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ORIGINAL ARTICLE

Quantitative assessment of pharmaceutical drugs in a municipal wastewater and overview of associated risks

Loide Ndelimona Ndapandula Shipingana[1] · Harikaranahalli Puttaiah Shivaraju[1,2] · Shivamurthy Ravindra Yashas[1]

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Abstract

Pharmaceuticals compounds are the emerging contaminants known for their refractory and environmental persistence, which pose threat to flora and fauna. In the present study, the occurrence and possible contamination sources of four drugs, namely paracetamol, diclofenac, salbutamol and ceftriaxone in wastewater of Mysuru, India, were investigated. The said pharma compounds were analyzed in the effluent of select health care establishments and municipal wastewater treatment plant (MWWTP). The results revealed that diclofenac was omnipresent in all the samples with the peak concentration of 4.2 µg/mL, whereas salbutamol and ceftriaxone were in the range of 0.7–18.7 µg/mL and 1.25–29.15 µg/mL, respectively. In addition, paracetamol was detected only at the inlet of MWWTP with a concentration of 4.6 µg/mL. Surprisingly, the presence of relative amounts of these drugs in the treated water released from MWWTP was observed. Further, the 'risk quotient method' for ecological risk assessment was adopted to assess the magnitude of risk toward aquatic species. Next, the study employed the concept of citizen science to gather information on disposal and management methods of unused and expired medications at household and health care centers. This survey revealed that hospital discharges and community disposal of unused medicines contributed to incidence of pharmaceutical compounds in the local environment. Finally, a precise perspective and future challenge for the safe management of drugs are presented.

Keywords Pharmaceutical drugs · Paracetamol · Diclofenac · Salbutamol · Ceftriaxone · Wastewater · Municipal sewage

Introduction

Pharmaceutical drugs are a class of emerging contaminants that have raised significant concerns due to their persistence in water resources (Bu et al. 2016). They pose a threat to the ecological environment, with an inherent ability to induce physiological effects such as endocrine disruption of aquatic organisms and increased antibiotic resistance in plants and animals (Ebele et al. 2017; Yi et al. 2017). Although they are developed to promote human and animal health and wellbeing, pharmaceutical compounds and their metabolites have entered the wastewater, rivers and in drinking water to some extent (Bu et al. 2013; Craig and Ziv-Gal 2018; Shanmugam et al. 2014). Moreover, they are repetitively being introduced into the environment as complex mixtures. After administration, these molecules are absorbed, distributed, metabolized, and finally excreted as metabolites or conjugates in feces or urine (Frade et al. 2014). However, this biotransformation may increase their toxicity (Xia et al. 2005). These biologically active compounds can enter different water bodies from discharges of treated domestic and industrial effluents, as well as commercial feeding operations and surface application of manure. Alternatively, the improper disposal of unused and expired medications and drugs accounts for the discharge of pharmaceuticals into the environment (Monteiro and Boxall 2010). Figure 1 specifically elucidates the plausible routes of drugs entering the drinking/water body (Puttaiah et al. 2021).

The occurrence of pharma drugs in wastewater and the environment has been studied in numerous countries, such as the USA, Canada, China, Spain, Greece, Netherlands and South Africa, which are in a range of ng/L to µg/L (Ebele et al. 2017; Valcárcel et al. 2011; Yang et al. 2017). Though

✉ Harikaranahalli Puttaiah Shivaraju
shivarajuenvi@gmail.com

[1] Department of Environmental Sciences, JSS Academy of Higher Education and Research, Mysore, Karnataka 570015, India

[2] Center for Water, Food and Energy, GREENS Trust, Harikaranahalli Village, Dombaranahalli Post, Turuvekere Taluka, Tumkur, Karnataka, India

