Poll Res. 39 (November Suppl. Issue) : S182-S185 (2020)

ISSN 0257–8050

PHARMACEUTICAL POLLUTION: A GRAVE CONCERN!!

MUKTA SHARMA[1], SHAGUFTA JABIN[1] AND MANOJ SHARMA[2]

[1]Department of Chemistry, Faculty of Engineering and Technology, Manav Rachna International Institute of Research & Studies, Faridabad, Haryana, India
[2]Global Drug Safety Department, Win Medicare Pvt. Ltd. 1311, Modi Tower, 98 Nehru Place, New Delhi, India

(Received 1 May, 2020; accepted 24 June, 2020)

ABSTRACT

Since the advent of human life the chemicals in the form of drugs and pharmaceuticals have been the life line. The advancements over centuries have led to discovery of pharmaceuticals from various sources like chemicals and from nature (plant, sea, animals). The innovation in screening methods introduces thousands of chemical entities for pharmaceutical use on daily basis. This has exponentially increased the presence of chemicals in the environment and have posed a concern across the globe. Humans, animals and plants are the major contagion. The metabolic profile of the pharmaceuticals has shown that many chemicals get disseminated and eliminated from the body in the unchanged form. These get continuously discharged in the ecosystem at high percentage. Some of the pharmaceuticals have long elimination half-life. Due to this, these get accumulated and get detected on reaching active levels. Eco toxicological studies have shown that there is an incomplete elimination of pharmaceuticals at sewage treatment plant. This has led to detection of varying concentration (high to low level) of drug chemicals in the environment. Due to the pollution of pharmaceuticals there is a pharmacological effect on microorganisms. Resistance get developed in bacteria and other microorganisms

KEY WORDS: Pharmaceuticals, Pollution, Chemicals, Ecotoxicology, Human health

INTRODUCTION

A pharmaceutical medicinal product, also known as a drug, medication or medicine is usually defined as any chemical substance proposed to be used in the treatment, diagnosis, cure, or in the prophylaxis of disease. Pharmaceuticals comprise of active pharmaceutical ingredients with a number of other recipients which are also chemical in nature. Pharmaceutically active compounds are produced and used in very large volumes. A survey by Quintiles (2016) has estimated that by 2021 global pharmaceutical market will reach nearly USD 1,485 billion. Globally there are approximately more than 14000 pharmaceuticals for human use and more than 3000 pharmaceuticals for veterinary use. The main contagion that poses risk to the environment is the active pharmaceutical ingredient. Studies on the human health risk assessment and on overall ecosystem have given rise the emergence of global issue due to the presence of these chemicals into the pharmaceuticals and personal care products. Modern research work in the corrosion sciences has also made use of potentially efficacious and trustworthy corrosion inhibitor(s) derived from various sources including but not limiting to pharmaceutical preparations such as drugs. The studies conducted by Mutiyar *et al.* (2018) and Sharma and Singh, 2011 has further explored these corrosion inhibitors to corroborate these aspects . In various studies, conducted by Kümmerer, (2009); Touraud *et al.* (2011) and Cesen *et al.* (2015) the residues from medicinal products of different categories for example anti-cancer, anti-inflammatory, antibiotics, hormones, antidepressants etc. have been detected in soil, surface water, groundwater, air, and in sewage (wastewater) at concentrations ranging from sub-ng/L levels to µg/L. Recently pharmacovigilance legislations across the globe have become more

focused on the issue of pollution of pharmaceuticals in the ecosystem and its adverse impact on the human and veterinary health. This has also leaded to the introduction of new branch of pharmacovigilance, i.e. Ecopharmacovigilance. The present review identifies the concern related to the risk associated with the pharmaceutical product to the entire ecosystem.

