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Review

Chemical nature evolution of solid supports used in electromembrane extraction procedures: A comparative analysis based on metric tools

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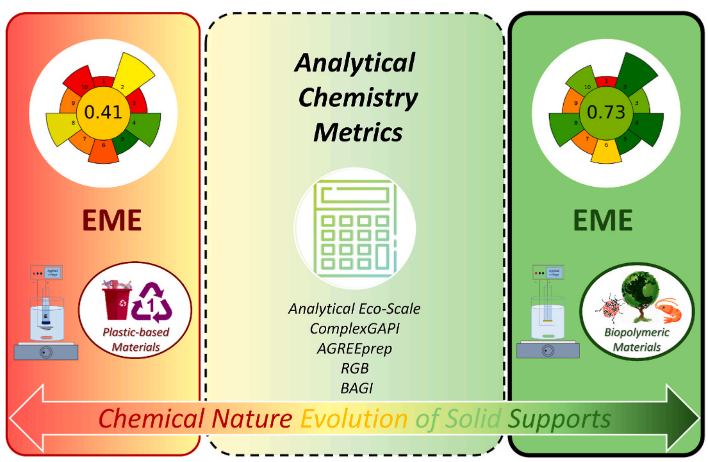
HIGHLIGHTS

- Importance of the support nature on the ecology and applicability of EME procedures.
- Comparative study of EME methods based on green metric tools.
- Green trend in EME systems with the use of biodegradable and renewable materials.
- AGREEprep, Analytical Eco-Scale, ComplexGAPI, BAGI and RGB as complementary metrics.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: In recent decades, green chemistry has been focusing on the adaptation of different chemical methods towards environmental friendliness. Sample preparation procedures, which constitute a fundamental step in analytical methodology, have also been modified and implemented in this direction. In particular, electromembrane extraction (EME) procedures, which have traditionally used plastic supports, have been optimized towards greener approaches through the emergence of alternative materials. In this regard, biopolymer-based membranes (such as agarose or chitosan) have become versatile and very promising substitutes to perform these processes.
Results: Different green metric tools (Analytical Eco-Scale, ComplexGAPI and AGREEprep have been applied to study the evolution of solid supports used in EME from nanostructured tissues and polymer inclusion membranes to agar films and chitosan flat membranes. The main goal is to evaluate the usage of these new biomaterials in

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the analytical procedure to quantify their environmental impact in the frame of Green Analytical Chemistry (GAC). In addition, both RGB model and BAGI metrics have been employed to study the sustainability of the whole procedure, including not only greenness, but also analytical performance and feasibility aspects. Results obtained after the performance of the mentioned metrics have demonstrated that the most efficient and environmentally friendly analytical methods are based on the use of chitosan supports. This improvement is mainly due to the chemical nature of this biopolymer as well as to the removal of organic solvents.

Significance: This work highlights the advantages of biodegradable materials employment in EME procedures to achieve green analytical methodologies. These materials also contribute to raise the figure of merits regarding to the quantification parameters in a wide range of applications compared to classical supports employed in EME, thus enhancing sustainability of procedures.

1. Introduction

Sample treatment methodologies are commonly mandatory when analysing complex matrices (biological, environmental or food samples), which contain low amounts of target analytes together with non-desirable compounds at higher concentration. In order to achieve a suitable method analytical performance, sample preparation is crucial, as it is often an unavoidable step in the overall analytical process that consumes most applied resources and time [1]. In this field, electromembrane extraction (EME) raised in 2006 as an efficient miniaturized liquid-phase extraction procedure for this purpose [2]. The basic principle of this methodology consists of extracting the compounds of interest through a hydrophobic organic membrane immobilized in a solid support immersed in the sample solution (donor phase) into a clean solution (acceptor phase). For achieving the extraction, an electrical field is sustained across the membrane and controlled by an external power supply. It is required the use of two electrodes, each immersed in the donor or acceptor solution, respectively. For the selective isolation of compounds and to ensure their electro kinetic migration from donor to acceptor phase, the target molecules must be present in their ionic form. Therefore, the pH media is a critical experimental factor which must be carefully controlled. The polarity of the electrodes must be chosen depending on the acidic or basic character of the analytes to be extracted [3].

Over the last two decades, a significant amount of research has been reported with multiple EME procedures applications, demonstrating their efficiency in pre-concentration and clean-up of complex samples prior to instrumental analysis [4–10]. Due to the increasing concern about environmental damages in chemical processes, the advances in the developments of EME processes have evolved according to the recommendations of Green Chemistry strategies. It includes aspects such as the use of renewable raw materials, reduction of reagent consumption and wastes, energy saving, procedure automation, multi-analyte on-site determinations, miniaturization, control and minimization of environmental side effects, among others [11,12].

