical Industry: A Review

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Wastewater treatment (WWT) plant treating pharmaceutical processing water produces sludge that may contain residue of the pharmaceutical products. This residue, known as Active Pharmaceutical Ingredient (API) is known to show ecotoxicity to the environment. The sludge potential to be utilised as value added products or to be used as raw material for other processes is explored in this review. Currently there is lack of studies on the content of pharmaceutical WWT (pWWT) sludge and its added value usage, partly due to vast varieties of pharmaceutical products, each utilising different process with different removal success in WWT and different effect on bacterial growth. Residue API from pharmaceutical manufacturing is known to be sorbed on the surface of the sludge. Cross comparison using limited sources of studies of bacterial composition in pWWT with municipal WWT (mWWT) shows that there are similarities between the bacterial compositions and thus sludge composition since sludge from biological WWT is constituted mainly of microorganism and Extracellular Polymer Substance (EPS). Studies on pWWT sludge composting shows usability of the sludge for agriculture purpose, but with concern over the sorbed API content causing ecotoxicity on the soil. Converting pWWT to energy using gasification and biodiesel production and construction material are the most promising value-added usage for the sludge.

1. Introduction

Pharmaceutical products are used in large amount in modern day society. The use ranges from diagnostic and treatment to prevention of illness and disease in human and animal. Manufacturing of pharmaceutical products by pharmaceutical industries is usually performed through direct chemical synthesis, fermentation process or natural product extraction (Jimenez-Gonzalez et al., 2011). Chemical synthesis route involves building up pharmaceutical compound by adding up blocks of molecules using purely chemical processes. Example of products made using this route is certain antibiotics, hormones, vitamins, cardiovascular agents, stimulants and anti-depressants. Fermentation route on the other hand involves cultivation of microorganism that may have been genetically modified to produce the desired product. The pharmaceutical product will then be extracted from the broth or from the microorganism using chemical and physical extraction. Examples of products manufactured using this route are antibiotics, vitamins and steroid. The last route is through natural product extraction where compound such as enzyme and vaccine are extracted from the source itself. Pharmaceutical production process is usually performed in batches using multiple steps to attain the final desired compound, sometime involving up to 30 steps (Schaber et al., 2011). Manufacturing of pharmaceutical products in pharmaceutical industry is associated with accompanying large amount of waste. Pharmaceutical process usually has E-value of 50 to 100 kg of waste per kg of desired product which is very high compared to other chemical industry. This high waste to product ratio is mainly attributed to multiple steps involved in the process and the use of solvent and pure water for extraction and washing up products (Gadipelly et al., 2014). The solvent and water used are mostly ended up as waste water and are treated before being discharge in the

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environment at Wastewater Treatment Plant (WWTP). The wastewater usually contains high number of organic contaminants and API that can adversely affect the environment.

Treatments of wastewater from pharmaceutical process may be done by biological process, physical/chemical process or filtration. The commonly used process, the biological process is the process of using microorganism to digest the contaminants. Similar to all biological wastewater treatment, production of high volume of sludge occurs in pharmaceutical wastewater treatment and this incurs more cost in the operation of the treatment. The sludge is usually dewatered and disposed as scheduled waste, landfill or incinerated depending on the local regulation. The sludge however is known to comprise mainly of biological material and may have potential for further utilisation. This paper reviews the potential of utilising sludge from biological processing used in treatment of pharmaceutical as value added products or to be used as raw material for other processes.

2. Pharmaceutical wastewater treatment

Pharmaceutical wastewaters contents vary depending on the type of process used and the products produced. The wastewater contains mixtures of solvents, unreacted raw materials, side products and other intermediates in the processing (Gadipelly et al., 2014). Due to the complexity of the mixtures, operation of wastewater treatment in industrial and pilot plant scale in most cases resort to reporting the content of the wastewater in the sump amount reflected as Chemical Oxygen Demand (COD), Biological Oxygen Demand (BOD_5), Total Organic Carbon (TOC), Total Kjehdal NItrogen (TKN), ammoniacal Nitrogen (NH_3-N), Total Dissolved Solids (TDS) and pH as shown in Table 1.