Life Cycle of a Medicinal Product

An active pharmaceutical ingredient after being discovered has to undergo various stages that constitute the life cycle for a pharmaceutical product. These stages are:

1. Research and Development: The active pharmaceutical ingredients are screened using different techniques of high throughput screening and other methods. Preclinical studies are conducted on the identified potential candidate (drug molecule) who include pharmacodynamics and dose derivation studies. Clinical Studies are conducted involving various phases of clinical trials. The drugs with positive benefit risk profile are manufactured and marketed based on the regulatory approvals and stipulated conditions associated with such approvals.
2. Consumption of Drugs: Drugs are prescribed in the indications or in the off label use for prevention, nutritional, diagnosis or prophylaxis. Although consumption of medicines for human use differ between countries but there is an average consumption of 15 grams of APIs per capita per year at global levelas assessed in Knappe project (2008). As compared to human use veterinary medicinal products are used in smaller quantities as these are widely used in farming for therapeutic and metaphylactic purposes (Kools *et al.*, 2008).
3. Pharmaceutical waste management: The waste from pharmaceutical products as reported by Castenson (2008) include unused human or veterinary medicinal products, other contaminated materials including packaging materials and other form of liquids that get produced at the time of administration and manufacturing. In one of the project, Start Project (2006) a global amount of 5700 tonnes /year of unused medicinal products was assessed.

Entry of Pharmaceutical product in the Environment

The original pharmaceutical substances and their residues, for example, metabolites, Active Pharmaceutical Ingredients and other transformed products get discharged in the environment during their life cycle as these can be released through leakages during manufacturing (Holm *et al.,* 1995 and Halling –Sorensen *et al.,* 1998).

Drugs get metabolized after administration in the body and generally get excreted as parent compounds and metabolites. These excretory products get emitted in the sewage system.In a case study conducted by Jabin *et al.* (2020) it was reported that through sewage effluent, the compounds get released in the surface waters or enter terrestrial systems. This had been reported earlier by Shore *et al.* (1993) that hormones,for example estrogen compounds are found in significant concentrations in sewage. Further in a study conducted by Fick *et al.,* (2009) it has been reported that the disposal of unused medicines also contribute to the presence of pharmaceutical compounds to the environment.

Environmental Hazard of Pharmaceuticals

The environmental hazards of pharmaceuticals are the ecotoxicological effects. These toxic effects may be acute and chronic which may further lead to carcinogenicity, mutagenicity, genotoxicity, hormonal interference, interference with immune system (pharmacological effects) and resistance development of micro-organisms. The studies conducted on the extensive use of antibiotics have shown that up to 95% of antibiotic compounds can be released unaltered into the sewage system. This phenomenon may be a cause of the accelerated resistance of bacterial pathogens to antibiotics (Qin *et al.,* 2006; Van den Bogaard *et al.*, 2001; Wegner, 2003). Antibiotics at high concentration alters structure of microbial community and affect food chain. The studies have shown that antibiotics, for example Erythromycin, Sulfamethoxazole, Trimethoprim, get effluxed into the water and become resistant to antibiotics. On exposure to low doses of antibiotics, the bacteria develop tolerance for same drugs. Subsequently few antibiotics become in effective when humans get infected with these drug-resistant bacteria. This poses a grave concern as approximately 14,000 death have been reported annually because of antibiotic resistance (Reckhow, 2007).

Green *et al.* (2004) reported that the pharmaceutical exposure leads to drastic ecotoxicological effect. For example, in Indian

subcontinent a decline of vulture populations due to ecotoxicological effect of Diclofenac poisioning is the most important case study. The vulture birds got exposed to diclofenac after feeding on carcasses of cattles previously treated with Diclofenac and then died of renal failure. The effect of Ethinylestradiol (EE2) a contraceptive which alters the reproduction exposed populations of fish is another example of ecotoxicological effects of pharmaceuticals as studied by Kidd *et al*. (2007). In another study, Porsbring *et al.* (2009) and Brosche, Backhaus (2010) reportedthe effect on communities of algae at picomolar concentration of anti-mycotic agent Clotrimazole and the effects of various antibiotics on environmental bacteria and algae; the effect of Oxazepam (a Benzodiazepine anxiolytic drug) on planktivorous fish was studied by Brodin *et al.,* (2017); and the effects of the parasiticide Ivermectin on dung faunawas studied by Jean –Pierre *et al.,* (1993). In Sweden, the pharmaceutical surface water concentrations were measured and evaluated. A comparison was made by Fick *et al.* (2011) to study critical environmental concentrations expected to elicit a pharmacological effect in fish. The observation in the samples showed that five medicinal products are expected to cause a pharmacological response in fish exposed to these waters.

