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Reduction of residual topical diclofenac in waste water by a wiping procedure before hand washing

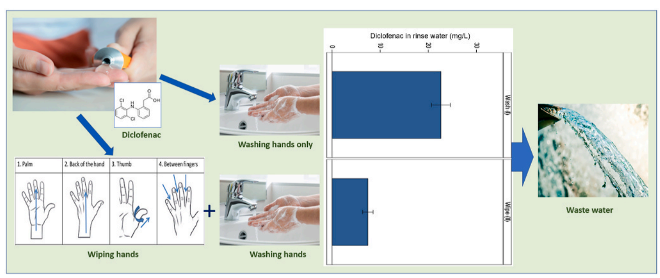
S. Bielfeldt[a,*], D. Urquhart[b], M. Brandt[a], N. Hennighausen[a], R. Bazzanella[b]

[a] ProDERM GmbH, Kiebitzweg 2, 22869, Schenefeld, Germany
[b] GSK Consumer Healthcare SARL, Route de L' Etraz, 1260, Nyon, Switzerland

HIGHLIGHTS

- Topical diclofenac is difficult and expensive to remove from waste water.
- A simple way to remove topical diclofenac from rinse water has been evaluated.
- Wiping hands before washing can reduce topical diclofenac in rinse water up to 70%.
- This simple method can reduce the release of topical drugs in the environment.

GRAPHICAL ABSTRACT



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1 ABSTRACT

Diclofenac is non-steroidal anti-inflammatory drug (NSAID) with widespread usage as a topical treatment for relief of pain and inflammation in soft-tissue injuries. While the permeation mechanisms of topically applied diclofenac are well documented, the fate of residual diclofenac not retained at the site of pain following subsequent hand-washing is still not well characterized. The aim of this study quantifies the amount of diclofenac present in rinse water after the application of a topical pain gel containing 23.2 mg/g diclofenac diethylamine, and subsequent washing of the hands. A comparison of two different hand washing techniques was completed with and without wiping hands directly after product application and before washing. A pilot study was completed to optimize the analytical procedures used in the quantification of diclofenac in the rinse water, followed by a main study with 24 test subjects. The data were first analyzed separately and subsequently pooled for statistical analysis.

To determine the amount of diclofenac in the rinse water samples, we used reverse phase-liquid chromatography-mass spectrometry (RP-LC-MS/MS). It was determined that a hand washing procedure with a pre-wash wipe of the hands with a paper towel resulted in a 66% reduction in diclofenac released into the waste water system (7.43 ± 3.02 mg/L). This study shows for the first time that a wiping procedure before hand washing will have a significant impact on the amount of diclofenac in the rinse water. Thus, it is possible to significantly impact the release of non-absorbed residual diclofenac after product application.

* Corresponding author.
E-mail address: sbielfeldt@proderm.de (S. Bielfeldt).

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1. Introduction

In the past two decades, international organizations (OECD, 2019), EU (EU, 2013), and governments became concerned about the contamination of fresh water and marine environments (Brozinski et al., 2013; Undeman, 2020; Sengar and Vijayanandan, 2021) with various substances including pharmaceuticals. The European Union has a clear Pharmaceuticals in the Environment strategy (EU, 2013) but, as demonstrated by the Dutch Chain approach (VROM, 2018), all stakeholders need to take actions to minimize residues in the environment to make significant progress on this complex issue, while ensuring the patients access to medicine. Diclofenac (DCF), a widely used NSAID has been detected in waste water, lakes, rivers and coastal waters (Brozinski et al., 2013). Specific treatments e.g. with ozone or H_2O_2 are required to remove DCF efficiently in municipal waste water plants, but this remains a costly procedure (Beltrán et al., 2009; Bielak et al., 2015). As toxicity to organisms in concentrations below 1 μg/l has been documented (Taggart et al., 2007; Vieno and Sillanpää, 2014), DCF is considered as a drug with a potential environmental impact by the EU watch list for emerging pharmaceutical water pollutants (EU, 2013; Sathishkumar et al., 2020).

Orally administered diclofenac reaches municipal waste water by excretion. Approximately 2/3 is excreted in urine and 1/3 in feces, being mostly conjugates and metabolites with 15% of the parent drug (Davies and Anderson, 1997; Vieno and Sillanpää, 2014, Mulkiewicz et al., 2021).

