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ORIGINAL ARTICLE / ÖZGÜN MAKALE

EVALUATION OF GREENNESS PROFILES OF VARIOUS DEVELOPED METHODS FOR THE DETERMINATION OF COMMONLY USED NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) IN ENVIRONMENTAL WATERS

SIK KULLANILAN NONSTEROİD ANTİ-İNFLAMATUVAR İLAÇLARIN (NSAİİ) ÇEVRESEL SULARDA TAYİNİ İÇİN GELİŞTİRİLMİŞ ÇEŞİTLİ YÖNTEMLERİN YEŞİLLİK PROFİLLERİNİN DEĞERLENDİRİLMESİ

Burcu SEZGİN[1]*, Murat SOYSEVEN[2]

[1]Eskişehir Osmangazi University, Eskişehir Vocational School, Department of Environmental Protection Technologies, 26110, Eskişehir, Türkiye
[2]Anadolu University, Yunus Emre Vocational School of Health Services, Department of Medical Services and Techniques, 26470, Eskişehir, Türkiye

ABSTRACT

Objective: *In our study, it was aimed to make a comparative analysis of the environmental impact profiles of two approaches including Gas Chromatography (GC) and Liquid Chromatography (LC) methods, which are frequently used techniques for the determination of non-steroidal anti-inflammatory drugs (NSAIDs) and their metabolites in environmental water samples.*
Material and Method: *The evaluation of the methods' environmental impact was performed using National Environmental Methods Index Label (NEMI), Analytical Eco-scale, Analytical GREEnness Metric (AGREE), and Green Analytical Procedure Index (GAPI).*
Result and Discussion: *The routine analysis of NSAIDs in environmental waters is carried out, resulting in a significant volume of chemical waste. In recent times, there has been a growing significance attributed to environmentally conscious analytical methodologies and the evaluation of methodologies through a green lens to confront this challenge. There is no statistically significant difference in terms of environmental impact profile was observed between the two methods compared.*
Keywords: *Environmental waters, green chemistry, greenness assessment, nonsteroidal anti-inflammatory drugs (NSAIDs)*

ÖZ

Amaç: *Çalışmamızda, çevresel su örneklerinde steroid olmayan antiinflamatuar ilaçların (NSAİİ) ve bunların metabolitlerinin tayininde sıklıkla kullanılan teknikler olan Gaz Kromatografisi (GK) ve Sıvı Kromatografisi (SK) yöntemlerini içeren iki yaklaşımın çevresel etki profillerinin karşılaştırmalı bir analizinin yapılması amaçlanmıştır.*
Gereç ve Yöntem: *Yöntemlerin çevresel etkisinin değerlendirilmesi, Ulusal Çevresel Yöntemler İndeks Etiketi (NEMI), Analitik Eko-ölçek, Analitik Yeşillik Metriği (AGREE) ve Yeşil Analitik Prosedür İndeksi (GAPI) kullanılarak gerçekleştirilmiştir.*
Sonuç ve Tartışma: *Çevresel sularda NSAİİ'lerin rutin analizi gerçekleştirilmekte ve bunun*

* **Corresponding Author / Sorumlu Yazar:** Burcu Sezgin
e-mail / e-posta: bsezgin@ogu.edu.tr, **Phone / Tel.:** +902222361415-4520

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sonucunda önemli miktarda kimyasal atık ortaya çıkmaktadır. Son zamanlarda, çevreye duyarlı analitik metodolojilere ve bu zorluğun üstesinden gelmek için metodolojilerin yeşil bir mercekle değerlendirilmesine atfedilen önem giderek artmaktadır. Karşılaştırılan iki yöntem arasında çevresel etki profili açısından istatistiksel olarak anlamlı bir fark olmadığı gözlenmiştir.
Anahtar Kelimeler: *Çevresel sular, nonsteroid anti-inflamatuvar ilaçlar (NSAİİ), yeşil kimya, yeşillik değerlendirmesi*