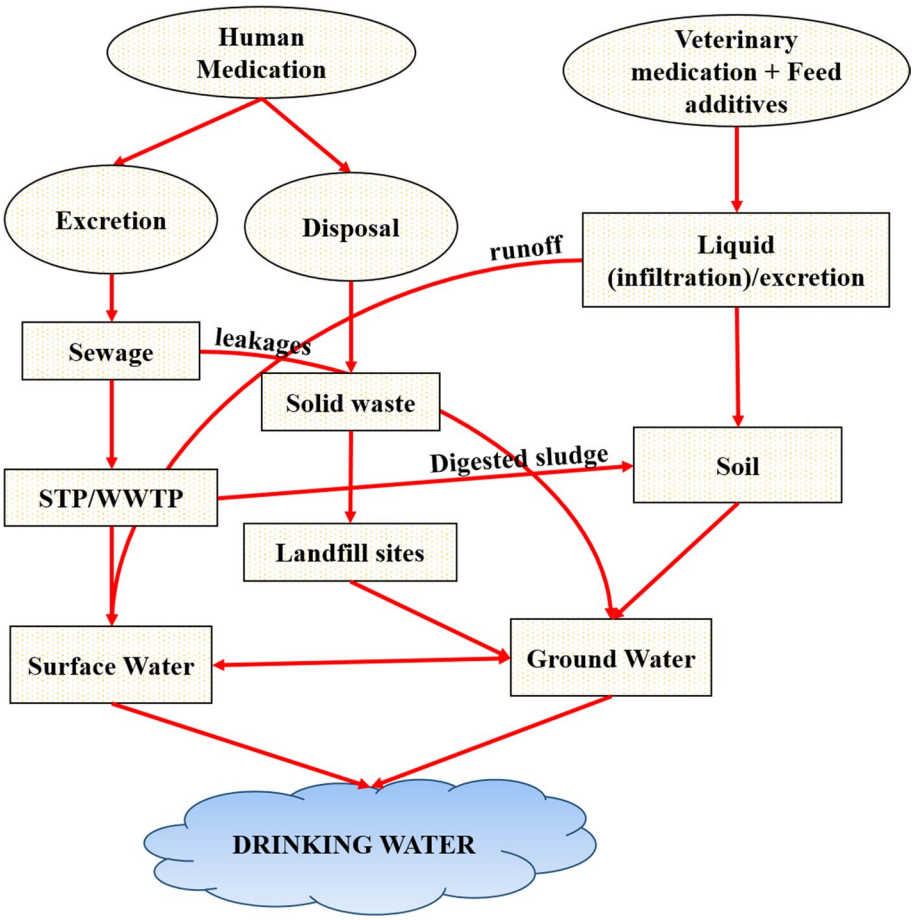

Fig. 1 Possible pathways of pharmaceuticals entering the water source (specific to study area)

these concentrations seem negligible, the long-term exposure to such low levels of multiple pharmaceuticals could be hazardous. For instance, half-life of paracetamol is around 1–3 h after a therapeutic dose (Gangishetty and Verma 2013) which would eventually enter the water cycle through urine or feces. Similarly, diclofenac has been linked to the severely reduced vulture population in India and Pakistan, and with histological changes in several organs of fish, and toxicity to algae (Kadam et al. 2016; Shanmugam et al. 2014). Some antibiotics have been reported to alter the pigmentation of *Artemia salina nauplii* or influence locomotor movements of *Daphnia magna* (Frade et al. 2014). As for personal care products, synthetic musks were detected in breast milk samples from the mothers residing in Chengdu of Southwest China (Yin et al. 2012). These scenarios can be compared to ecological disasters caused by DDT found in insecticides (Rattner 2009).

With these established detrimental effects of pharmaceutical compounds when present in water samples of the environment, the present study assessed the levels of four recurrently detected drugs, paracetamol, diclofenac, salbutamol, and ceftriaxone, in the city of Mysuru, India, which are being ubiquitously prescribed to public in the study region. In addition, results of a questionnaire survey are discussed with relevance to methods employed in the disposal of unused, leftover or expired medications by the local households. Finally, the work comprehends ecological risk through risk-quotient methods and presents the limitations in effective management of pharmaceutical drugs.