The adsorption of DCF as a topical gel has been found to be about 10% with high subjects' variability (Davies and Anderson, 1997). In this case, the remaining DCF was deemed to mainly enter the waste water by means of either a direct washing of the skin or by the washing of clothing previously exposed to the drug (Vieno and Sillanpää, 2014).

This study looks at one possible way to reduce the amount of pharmaceutical residue in the environment without affecting the patient's clinical benefit and associated quality of life. As such the study could be part of a program of useful measures designed to minimize pharmaceutical residues. A wiping procedure with a paper towel directly after DCF gel application and before the washing of the hands was shown to significantly reduce the amount of DCF detected in rinse water.

2. Materials and methods

2.1. Materials

A topical gel (Voltaren Forte™) corresponding to 92.8 mg DCF diethylamine per application was used as a source of DCF. 0.45 μm Polytetrafluorethylenefilters were used during the analysis by RP-LC-MS/MS for rinse water sample filtration. Approximately 1 mL of liquid soap Bode Baktolin® ("Pure Waschlotion") was used per subject during both hand washing routines.

2.2. Subjects

A pilot study was conducted to optimize the analytical procedures for the quantification of diclofenac in water. The data from the subsequent main study fully conformed to the results of the pilot study, allowing for a pooling of results. Thirty-two subjects with healthy skin werethen enrolled from the general population of Schenefeld/Hamburg (Germany) and analyzed Prior to the investigation, each potential subject was informed as to the purpose and nature of the study in full compliance with applicable regulations. Each subject provided written informed consent to the investigator/designee and was informed that they retained their rights to withdraw at any time. Before initiating the trial, the study, study protocol, protocol amendments and the informed consent forms were reviewed by an independent institutional review board and the review board of proDERM GmbH (Schenefeld, Germany).

2.3. Test product application

Every subject underwent two identical product application procedures on days 1 and 3 of the study, respectively. Subjects were first required to wash their hands with water and soap according to normal use conditions prior to product application to avoid sample contamination. Each subject was designated a test area (elbow) determined by the handedness of the subject, e.g. left handed subjects were designated the right elbow as their test area. A technician supplied each subject with 4 g (±0.4 g) of test product corresponding to 92.8 mg Diclofenac-diethylamine. The subjects were then instructed to gently massage the test product into the test area for 30–60 s using only their dominant hand.

2.4. Washing procedures

Two washing procedures were completed, with one washing procedure occurring per application procedure. All subjects completed both washing routines by the end of the study. The two procedures were used as points of comparison regarding diclofenac amounts in their respective rinse water samples. Washing routine 1 was completed after product application on Day 1 of the study in accordance with the following description:

The hands of the subjects were wetted by a technician immediately after test product application. Approximately 1 mL of soap (see section 3.1) was massaged into the entire palm and outer surface of both hands by the subjects for 10 s. The soap was then rinsed off using 2 L of lukewarm water over 30 s, ensuring a complete absence of visible soap residues. All the rinse water was collected.

Washing routine 2 differed only in that subjects also completed a defined wiping procedure immediately post-test product application (Fig. 1). The rest of the washing routine was completed identically to washing routine 1 and all rinse water was collected (see Fig. 2).

2.5. Rinse water sample analysis

Three 100 mL water samples per subject, per wash routine were taken from the collected rinse water for triplicate analysis. Samples of the same tap water used for rinsing serve as a blank. Each sample was taken from different locations in the jar. The samples were shipped to the Umweltbundesamt GmbH laboratory (certified in accordance with ISO) in Vienna for HPLC analysis. A negative control consisting of tap water was also analyzed.

The rinse water samples were diluted (1:1,000,000 and 1:100,000) and mixed with an isotope-labelled standard (diclofenac-D4). The determination was performed by direct injection of the sample into two different ultra-high performance liquid chromatography-tandem mass spectrometer systems (UPLC-MS/MS; system 1: Waters Xevo TQ-S, system 2: Shimadzu LCMS-8060) in positive ionization mode.