INTRODUCTION

Pharmaceuticals used for various purposes, such as the treatment and prevention of diseases, along with improperly disposed waste medications, result in high concentrations of active pharmaceutical ingredients and their metabolites contaminating wastewater. Substantial quantities of these substances reach wastewater treatment plants, and some of these may also directed to surface waters. In fact, in the effluent from agricultural areas irrigated with treated wastewater, pharmaceuticals, including non-steroidal anti-inflammatory drugs (NSAIDs), have been detected [1-3]. While some of these substances can be completely removed by traditional treatment systems, some drugs, such as diclofenac, an NSAID drug, can only be partially removed [4].

Since the discovery of aspirin (acetylsalicylic acid), NSAIDs have become globally popular over-the-counter drugs, constituting approximately 5% of all prescription medications. While NSAIDs are classified based on their chemical properties, selectivity toward the inhibition of their target enzymes, and half-lives, their functions are relatively similar. NSAIDs are commonly used for the treatment of patients experiencing chronic pain, rheumatoid arthritis, menstrual cramps, postoperative surgical conditions, osteoarthritis, and other painful and inflammatory conditions. They are also widely used as analgesics and antipyretics. Studies have demonstrated the significant role of NSAIDs in a protective capacity against various cancers. Despite their non-addictive nature and broad therapeutic benefits, NSAIDs come with numerous serious side effects, such as cardiovascular risks, gastrointestinal toxicities, kidney injuries, and hypertension [5-7].

In wastewater treatment plants, the removal rate of acidic compounds such as NSAIDs is quite low due to their high solubility in water and poor degradability. While the individual concentrations of these residues in the aquatic environment may be low, the coexistence of drug combinations that share a common mechanism of action introduces the potential risk of synergistic effects. Therefore, the development of analytical methods that enable the determination of NSAIDs and their metabolites at low concentrations in the aquatic environment has become an important part of studies aimed at determining the formation, fate, and effects of pharmaceuticals [2,8].

NSAIDs and their metabolites are among the most frequently detected analytes among pharmaceuticals. Methods based on gas chromatography (GC) [3,9-18], liquid chromatography (LC) [19-31], and electrophoretic techniques [32-36] are used for the determination of NSAIDs and their metabolites in environmental water samples.

GC devices are primarily used due to their widespread availability and low cost in environmental laboratories and are often combined with mass spectrometry (GC-MS). Due to the polarity of NSAIDs, derivatization of the analyte is required for GC-MS analysis. The derivatization step brings disadvantages such as difficulties encountered in the case of many samples, loss of time, reproducibility problems, and possible formation of artifacts. With this technique, the carboxyl group of NSAID drugs can be converted to methyl ester with excellent yield using diazomethane, but due to the high toxicity and low stability of this reagent, LC and electrophoretic techniques that do not require derivatization can be preferred. LC-MS techniques have advantages such as low LODs, high sensitivity, and good linear range for quantitative analysis, but also disadvantages such as high acquisition and maintenance costs. Capillary electrophoretic techniques, on the other hand, are a good alternative for the determination of NSAIDs thanks to their high efficiency, rapid analysis, and the possibility of combining with an MS detector, but they have low analyte detectability, especially in the determination of trace levels, due to the small amount of sample that can be injected into the capillary [2,37,38].

As a result of analytical methods used in the determination of various analytes, including studies in environmental waters, millions of liters of chemical waste are generated, most of which are toxic and

ecologically hazardous [39,40]. Hence, researchers have directed their attention towards green analytical chemistry as a strategic approach to protect the environment and human health, and greenness evaluations of applied analytical methods have become an important parameter in method selection. In this context, various greenness evaluation methods have been developed [41-43]. In our study, greenness profiles were created and compared using various greenness assessment tools, for two different methods reported in the literature for the determination of NSAIDs in environmental waters.