Experimental

Study area

This study focused on the third most populous region of Karnataka state and second largest city, Mysuru (12.2958° N, 76.6394° E), known as Heritage City (Pallavi et al. 2021; Sharifi et al. 2016). Mysuru City comprises five drainage districts which feed into three MWWTPs, all of which are facultative aerated lagoons with sedimentation basins (Bai et al. 2010). More than 50% of the sewage generated in Mysuru City is received by Vidyaranyapuram MWWTP (Prashanthi and Sundaram 2016). Moreover, the treated wastewater of Vidyaranyapuram MWWTP crosses the Dalavai Lake and reaches the Kabini River, the main source of drinking water of the region. The current study sought to detect the presence of paracetamol, diclofenac, salbutamol, and ceftriaxone in

wastewater of healthcare institutions and treatment plants by high-performance liquid-chromatography (HPLC) technique. The details of sample sites are tabulated in Table 1 and the respective location is presented in Fig. 2. The HPLC analysis is confined to the US, EPA method 1694 with slight modifications (Environmental Protection Agency 2007; Fisher and Lopez 2016). In addition, a descriptive cross-sectional survey was employed to assess the awareness of methods employed in the disposal of unused, leftover or expired medication.

Table 1 Details of sampling sites

Sampling site code	Location	Size of the hospital beds
1 (Taluk level hospital)	12° 18′33.912″ N 76° 17′18.456″ E	100
2 (Multispecialty hospital)	12° 29′58″ N 76° 65′59″ E	1800
3 (Taluk level hospital)	12°09′03.684 N	114
4 (Community hospital)	76° 30′58.086 E	55
5 (Primary healthcare center)	12°17′18.996″ N 76°38′32.113″ E	10–15
6 (Community hospital)	12°17′29.369″ N 76°38′44.584″ E	30
7 (Primary health care centre)	12°17′41.351″ N 76°38′44.350″ E	15–20
8 MWWTP* (inlet)	12°16′23.753″ N 76°39′16.590″ E	–
9 MWWTP* (outlet)	12°16′23.753″ N 76°39′16.590″ E	–

*Sites 8 and 9: MWWTP, capacity: 67.65 MLD, treatment: biological treatment, principal units: maturation ponds and facultative lagoons, residence time: ~ 12 and ~ 2.5 days, respectively, in facultative and maturation ponds

Sample collection

Two samples (influent and effluent) were collected from Vidyaranyapuram MWWTP inlet and outlet points. In addition, seven hospital effluents (at the outlet) were sampled based on their capacity with respect to level of hospitalization, which was determined by the number of beds. Table 1 summarizes the details of the sampling sites (hospitals). On average, each sample site was grab sampled for about 200 mL of wastewater. Samples were brought to the laboratory and stored in the freezer (at − 20 °C) until used for analysis. To know the magnitude of vital physico-chemical wastewater parameters, the sample collected at the inlet of MWWTP (location 8) and a health care effluent (location 2) was analyzed in triplicates. Table 2 presents the average values ($n = 3$) of parameters at the said locations. As observed, the values obtained are on par with the previous reports from the same study region (Singh et al. 2019).

Chemicals and reagents

Acetonitrile for HPLC, water for HPLC, potassium, dihydrogen ortho-phosphate, sodium hydroxide, Buffer pH 3.5 (0.1% trimethylamine), 1% formic acid in methanol and potassium dihydrogen phosphate buffer, as well as standards of paracetamol, diclofenac, salbutamol and ceftriaxone were procured from Sigma Aldrich, India. All the reagents were confirmed to analytical standards and consumed without further purifications.