Table 1: Summary of the composition of pharmaceutical wastewater

Composition	Values								Min - Max
COD, mg/L	200 - 1,000	240	188,108	13,093	7,000 - 12,000	415 - 843	12,000	7,000	200 - 18,8108
BOD, mg/L	50 - 300	23.4	n/a	0	5,000 - 7,000	0 - 51	n/a	3,500	0 - 7,000
BOD/COD	0.25 - 0.3	0.01	n/a	n/a	0.58 - 0.71	0 - 0.06	n/a	0.5	0 - 0.71
TDS, mg/L	500 - 1,300	2,460	n/a	n/a	n/a	n/a	n/a	n/a	500 - 13,000
pH	n/a	7.8	11	5.6 8.3	- 2.6 - 5.2	6.8 - 7.8	8.5	5.2 6.8	- 2.6 - 11
TOC, mg/L	n/a	n/a	46,000	n/a	n/a	n/a	1,600	n/a	1,600 - 46,000
TKN, mg/L	n/a	n/a	n/a	n/a	n/a	n/a	n/a	364	0 - 364
NO_3, mg/L	5 - 10	n/a	n/a	n/a	n/a	n/a	n/a	n/a	5 - 10
PO_4, mg/L	10 - 20	n/a	3,000	n/a	n/a	n/a	n/a	n/a	10 - 3,000
NH_3N, mg/L	n/a	13.5	n/a	650.02	n/a	123 - 257	n/a	n/a	13.5 - 650.2
P, mg/L	n/a	13.8	30,000	n/a	n/a	n/a	n/a	n/a	13.8 - 30,000
References	a	b	c	d	e	f	g	h	

a- Farhadi et al. (2012); b- Wei et al. (2010); c- Wang et al. (2012); d- Chen (2011); e- Zheng (2011); f- Tang et al. (2011); g- Domínguez (2012); h-Chelliapan et al. (2011)

Further parameter is calculated as BOD_5 to COD ratio, reflecting the amount of organic content digestible by microorganism compared to the number of contaminants oxidisable. The ratio shows the degree of treatment difficulty using biological process to treat the water.

As summarised in Table 1 the wastewater from pharmaceutical process contain very high COD and BOD value up to tens of thousands mg/L COD and thousands mg/L BOD with low BOD/COD ratio of from 0.1 to 0.6, considered as difficult for treatment. The wastewater also contains nitrogenous nutrient in TKN and NH_3-N that need to be removed and pH requiring adjustment.

To remove the high COD and BOD content, biological process is still the mostly found used method. Biological treatment is commonly divided into two types which are aerobic and anaerobic processes. Aerobic treatments is usually done using Conventional Activated Sludge process (CAS), trickling filter (TF) and Membrane Bio Reactor (MBR) (Deegan et al., 2011). The CAS is operated by growing up microorganism in tanks to digest the organic material in the wastewater into microorganism cellular material and carbon dioxide gas (CO_2). The microorganism material will form floc and settle down to bottom and removed as sludge. MBR use the same principle except that the sludge and water is separated using membrane. Anaerobic treatment treats the wastewater by growing microorganism in oxygen depleted condition, performed in reactor commonly called

Anaerobic Digester (AD). The microorganism in AD utilises the waste to build up cellular material producing CO_2 gas and methane (CH_4) in the process. The cellular material together with untreated contaminant will later be removed as sludge (Christensen et al., 2015). Physical-chemical processes are also used to treat pharmaceutical wastewater, performed by reacting the contaminants with chemicals.

This may be done by using Fenton or Fenton-like process to oxidise the contaminants using oxygen radicals. Some facility are reported to use the Fenton/Fenton like process with many study done in lab and pilot scale on utilising this physical/chemical process for treatment (Farhadi et al., 2012)

The properties that make pharmaceutical WWTP different from municipal and sewage WWTP is the presence of API from the manufacturing processes. API are substances that are biologically active and can cause toxicity, be it ecotoxicity or phytotoxicity when they are disposed to the environment. The API such as antibiotics classes are designed to treat bacterial related disease in human or animal, thus adversely affect the growth of bacteria that are used in biological WWT processes. The key target of pWWT is not only to remove the regular contaminants such as COD and BOD_5, but also to remove API from wastewater.

Studies on API in WWT from pharmaceutical industry and mWWT found that transformation (oxidised or turned to sludge) of API depends heavily on the API. For example studies using CAS, MBR and Fixed Bed reactor found that API such as ibuprofen has a very high removal rate of 90 % while naproxen is only removed from 50 to 80 % and no removal at all for carbamazepine (Joss et al., 2005) Studies also indicated that for API that is not able to be transformed, it can stick to the sludge through sorption and remain on the sludge (Sathyamoorthy and Ramsburg, 2013). Due to this effect, sludge from pharmaceutical WWTP also contains API raising concern over toxicity to environment.