MATERIAL AND METHOD

Greeness Assessment Tools

In the context of the study, an LC-MS [31] and a GC-MS [3] application have been chosen as exemplary analytical methods from the literature. Within the scope of this research, we employed four different tools to evaluate the greenness assessment of the selected methods. These tools include National Environmental Methods Index Label (NEMI) Analytical Eco-Scale, Green Analytical Procedure Index (GAPI), and Analytical GREEnness Metric (AGREE). Our objective was to conduct a thorough greenness assessment and evaluate the environmentally friendly characteristics inherent in the investigated chromatographic methods.

National Environmental Methods Index (NEMI)

NEMI is one of the earliest greenness analytical tools to evaluate the sustainability of analytical procedures. This method contains a circle symbol including four quarters (Pictogram) is drawn and each quarter illustrates an aspect of the method that may pose a potential environmental hazard. Achievement of the prescribed requirements results in the display of relevant fields in a green format. The determination of this state is contingent upon the fulfilment of the following conditions: firstly, a chemical utilized in the method must be identified as a PBT (persistent, bioaccumulative, and toxic) according to the Environmental Protection Agency's Toxics Release Inventory (EPA's TRI). Secondly, the chemical's inclusion on either the TRI or on the Resource Conservation and Recovery Act's (RCRA) D, F, P, or U hazardous waste lists signifies its categorization as hazardous. Corrosiveness is established if the pH level during analysis falls below 2 or exceeds 12. Lastly, the generation of waste surpassing 50 grams is a prerequisite for the classification of the method under the waste criterion [44].

Analytical Eco-Scale

The Analytical Eco-Scale assesses the environmental impact of an analytical method by deducting penalty points (PP) from a maximum score of 100. This scoring system provides a quantitative measure of the method's eco-friendliness, with a flawless green analysis achieving a perfect score of 100. The allocation of penalty points takes into account various factors (the types and quantities of solvents and reagents utilized, energy consumption, occupational hazards, waste generation, and strategies for waste management). The resulting numerical output from the eco-scale reflects the overall environmental performance, where a higher score indicates a more sustainable and environmentally friendly analytical approach, while a lower score suggests a greater negative impact on the environment [45].

The output of the eco-scale is a numerical value derived by subtracting the cumulative penalty points from 100 and its calculation is performed according to the "*Analytical Eco-Scale = 100 – total penalty points (PP)*" formula. The results are categorized on a scale as follows: an excellent green analysis (>75 points); an acceptable green analysis (>50 points); and an inadequate green analysis (<50 points) [45].

The Analytical Greenness Metric (AGREE)

AGREE is a metric system that enables the evaluation of an analytical procedure based on 12 green principles. This software offers advantages such as comprehensiveness, rapid, simplicity, flexibility, and ease of interpretation. The assessment result is visualized in the shape of a circular clock, with the total score displayed at the centre. This score present as a representation of the overarching environmental sustainability of the assessed process or methodology. Furthermore, a visual representation in colour (green, yellow, red colour scale) is used to depict the assessment result,

facilitating swift comprehension and comparison. The score is indicated on a 0-1 scale, with a higher score approaching 1 signifying a heightened degree of greenness. This suggests that the assessed process or methodology is more closely aligned with the principles of green analytical chemistry [46,47].

Green Analytical Procedure Index (GAPI)

GAPI, frequently used as one of the most important tools for assessing eco-friendliness, was employed to evaluate both analytical methods. GAPI is represented by a pictogram consisting of a total of 15 subcategories, each with 3 colour criteria for every stage. Red, yellow, and green colours are depicted on 5-pointed star symbols. The pictogram provides information about the extent to which the analytical procedures meet green requirements [48].

RESULT AND DISCUSSION

Greenness Assessment of the Methods

NEMI

The NEMI labeling of the examined methods is presented in Figure 1. The results show that the methods meet the same green requirements such as PBT, corrosive, and waste except for the hazardous criteria section.