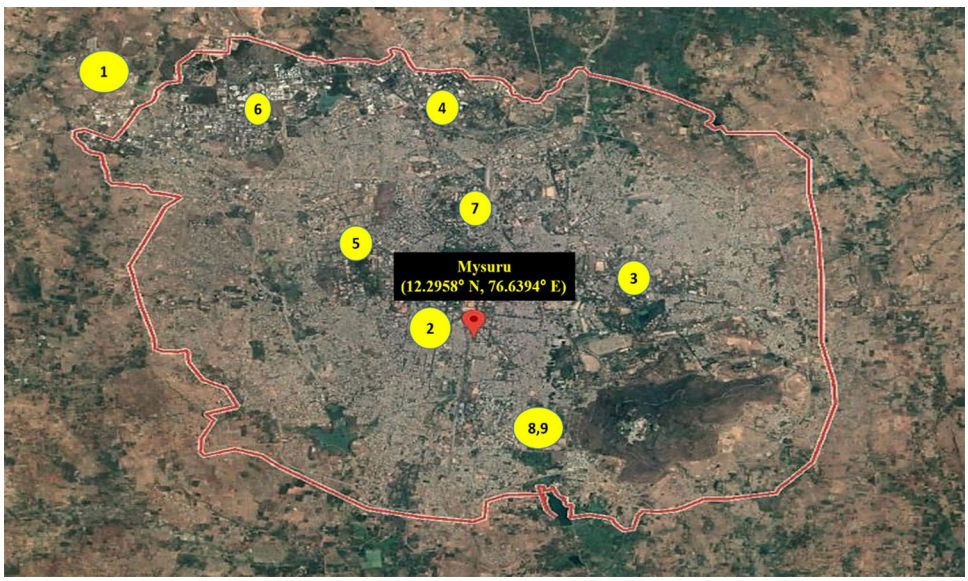

Fig. 2 Sampling sites represented on the map of study region

Table 2 Physicochemical characteristics of wastewater at location 2 and location 8

Parameter	Unit	Value	
		Location 2	Location 8
pH	–	6.5–7.5	6.8–7.6
Color	PCU	56–112	35.2–75.9
BOD_5	mg/L	410–456.2	498.6–605
COD	mg/L	830–1200	780–1300
Chlorides	mg/L	376–590	300–500
Sulfates	mg/L	28–32	25–30
Escherichia coli	CFU/mL	3.6×10^5	4.2×10^5

Location 2: multispecialty hospital of 1800 beds; Location 8: inlet of MWWTP; BOD: biochemical oxygen demand; COD: chemical oxygen demand; PCU: platinum–cobalt units

HPLC analysis

The extraction and HPLC execution were based on the guidelines from the US EPA method 539: Determination of Hormones in Drinking Water by Solid Phase Extraction (SPE) and Liquid Chromatography Electrospray Ionization Tandem Mass Spectrometry (LC–ESI–MS/MS). The chromatographic analysis was carried with AHT2010 model, HPLC (Shimadzu, Japan), equipped with an autosampler, deuterium (D2) and photodiode array detector (PDA). The Phenomenex C-18 column (250 × 4.6 mm) was used for separation. The chromatographic conditions, such as pH of mobile phase, flow-rate, and solvent ratio were optimized followed by calculation of the asymmetric factor, capacity factor, and column efficiency prior to analysis. Mobile phases for each analyte were prepared, respectively, filtered through 0.45 µm filters and sonicated for 10 min to degas. 60 mL mobile phase was added to 20 mg of each analyte working standard solution to make a 200 mg/mL concentration. Different concentrations of stock solutions of analytes were prepared as 10, 15, 20, 25 and 30 µg/mL for salbutamol; 50, 100, 150, 200, 250, and 300 µg/mL for Paracetamol; 2, 4, 6, 8, and 10 µg/mL for diclofenac; and 2, 4, 6, 8, and 10 µg/mL for ceftriaxone. Each of these solutions was chromatographed at a flow rate of 0.4 mL/min for salbutamol and 1.00 mL/min for diclofenac, ceftriaxone and paracetamol. Detection for ceftriaxone and salbutamol was both carried out at 227 nm and diclofenac and paracetamol at 276 nm and 240 nm, respectively. The injection volume was 20 µl for each sample, which was run for 10 min each at ambient temperature.

Data collection and analysis

The survey questionnaire was designed based on various literature to identify quantifiable aspects of medicine disposal in terms of demographics (age, gender, education) and disposal practices (Aditya 2013; Azad et al. 2012; Bashaar et al. 2017; Kumar et al. 2013). The respondents were also given the opportunity to offer qualitative comments based on the survey. The questionnaires were circulated in February 2019 and closed at the end of May 2019 which was responded to by 100 samples ($n=100$). The collected data was de-identified and exported into excel, on which descriptive analyses were performed.