Apart from the pharmaceutical industry, pharmaceutical products are also detected in municipal wastewater and treated as municipal wastewater. The municipal WWTP traditionally operates using biological treatment process similar to pharmaceutical WWTP. Certain drugs frequently used in residential area such as painkiller paracetamol and ibuprophen are detected in high amount in municipal wastewater and is processed using CAS where the success of treatment in removing API varies from API to API (Mohapatra et al., 2014).

3. Composition of sludge from biological pWWT

Sludge composition from WWT varies depending on the types of processes and types of wastewater treated. Sludge from biological treatment are mainly composed of microorganism (filamentous bacteria, single or colony), organic fiber, inorganic material (salt or sand) and extracellular polymeric substance (EPS). The EPS are macromolecules that are negatively or neutrally charged protein made of humic-like substances, polysaccharides, nucleic acid or lipids. EPS are one of main constituent as it constitutes almost 50 % of dry mass of the sludge (Christensen et al., 2015). Since EPS made up major component of the sludge, identifying the source of EPS in sludge is crucial in determining the characteristics of the sludge and hence its potential use. Studies done by Bala Subramanian (2010) on EPS producing bacteria from mWWT found that major bacteria producing EPS consists of pseudomonas, bacillus, yersinia, microbacterium, serratia, and enterobacter. Rani et al. (2008) found that in multivitamin and protein hydrolase pWWT, the bacterial strain found in the treatment are from strain of Alcaligenes, Bacillus, Agrobacterium, Brevibacterium, Micrococcus, Microbacterium, Paracoccus and Rhodococcus. The similarities of species notably mycobacterium and bacillus between the two WWT indicates that pharmaceutical and municipal WWTP using aerobic processes harness few similar bacterial community in their process and these bacteria produce EPS, the main constituent in WWT sludge. Kraigher et al. (2008) studied on sludge from small scale WWT using activated sludge treating wastewater containing ibuprofen, naproxen, ketoprofen, diclofenac and clofibric found that main bacterial communities in the WWT are proteobacteria, which are predominantly Betaproteobacteria. In this group bacterial species of Thauera, Sphaerotilus, Ideonella and Acidovorax related species and nitrite-oxidising bacteria of the genus Nitrospira are notably presences in large proportion. Other class of preteobacteria also exist such as alphaproteobacteria, gammapreteobacteria and deltapreteobacteria of which all of these bacteria are also reported to be present in mWWT activated sludge by Ye and Zhang (2013) and Ju and Zhang (2015). Other than that Kraigher et al. (2008) also found a phylum of bacteria called Chloroflexi to be presences in large quantity. Chloroflexi is a class of filamentous bacteria that forms the bulk of the sludge. Based on the comparison above on the type of bacteria presences between municipal and pWWT and the utilisation of biological process in the treatment of both wastewater, the content of the sludge of pharmaceutical and municipal wastewater may be concluded to be constituted of the same composition. This is due to the fact that sludge from biological treatment is usually composed of growth of microorganism, organic fiber and EPS. Currently there are many value added usage of sludge from municipal wastewater and this may be benefited to be implemented on pharmaceutical wastewater.

4. Added value use of pWWT sludge and waste

There is currently little documentation on the added value usage of sludge from pharmaceutical industry wastewater treatment. Similar to the anaerobic treatment sludge in municipal/sewage WWT plant, few documentations exist in investigating the use of pWWT sludge as compost intended for soil fertiliser are shown in Table 2.

Table 2: Sludge and anaerobic digestate potential as compost

Source	Sludge source	Remark
Cucina et al. (2018)	Anaerobic treatment of pharmaceutical (daptomycin)WWT	Compost from sludge contain high amount of plant macronutrient (N,P,K), low heavy metal and low pharmaceutical residue
Fornes et al. (2014)	Pharmaceutical process	Composting of toxic polyphenol and fatty-proteinaceous containing waste did not cause abnormal growth in alfalfa plant.
Barrera-Díaz et al. (2011)	Erythromycin production waste (include activated sludge waste)	PWWT sludge can have effect on soil but minimal
Martín et al. (2012)	MWWT	Some pharmaceutical compound detected in compost from WWT sludge but concentration too low to cause ecotoxicological problem.