Chromatographic separation was performed on a reversed-phase C18 UPLC column (system 1: Waters ACQUITY UPLC BEH C18 1.7 μm 2.1 × 50 mm, system 2: Agilent ECLIPSE plus C18 RRHD 1.8 μm 2.1 × 50 mm) using a solvent gradient of water and methanol, each modified with 0.1% formic acid. For quantification, the mass transition m/z 296 > 214 was used in multiple reaction monitoring mode, and for qualitative confirmation, the transition m/z 296 > 215 was used.

A 13 point calibration curve was used for evaluation, with concentrations ranging from 0 to 1 mg/L (Matrix effects were corrected by recovery of the isotopically labelled standard (mass transition m/z 300 > 218).

2.6. Data analysis

All analyses performed included the panel of the main study and for the pooled panel of pilot and main study data.

N, mean, standard deviation, minimum, maximum, and 95%

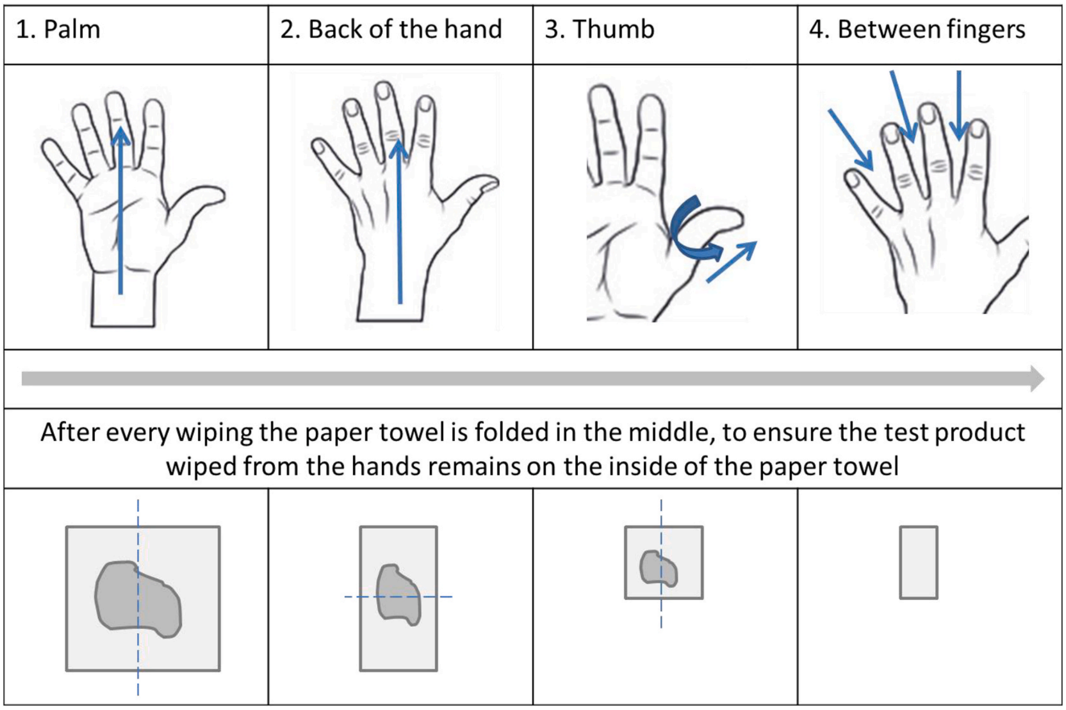

Fig. 1. Visual representation of the hand wiping procedure completed by all subjects during washing procedure 2.