Risk assessment

The ecological risks associated with pharmaceutical drugs were determined by risk quotient method (RQ) (Shivaraju et al. 2021). The key parameters measured were environmental concentrations (MEC) and predicted no-effect concentrations (PNEC) for each compound was adopted to arrive at respective RQs using Eq. (1) (Prescribed by European technical guide on risk assessment (EC 2003).

$$\mathrm{RQ}=\frac{\mathrm{MEC}}{\mathrm{PNEC}} \tag{1}$$

here MEC was the mean concentrations found in the water samples, whereas the $PNEC_{water}$ considered were adopted from the literature. Specifically, $PNEC_{water}$ of paracetamol was considered as 12.9 µg/L sensitive to *D. magna* (Bouissou-Schurtz et al. 2014); diclofenac was 729 ng/L sensitive to fishes (Guruge et al. 2019), Salbutamol was 4 µg/L (Patel et al. 2019) and ceftriaxone was 0.02 µg/L (Kümmerer 2003), respectively. Further, the risks were characterized as high risk (if $RQ>1$), medium risk ($0.1<RQ<1$), low risk ($0.01<RQ<0.1$) and safe ($RQ<0.01$) (Lemly 1996).

Results and discussion

Quantitative analysis of pharmaceutical compounds

The correlation coefficient of paracetamol, diclofenac, Salbutamol and ceftriaxone standards was evaluated in the range of 50–300, 2–10, 10–30 and 2–10 µg/mL, respectively. The results were found to be linear, with a regression (R^2) in a range of 0.9956 and 0.9989. More standardization results are summarized in Table 3. Based on standard retention time, peaks at time 3.7, 3.92, 5.466 and 3.012 min indicated the paracetamol, diclofenac, salbutamol, and ceftriaxone in the samples, respectively. The concentrations were then determined using the formula $y=Mx+C$, where y is the peak area and x is the concentration of the analytes in the samples. The results indicated that paracetamol was only detected in the MWWTP inlet at a concentration of 4.60 µg/mL. As for diclofenac, it was detected in all the samples, with the highest concentration recorded at 4.2 µg/mL

Table 3 Summary of calibration and standard results of HPLC analysis

Parameters	Paracetamol	Diclofenac	Salbutamol	Ceftriaxone
Mobile phase	ACN: KH_2PO_4 (50:50 v/v)	MeOH HCOOH: CAN (50:50 v/v)	TEA: CAN (60:40 v/v)	ACN: water (70:30 v/v)
Linear regression (R^2)	0.9989	0.9917	0.967	0.9956
Concentration (ug/mL)	300	10	30	1000
Retention time (min)	3.75	3.92	5.466	3.012
Peak area	19,483,721	184,851	826,503	1,561,915
Tailing factor	1.7	0.968	1.28	0.812
*Concentration equation (ug/mL)	$y=66449x-304054$	$y=18288x-6438.8$	$y=25638x-3240$	$y=34387x-10209$

*In order to determine the concentration of the four pharmaceuticals in the samples, the formula $y=mx+c$ was used, whereby x is the concentration in ug/mL

[a]CAN: acetonitrile; KH_2PO_4: potassium dihydrogen phosphate buffer; MeOH HCOOH: 1% formic acid in methanol; TEA: Triethylamine (pH 3.5, 0.1%TEA)

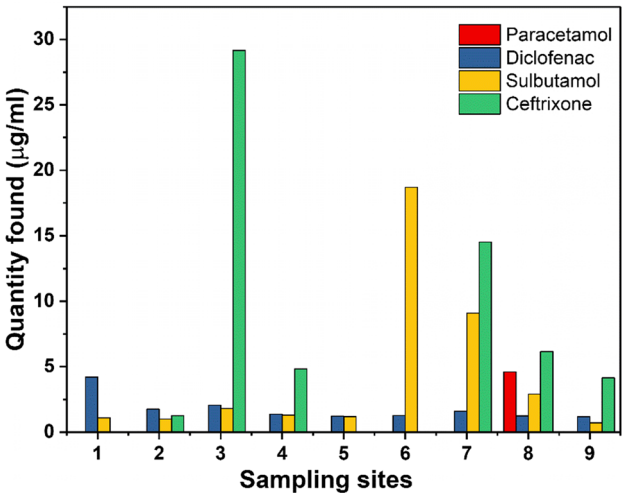

Fig. 3 Quantities of pharmaceuticals recovered from samples

in hospital effluent samples. Salbutamol was also detected in all the samples, in a range of 0.7–18.7 µg/mL. A concentration range of 1.25–29.15 µg/mL was recorded for ceftriaxone. Figure 3 summarizes the concentrations of analytes found in samples. Similar observations on the presence of these drugs were reported previously in a review by Gadipelly et al. (2014).