Cucina et al. (2018) investigated WWT sludge from daptomycin production to be used as compost for fertiliser and found that even though the sludge and anaerobic digestate themself show phytotoxicity, the compost derived from the sludge did not exhibit the same property. The compost contains high amount of plant macronutrient (N, P, K), low heavy metal and low pharmaceutical residue. Fornes et al. (2014) investigated the composting of waste containing toxic polyphenol and fatty-protein from pharmaceutical industry found that normal growth in alfalfa plant is observed upon treatment with the compost with no sign of toxicity.

Toxicity concern about the API that sorbed on the sludge the soil may arise due to the composting action. Barrera-Díaz et al. (2011) in their investigation on erythromycin (antibiotic) production waste (include activated sludge waste) disposed on soil found that the bacterial viability is low at the soil but limited to certain depth. Martín et al. (2012) on investigation of presence of API in compost of sludge from mWWT on the other hand found that although the API is detected in the final compost, the composting process greatly reduced the concentration of the API from the sludge and anaerobic digestate. This reduction made the ecotoxicity of the API in the compost to be nearly undetectable, making composting promising method on transforming the sludge and anaerobic digestate to other valuable product.

5. Other potential of added value use of pWWT sludge

Since toxicity of the API may cause concern on environmental and safety, the use of sludge in other area that did not share this concern need to be explored. Currently municipal/sewage WWT sludge potential as value added product is widely explored as shown in Table 3 and due to the similar characteristics of sludge, pWWT sludge may share these same potentials.

Table 3: Potential use of pWWT sludge based on municipal/sewage sludge

Source	Usage	Source of sludge
Li et al. (2013)	Compost	Sewage WWT sludge
Hossain et al. (2011)	Biochar for plant	Biological treatment of mWWT
Akkache et al. (2016)	Co-gasification	Aerobic and Anaerobic Biological treatment of mWWT
Nipattummakul et al. (2010)	Gasification	Sludge from sewage WWT
Zhang et al. (2014)	Biodiesel (microbial)	Biological treatment of Municipal & paper industry sludge
Barrera-Díaz et al. (2011)	Concrete mix	Biological process
Martinez (2012)	Clay mix (bricks)	Wastewater Biological treatment of sewage water
Wu et al. (2011)	Ceramic for biological aerobic filter WWT	As of mWWT
Pastore et al. (2013)	Biodiesel	As of mWWT (extraction/recovery)
Siddiquee and Rohani (2011)	Biodiesel	As of mWWT (extraction/recovery)
Mustapha et al. (2017)	Lipid for biodiesel	Sewage sludge (extraction/recovery)

6. Resources Recovery

Apart from the usage of sludge for other value, nutrient or elements in pWWT may be extracted directly for recovery. Since antibiotics often have nitrogen and phosphorus in their molecular structures, these plant macronutrients may be recovered directly. Studies in extraction of phosphorus from Fosfomycin production wastewater using wet air oxidation-phosphate crystallisation process shows promising result in achieving this recovery (Qiu et al.,2011).

7. Conclusions

There is currently lack of studies in the added value usage of pWWT sludge. This problem may also be rooted by the vast varieties of pharmaceutical products with each utilising different process with different removal success in WWT and different effect on bacterial growth. API failed to be treated in WWT is known to be sorbed on the surface of the sludge further limiting the option for sludge repurposing. Studies has been done on sludge composting shows usability of the sludge for agriculture purpose, but with concern over the sorbed API content causing ecotoxicity on the soil. There is also lack of studies regarding the content and composition of the pWWT sludge. Cross comparison using limited sources of studies of bacterial composition in pWWT with mWWT shows that there are similarities between the two bacterial compositions. Since sludge from biological WWT is constituted of microorganism and EPS, similar microorganism or bacterial communities between pharmaceutical and mWWT sludge shows that the sludge content is actually the same and hence may be repurpose using the same method. Usage of municipal and sewage sludge for purpose that did not risk ecotoxicity in the field of energy production such as gasification and biodiesel production and construction field provide potential for pWWT sludge to be repurposed for the same use. Converting pWWT to energy using gasification and biodiesel production and construction material are hence the most promising value-added usage for the sludge.

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