Prevention of pollution from Pharmaceuticals

The pharmaceutical pollution can be reduced by preventing the pharmaceutical products during manufacturing. Major pharmaceutical companies owing to their responsibility and concern towards ecosystem have implemented techniques of prevention of pollution. These techniques improve efficiency, resulting profits and minimize impact on environment. The introduction of prevention of pollution at the beginning of new drug development process is more economical, efficient, and environment friendly. A large number of pharmaceutical companies have introduced and implemented pollution prevention techniques and programs in their manufacturing facilities. Although prevention of pollution will not be a substitute for control technologies, however it is often viable and always remain a popular method for adherence to compliance requirements. For example in the tablet coating process the substitution of material (methylene chloride and other chlorinated solvents with aqueous based coating films) reduces the hazardous waste content in the air, effluent in waste streams and the cost of purchasing chemicals. Now a day's aqueous-based cleaning solutions are more popular and are used more frequently for equipment cleaning instead of solvent-based solutions.

CONCLUSION

The pharmaceutical products are ubiquitous especially in aquatic environment. The existing sewage treatment systems cannot remove them. Therefore it becomes imperative to prevent harm in the ecosystem. The pharmaceutical compounds such as endocrine disrupting compounds are known to elicit serious chronic effects even at low concentrations. Hence detection and monitoring of impact of pharmaceutical product on environment is the need of hour. Not only India but the advanced regulatory markets are also facing menace of multidrug-resistant bacterial infections. Studies on environmental impact of majority of pharmaceutical compounds have not been well studied as their disposal is not regulated. Further studies on effects of exposure to pharmaceutical compounds are valuable to determine health risk assessment and ecotoxicological risk assessment.

REFERENCES

Brodin, Tomas, Nordling, Johanna, Lagesson, Annelie, Klaminder, Jonatan, Hellström, Gustav, Christensen, Bent and Fick, Jerker, 2017. Environmental relevant levels of a benzodiazepine (oxazepam) alters important behavioral traits in a common planktivorous fish, (*Rutilus rutilus*). *Journal of Toxicology and Environmental Health, Part A.* 80: 1-8. 10.1080/15287394.2017.1352214.

Brosche, Sara, Backhaus and Thomas, 2010. Toxicity of five protein synthesis inhibiting antibiotics and their mixture to limnic bacterial communities. *Aquatic Toxicology* (Amsterdam, Netherlands). 99 : 457-465. 10.1016/j.aquatox.2010.06.008.

Castensson, 2008. Part V - Pharmaceutical Wastes. In: Kümmerer, K. (Ed.) *Pharmaceuticals in the Environment,* 489499.

Cesen, M., Kosjek, T., Laimou-Geraniou, M., Kompare, B., Sirok, B., Lambropolou, D. and Heath, E. 2015. Occurrence of cyclophosphamide and ifosfamide in aqueous environment and their removal by biological and abiotic wastewater treatment processes. *Sci Total Environ*. 527 : 465-473. doi:10.1016/j.scitotenv.2015.04.109.

Fick, J., Lindberg, R.H., Kaj, L. and Brorström-Lundén, E. 2011. Results from the Swedish *National Screening*

Programme 2010. Subreport 3. Pharmaceuticals. IVL B2014 December 2011.

Fick, J., Söderström, H., Lindberg, R.H., Phan, C., Tysklind, M. and Larsson, J.D.G. 2009. Contamination of surface, ground and drinking water from pharmaceutical production. *Environ Toxicol Chem.* 28 : 2522-2527. DOI: 10.1897/09-073.1.

Green R., Newton, I., Shultz, S., Cunningham, A., Gilbert, M., Pain, D. and Prakash, V. 2004. Diclofenac Poisoning as a Cause of Vulture Population Declines across the Indian Subcontinent. *Journal of Applied Ecology*. 41 : 793 - 800. 10.1111/j.0021-8901.2004.00954.x.

Halling-Sørensen, B., Nors Nielsen, S., Lanzky, P.F., Ingerslev, F., Holten Lu¨tzhøft, H.C. and Jørgensen, S.E. 1998. Occurrence, fate and effects of pharmaceutical substances in the environment - a review. *Chemosphere*. 36: 357-339

Holm, J.V., Rugge, K., Bjerg, P.L. and Christensen, T.H. 1995. Occurrence and distribution of pharmaceutical organic compounds in the ground water down gradient of a landfill (Grinsted Denmark). *Environ. Sci. Technol*. 29 : 1415-1420.