The above-quoted results could be very helpful to perceive the typical scenario of these drugs occurring in the effluents. The paracetamol being the cheapest drug which is readily available with or without prescription over the counter is most used by people for almost any health abnormality that comes with pain and therefore its chances of being wasted and winding up in the wastewater is very high. Interestingly, no paracetamol was detected in the effluent of the MWWTP that accounts for efficient degradation by the existing treatment systems. It is important to acknowledge the presence of other peaks in the different sample chromatograms. These peaks indicate the presence of other compounds that can be detected at the same wavelength as paracetamol but these compounds were not directly analyzed.

As for diclofenac, different concentrations were recorded for different samples. It is evident from the results that diclofenac was present in all the samples analyzed in this study. According to Qin and team, diclofenac is the most repeatedly detected compound in the water cycle (Qin et al. 2012). Some of the most significant cases of diclofenac toxicity were recorded, for example, after the rapid and enormous decline (> 95%) of oriental white-backed vultures that was triggered by residues of veterinary diclofenac in scavenged cattle remains (Bartrons and Peñuelas 2017). Just like paracetamol, a variation in concentration does not necessarily mean that diclofenac is treated for during the MWWTP processes. Rather, one should look into secondary compounds of diclofenac present in the effluents. This can also be explained by the various peaks observed in the chromatograms, but not at the required retention time.

Salbutamol was also recovered from all samples in this study, with the concentrations ranging from 0.7 (MWWTP effluent) to 18.7 µg/mL (hospital sample). Therefore, all the sampled hospitals released salbutamol into the MWWTP at different concentrations. Just like the other two parameters (paracetamol and diclofenac), a decrease in MWWTP concentration of salbutamol at influent and effluent level has been recorded, with influent at 2.9 µg/mL concentration and effluent at 0.7 µg/mL. Consequently, salbutamol is either removed during the wastewater treatment process, photodegraded or has undergone biodegradation. There is however a lack of literature on the ecotoxicity of salbutamol on mainly the aquatic organisms which are readily exposed to the contaminated water.

On the other hand, the antibiotic ceftriaxone recorded the highest concentration among the other drugs. Although ceftriaxone was not present in all the samples, it was present

in most samples, with the highest concentration recorded at 29.15 µg/mL (hospital effluents) and the lowest concentration recorded at 1.25 µg/mL (hospital effluents). Ceftriaxone, among other antibiotics such as metronidazole, norfloxacin, sulfamethoxazole, ofloxacin, ciprofloxacin, levofloxacin and tinidazole were detected in a range of 1.4–236.6 μg^{-1} in two hospital effluents in India (Diwan et al. 2009). The MWWTP influent recorded a concentration of 6.16 µg/mL and the MWWTP effluent recorded 4.15 µg/mL. Again, this directs a decrease in the concentration, which could be due to various reasons such as biodegradation, photodegradation or actual removal of ceftriaxone by the treatment plant processes.

Ecological risk assessment of pharmaceutical compounds

The ecological risks for sensitive aquatic species were carried out by risk quotient method. Table 4 presents the risk analysis data at each site. As evident from the RQ calculated, every sampling site has the highest risk to specific aquatic organism. This observation clearly indicates that the water is not safe or the contamination caused by these drugs is anticipated to cause acute or chronic ecological imbalance. This further may affect humans and animals if these toxic compounds enter freshwater sources. Though there are countable reports on direct human health implications by these pharma compounds but can gradually lead to antibiotic resistance in them. The witnessed trend in drug distribution as in this case is similar to previous reports (Zheng et al. 2020; Keerthanan et al. 2020).