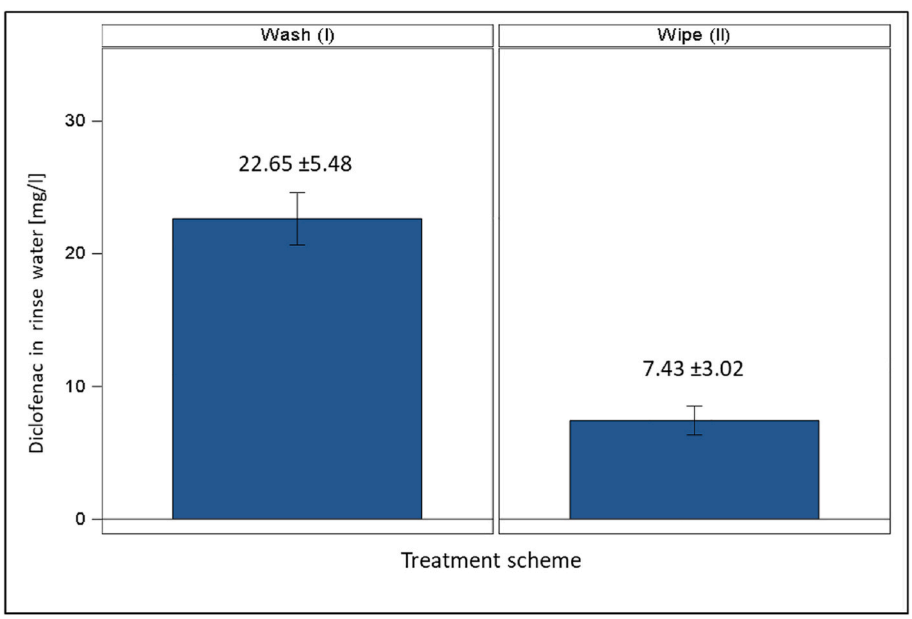

Fig. 2. Pooled Analysis for Pilot and Main Study: Amount of Diclofenac in Water [mg/L] -Mean Values and 95% Confidence Intervals of Raw Data: A significant difference was found ($p < 0.001$); ($n = 32$).

confidence limits were calculated for raw data by washing routine. The mean values of raw data were presented in bar charts with 95% confidence limits. A significance level of 0.05 (alpha) was chosen for statistical analysis. The data of differences used in the statistical test was normally distributed (Shapiro-Wilk test: $W = 0.960$; $p = 0.281$). For DCF determination, pairwise comparisons of washing routines were performed on raw data with paired *t*-test.

The computation of the statistical data was carried out using SAS for Windows (version 9.4).

3. Results

The HPLC analysis of rinse water samples showed that DCF levels were approximately three times higher (Fig. 1) in water samples originating from washing routine 1 (Wash (I); without wiping the hands) in comparison to washing routine 2 (Wipe (II; with wiping the hands)).

The statistical comparison of washing routines, including the main and pilot studies as a pooled dataset, showed that the difference in DCF levels in the rinse water between the two routines was significantly different No DCF content was detected for the negative control.

4. Discussion and conclusion

Topically applied DCF represents an important fraction of all administered pharmaceutically available DCF (Undeman, 2020). It can be expected that only 10% or less of topically applied DCF enters the skin after application (Davies and Anderson, 1997), so a significant fraction of the administered pharmaceutical stays on the hands. Most of this fraction may enter waste water systems, potentially impacting the waste water facilities.

Our study shows that wiping hands reduces by 60% the amount of DCF that would otherwise directly enter the waste water system following usual hand washing A simple hand wiping procedure before washing drastically reduced the amount of DCF that could be discarded through rinse water. Solid waste elimination of the used paper towel would help to mitigate the potential impact of topical pharmaceuticals like DCF in waste water. Pharmaceuticals within waste water are of primary concern compared to solid waste (EU, 2013). Incineration, despite not being available everywhere, is leading to solid waste elimination. Also land fill leachate was shown to have negligible contribution in the surrounding surface water environment (Yu et al., 2020).

These first results suggest that it is possible to propose simple ways to control and significantly reduce the release of non-absorbed topical pharmaceuticals after skin product application, and this could be applicable in many different settings. all topical pharmaceuticals to minimize their impact on the environment. It is not meant as a sole measure to minimize the residues but could be used as part of a suite of measures, upstream and downstream of the user. Further research and modelling are needed to estimate the amount of DCF and other topical components as e.g. sunscreen filters that can be detracted from waste water or retained from direct water contamination by introducing and promoting skin-wiping procedures after topical usage in all relevant user-groups.

Contribution of authors

SB Investigation, review of study data and report, writing draft, review & editing. **DU** Conceptualization, Methodology, review & editing. **MB** Methodology, Investigation, review of study data and report, review & editing. **NH** Investigation, writing study report, review & editing. **RB** Conceptualization, Methodology, review & editing

Declaration of competing interest

We declare no competing interests. The study has been financially supported by GSK Consumer Healthcare.The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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