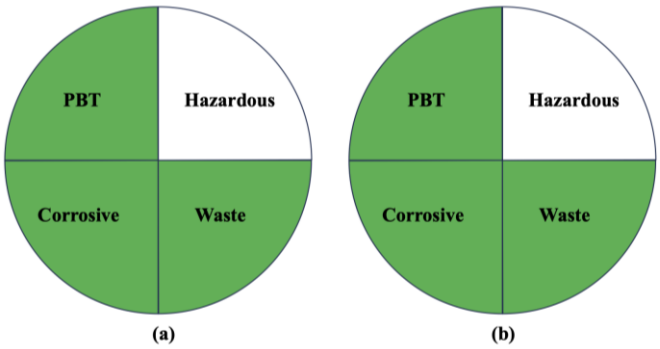

Figure 1. NEMI pictograms for the methods (a) LC-MS (b) GC-MS

Analytical Eco-Scale

A higher score denotes a more environmentally friendly analysis, signifying that the method has effectively minimized its ecological impact and inherently possesses greater sustainability. Conversely, a lower score indicates a more substantial negative impact on the environment. The Analytical Eco-Scale points of the investigated methods are shown in Table 1 and Table 2. Analytical Eco-Scale points were found to be as 76 for LC-MS method which is classified as excellent green analysis and 73 for GC-MS method which is classified as acceptable green analysis.

AGREE

The AGREE pictograms of the investigated analytical methods are given in Figure 2. AGREE scores are found to be as 0.52 and 0.48, respectively. The sections in the pictogram represent (1) sampling procedure, (2) amount of sample, (3) device positioning, (4) sample preparation steps, (5) degree of automation, (6) derivatization, (7) amount of waste, (8) number of analytes in a single run, (9) total power consumption, (10) type of reagents, (11) use of toxic reagents, (12) safety of the operator [49].

The weakest sections were determined as 3 and 9 for LC-MS method, 2, 3 and 9th section for GC-MS method. The sections marked in red, namely 2, 3, and 9, correspond to the minimum sample size, device positioning, and total power consumption ($\geq$ 1.5 kWh) of a single analysis, respectively. As a result, since the scores of both analytical procedures is below 0.6, it does not meet the greenness score in terms of AGREE [49].

Table 1. Analytical Eco-Scale penalty points for evaluated LC-MS method [31-45]

Components	Pictograms	Signal word	Used in method	Penalty Point
Reagent				
Ammonium acetate	No hazard pictogram	-	< 10 ml (g)	**0**
Methanol		Danger	< 10 ml (g)	**6**
Formic acid		Danger	< 10 ml (g)	**6**
Acetic acid		Danger	< 10 ml (g)	**4**
Monosodium phosphate	No hazard pictogram	-	< 10 ml (g)	**0**
Water	No hazard pictogram	-	< 10 ml (g)	**0**
Sodium hydroxide		Danger	< 10 ml (g)	**2**
Instruments				
LC-MS/MS			> 1.5 kWh per analysis	**2**
Sonicator			≤ 0.1 kWh per analysis	**0**
Centrifuge			≤ 1.5 kWh per analysis	**1**
Occupational hazard			Analytical process hermetization	**0**
Waste			1-10 ml (g) per analysis	**3**
Total Penalty Point				**∑=24**
Eco-Scale Score			**100 - ∑**	**76**

Table 2. Analytical Eco-scale penalty points for evaluated GC-MS method [3-45]

Components	Pictograms	Signal word	Used in method	Penalty Point
Reagent				
Trimethylsilyl		Danger	< 10 ml (g)	**4**
Methanol		Danger	< 10 ml (g)	**6**
Toluene		Danger	< 10 ml (g)	**6**
Water	No hazard pictogram	-	< 10 ml (g)	**0**
Helium		Warning	< 10 ml (g)	**1**
Instruments				
GC-MS			> 1.5 kWh per analysis	**2**
Occupational hazard			Emission of vapours and gases to the air	**3**
Waste			>10 ml (g) per analysis	**5**
Total Penalty Point				**∑=27**
Eco-Scale Score			**100 - ∑**	**73**