Pharmaceuticals management by households

The questionnaire survey was carried out to assess the medications/drugs management at household level with maximum of 100 subjects ($n = 100$). The majority of the respondents were female (63 nos.) with broad age range, with the highest number of female respondents in the 18–25 age group (52%). Furthermore, none of the respondents were illiterate. Table 5 summarizes their demographics in detail. A majority (73%) of respondents reported storage of up to five types of medications in their households. As indicated in Fig. 4, respondents tend to store medications for cold, cough and flu the most. It is however important to note that respondents indicated storage of more prescription pain

Table 4 Risk quotients of pharmaceutical compounds in water samples (Sites 1–9)

Sampling site	Compound	Concentration found (µg/mL)	$RQ = \frac{MEC}{PNEC}$	Risk category
1	Diclofenac	4.2	5761.31	High risk (RQ > 1)
	Salbutamol	1.1	275	
2	Diclofenac	1.76	2414.26	
	Salbutamol	1.0	250.0	
	Ceftriaxone	1.25	62,500.0	
3	Diclofenac	2.07	2839.50	
	Salbutamol	1.8	450.0	
	Ceftriaxone	29.15	1,457,500.0	
4	Diclofenac	1.37	1879.28	
	Salbutamol	1.3	325.0	
	Ceftriaxone	4.83	241,500.0	
5	Diclofenac	1.23	1687.24	
	Salbutamol	1.2	300.0	
6	Diclofenac	1.27	1742.11	
	Salbutamol	18.7	4675.0	
7	Diclofenac	1.6	2194.78	
	Salbutamol	9.1	2275.0	
	Ceftriaxone	14.52	726,000.0	
8	Paracetamol	4.6	356.58	
	Diclofenac	1.24	1700.96	
	Salbutamol	2.9	725.00	
	Ceftriaxone	6.16	308,000.0	
9	Diclofenac	1.17	1604.93	
	Salbutamol	0.7	175.0	
	Ceftriaxone	4.15	207,500.0	

Table 5 Demographic and disposal practices of unused medication in households ($n = 100$)

Details	Number of respondents
Gender	
Male	37
Female	63
Age	
18–25	52
26–35	18
36–45	10
46–55	12
> 56	5
Marital status	
Single	69
Married	31
Educational level	
Primary school	3
Secondary school	18
University	76
Other	3

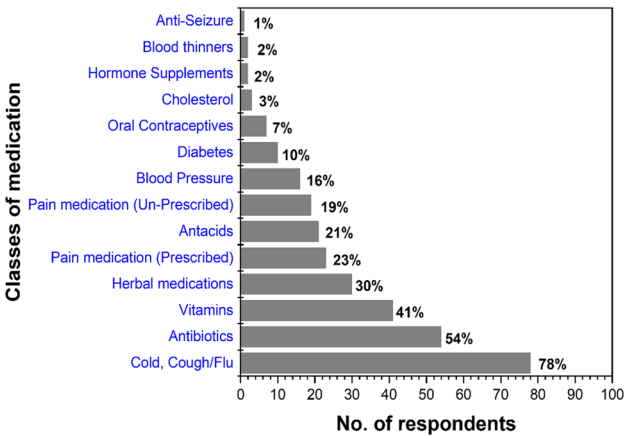

Fig. 4 Different types of medications that were stored in households ($n = 100$)

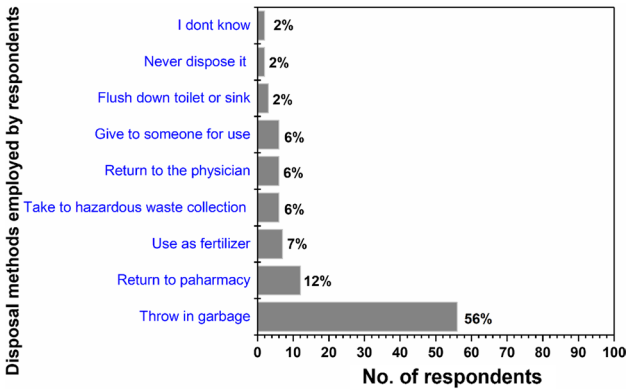

Fig. 5 Different disposal methods employed by respondents ($n = 100$)