Jabin Shagufta, Gupta Sonal, Rajput Anupama and Mukta Sharma, 2020. Conservation and Management of Urban Lakes; A case study of Udaipur City. *Eco. Env. & Cons*. 26 (August Suppl. Issue) : S156-S159.

Jean-Pierre, Lumaret, Galante, Eduardo, Lumbreras, C., Mena, J., Bertrand, Michel, Bernal, J., Cooper, J., Kadiri, Nassera and Crowe, Deirdre, 1993. Field Effects of Ivermectin Residues on Dung Beetles. *The Journal of Applied Ecology*. 30 : 428. 10.2307/2404183.

Kidd, K., Blanchfield, P., Mills, K., Palace, V., Evans, R., Lazorchak, J. and Flick, R. 2007. Collapse of a Fish Population After Exposure to a Synthetic Estrogen. *Proceedings of the National Academy of Sciences of the United States of America.* 104. 8897-901. 10.1073/pnas.0609568104.

KNAPPE project, 2008. Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters. Final report, available at: e n v l r o n m e n t a l h e a l t h c o l l a b o r a t i v e org/images/KNAPPE_REPORT_FINAL.pdf.

Kools, S.A.E., Moltmann, J.F. and Knacker, T. 2008. Estimating the use of veterinary pharmaceuticals in the European Union. *Regulatory Toxicology and Pharmacology*. 50 : 59-65.

Kümmerer, K. 2009. The presence of pharmaceuticals in the environment due to human use: present knowledge and future challenges. *J. Environ. Manage*. 8 : 2354-2358. h t t p s : / / d o i . o r g / 1 0 . 1 0 16/j.jenvman.2009.01.023

Mutiyar, P., Gupta, S. and Mittal, A. 2018. Fate of pharmaceutical active compounds (PhACs) from River Yamuna, India: An ecotoxicological risk assessment approach. *Ecotoxicology and Environmental Safety*. 150. 297-304. 10.1016/j.ecoenv.2017.12.041.

Porsbring, Tobias, Blanck, Hans, Tjellström, Henrik, Backhaus and Thomas, 2009. Toxicity of the pharmaceutical clotrimazole to marine microalgal communities. *Aquatic Toxicology*. 91: 203-211. 10.1016/j.aquatox.2008.11.003.

Qin, X., Razia, Y. and Johnson, J.R. 2006. Ciprofloxacin-resistant Gram-negative Bacilli in the Fecal Microflora of Children. *Antimicrob Agents Chemother*. 50 (10) : 3325-3329.DOI: 10.1128/AAC.00548-06.

Quintiles IMS Institute, 2016. Outlook for Global Use of Medicines through 2021. http://www.imshealth.com/en/thought-leadership/quintilesims.

Reckhow, D. and Anastas, N.U. 2007. Investigating treatment effects on targeted endocrine disrupting compounds and pharmaceuticals in drinking water.

Sharma Mukta and Singh Gurmeet, 2011. Effect of Brij35 on mild steel corrosion in acidic medium. *IJCT*. 18 (5). http://hdl.handle.net/123456789/13029.

Shore, L.S., Gurevita, M. and Shemesh, M. 1993. Estrogen as an environmental pollutant. *Bulletin of Environmental Contamination and Toxicology.* 51 : 361-366.

START, 2006. Pharmaceuticals for Human Use: Options of Action for Reducing the Contamination of Water Bodies. Available at : http://www.start -project.de/downloads/start_Practical_Guide.pdf. [Accessed on April 2020]

Touraud, E., Roig, B., Sumpter, J. and Coetsier, C. 2011. Drug residues and endocrine disruptors in drinking water: Risk for humans?. *International Journal of Hygiene and Environmental Health*. 214. 437-41. 10.1016/j.ijheh.2011.06.003.

Van den, Bogaard, A.E., London, N., Driessen, C. and Stobberingh, E.E. 2001. Antibiotic Resistance of Faecal *Escherichia coli* in Poultry, Poultry Farmers and Poultry Slaughterers. *J Antimicrob Chemother.* 47 (6) : 763-771.DOI: 10.1093/jac/47.6.763.

Wegener, H.C. 2003. Antibiotics in Animal Feed and their Role in Resistance Development. *Curr Opin Microbiol.* 6 (5) : 439-445.