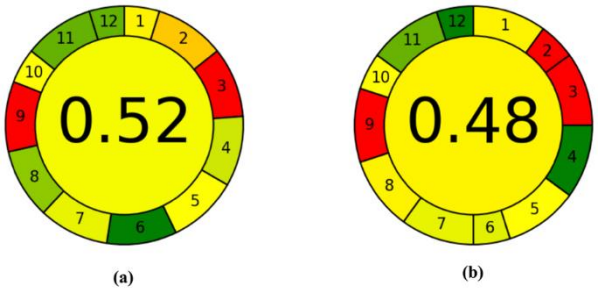

Figure 2. AGREE pictograms for the methods (a) LC-MS (b) GC-MS

GAPI

The GAPI pictograms for both analytical methods examined in this study are presented in Figure 3. The pentagrams of the examined HPLC methods reveal negative environmental impact due to the characteristics of its off-line sample collection, transport, require extraction procedure, use of non-green solvents or reagents, energy consumption (≥ 1.5 kWh) and no treatment for waste, in which case all coded red. Physical preservation, storage under normal conditions, apply micro extraction process, use moderately toxic reagent and highest NFPA flammability or instability score of 2 or 3, or a special hazard solvent and 1–10 ml (1–10 g) waste produce is represent the yellow part of the both methods and no additional treatments, use under 10 ml (or < 10 g) solvent are shows the green environmental impact of the analytical procedures.

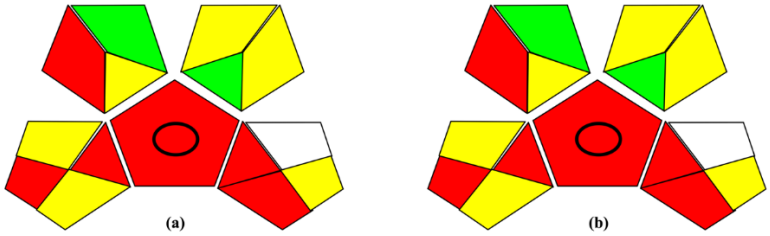

Figure 3. GAPI pictograms for the methods (a) LC-MS (b) GC-MS

The increasing prevalence of high concentrations of active pharmaceutical ingredients and their metabolites in environmental waters, as a result of the frequent use of non-steroidal anti-inflammatory drugs (NSAIDs), has become a significant area of research. The determination of these NSAID drugs in water samples has been widely investigated using various analytical methods such as LC/MS and GC/MS. However, in recent years, growing environmental concerns have directed researchers to examine the environmental impact of the conducted analyses. The environmental impact assessment of these analytical methods has gained attention due to the escalating environmental issues. This shift in focus reflects a broader awareness among researchers regarding the potential ecological consequences of pharmaceutical contamination in environmental water. As a result, the exploration of analytical techniques for NSAID detection now not only encompasses accurate and sensitive measurements but also considers the broader implications on the environment. This multidimensional approach aims to address both the analytical aspects of pharmaceutical detection and the environmental repercussions of these methods. The derivation of greenness profiles for the recommended methods in the literature should be an integral part of method development studies. Analytical methodologies should not only strive for accuracy, sensitivity, and efficiency but also consider their ecological impact, thereby contributing to the broader framework of green analytical chemistry.

AUTHOR CONTRIBUTIONS

Concept: B.S., M.S.; Design: B.S., M.S.; Control: B.S., M.S.; Sources: B.S., M.S.; Materials: B.S., M.S.; Data Collection and/or Processing: B.S., M.S.; Analysis and/or Interpretation: B.S., M.S.;

Literature Review: B.S., M.S.; Manuscript Writing: B.S., M.S.; Critical Review: B.S., M.S.; Other: -

CONFLICT OF INTEREST

The authors declare that there is no actual, potential or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that ethics committee approval is not required for this study.

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