medication as opposed to over-the-counter pain medication. More than half of the respondents indicated that the accumulation of unused medication in households was due to self-discontinuation of medication (31%) and in case they needed medication for later use (21%), which were usually disposed of in garbage (56%) or flushed down the toilets (22%) (Fig. 5). The study however found that only 35% of the respondents received information on safe disposal of medication from pharmacists. On the contrary, about 97% of the respondents wish to learn and to be informed about safe disposal of medication at the point of distribution. Despite the willingness to learn about safe disposal, not all respondents are willing to safely dispose of medicines, as only 52% respondents were willing to dispose of medicines safely, provided that a convenient location is provided. It is however troublesome that only 14% of the respondents knew about the drug take-back program of which only eight respondents have made use of it.

The aforementioned situation of storing medications may be due to self-discontinuation of medication due to side effects or cure and in case the medicine is needed later. This is not surprising, because in developing countries, self-medication is highly observed and tablets are stockpiled for future use in the event of a similar illness or to provide it to someone else who might have an alike problem. Moreover, change in doctors' treatment was also one of the reasons respondents stored medicines in their households. Apart from these reasons, Azad and team describe that excess of medications at home is primarily due to change in treatment, condition healed/cured, excess procured and expiry dated (Azad et al. 2012). Subsequently, the excess of medications at homes leads to inappropriate disposal that has potential threat of accidental ingestion by children. The responses recorded for different modes of disposal of medicines may highlight the lack of awareness or basic education on safe disposal of solid wastes. Similarly, results obtained by other researchers indicated that most respondents (72.2%) of the respondents reported disposing of their unused medicines in the trash bins. A study on household clearance of medications as a potential pathway for water body contamination in Mysuru City marked the pharmaceutical disposal is either associated with household solid wastes, sink or toilets, that requires greater attention.

Potential lacunae in pharmaceutical compounds management

Currently, protocol for estimation of pharmaceutical product levels in MWWTPs has not been standardized in spite of increasing evidence that they pose a serious

environmental health risk. There are various methods, which could be employed to control the exposure of living organisms to pharma products, ranging from consumer awareness on government regulations, medical innovations, proper disposal methods and mainly effective filtration in wastewater treatment facilities. A multinational collaboration is necessary and through combined efforts from the manufacturers of these drugs, the government, private organization and even individuals that the Green Pharmacy vision becomes a reality. The following areas would assist in assessing the impact of pharmaceuticals on the environment: (1) Genetic adaptations, such as genetic-drift during species isolation or homeosis; and (2) modifications in the timing, presence or amount of chemical, as it influence on genotoxicity and eco-pharmacological studies in order to reduce the ecological footprint of pharmaceuticals. Further, the concept of 'green pharmacy' could be considered at the local and regional levels to manage the contamination. This concept proposes a holistic approach for pharma products management. It engages the stakeholders like pharma industries, doctors and consumers who would follow scientific operating procedures that minimize the ecological pollution by medications (Toma and Crişan 2018).

Conclusions

The present study was motivated by the lack of information on local environmental contamination by pharmaceutical compounds. Therein, present study highlighted the occurrence of the four pharmaceuticals in the MWWTPs that indicated relatively high stability of these medicinal compounds under environmental conditions. The diclofenac was detected in all the samples and recorded the chief concentration of 4.2 µg/mL. In addition, the study found these pollutants in the treated wastewater which could antedate devastating long-term consequences. The risk quotient method adopted inferred high risk from all the drugs considered at each of the sampling sites. The survey initiated to know the management of the medicines at household level showed the deficiency of awareness and good practices. The public awareness on rational use and disposal of pharma products are of the supreme priority. With proper guidelines in place, pharmaceuticals could be monitored, controlled, degraded and eliminated. Substantially, a closed system for recycling wastewater is best, in order to avoid contamination of freshwater and other water bodies.

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Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of interest None of the authors have any competing interests in the manuscript.

Ethical approval Approval for wastewater sampling from hospitals was granted by the respective hospital superintendents. Moreover, participants were informed and required to read and understand the information provided, the purpose for the survey and their participation, the potential benefits and risks of the research, as well as voluntary participation consenting.

Consent for publication All the authors are aware of Springer's rules and regulation and hereby consent to the publication of the submitted article.

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