After an overview of EME developments since its first application, different set-ups and configurations have been proposed in order to improve performance, costs and time [13]. Mainly, EME devices can be classified into two different types, those in which the hydrophobic membrane is immobilized in a physical support (supported liquid membrane, SLM) and those in which no physical support is used (free liquid membrane). In the first category and from the emergence of EME, the main material employed as a hydrophobic membrane support has been polypropylene (PP). At the beginning, this porous polymeric material was hugely used either in hollow fiber format or as a flat sheet, commercially available in different thicknesses and pore sizes. To a lesser extent, other plastic polymers such as polyvinylidene difluoride (PVDF) or polyacrylonitrile (PAN) were also used in reported literature [14]. Although many applications have been successfully carried out using these supports, several disadvantages were revealed, mainly the low conductivity during EME process, which conditions the number of organic solvents that can be used as liquid membranes and, in some cases, leads to non-extraction. In addition to the fact that these polymeric supports have a passive role in the extraction procedure, they are all plastic in nature and have a single use, which is harmful to the environment.

Furthermore, efficiency of polar compounds (logP$<$2) extraction is usually difficult because high applied voltages are needed to overcome the hydrophobicity of the SLM. Thus, different strategies to improve this handicap have been presented in the literature. Addition of carriers, chemical modification of the SLM, different organic solvents or the use of gels to replace the SLM have been proposed [15]. Consequently, many efforts of the scientific community have been focused on the development of alternative and more advantageous materials for their usage as improved supports. In this way, several proposals raised including functional materials resulting from the physical/chemical modification of commercial plastic-based ones with carbon nanomaterials or metallic nanoparticles, among other additional species [16–18]. On the other hand, novel manufactured supports such as molecularly imprinted polymers (MIPs), polymer inclusion membranes (PIMs) and nanostructured tissues (acrylic nanofibers, Tiss®-OH) have emerged as effective alternatives for this purpose [19,20].

In the context of green chemistry and looking for more sustainable and environmentally beneficial raw materials, the use of various types of biopolymers as versatile supports in EME has come to the forefront. Thus, in recent years there has been an increasing number of published works in which the extraction device includes natural biopolymers-based supports, as numerous advantages stand behind the usage of this kind of materials. First, the low cost due to their abundance and availability from natural sources (microorganism, animals and plants) [21], non-toxic and biodegradable (eco-friendly wastes), possibility of functionalization due to their chemical structure, thus allowing the availability of requested supports as well as high selectivity and wide fields of application [22]. All these features make these compounds very suitable and advantageous for their use as supports in EME.

Agarose and chitosan are the most common biopolymers reported for this purpose. In 2015, the first use of agarose films with silver nanoparticles as a support in an EME device was reported [23]. Later, in 2017, Tabani et al. were the first ones to propose the use of agarose gel without the need for any organic solvent as a liquid membrane [24]. Since then, numerous works have been reported using this biopolymer as a green membrane in different formats (gel and films) [20]. On the other hand, chitosan is another natural biopolymer which has emerged as a promising raw material in this field. In 2019, a chitosan-based film was introduced for the first time to be successfully used in an EME procedure, demonstrating the active role of chitosan in the extraction procedure [25]. In subsequent works, analytes belonging to different families have been successfully and selectively extracted from several kinds of matrices (biological, environmental and food samples) [26–28]. In addition to the above-described properties of the biopolymers, a unique feature of chitosan-based membrane used in EME procedures is that no organic solvent is required. It has been demonstrated that chitosan has an active role in the extraction procedure through the amine and hydroxyl groups in its chemical structure, enabling the selective transport of the target analytes from sample to acceptor phase [26]. Consequently, organic solvent is not necessary as a liquid membrane which is an additional and very important advantage from a green chemistry point of view. Therefore, this material itself is clearly very suitable in the framework of promoting sustainable sample processing methodologies. On a lesser extent, other biopolymers such as cellulose or tragacanth gum (pure or conjugated with silver nanoparticles) have also been proposed as supports in EME procedures [29,30].

The introduction of greenness in analytical procedures, according to the twelve principles of Green Analytical Chemistry (GAC), has become an almost mandatory aim to be followed by the analytical community. In this sense, the use of natural biopolymer-based supports in EME processes meets many of the requirements promoted by GAC (miniaturized devices, solvent-free and/or less toxic reagents, multi-analyte methods) [31].

In the last years, numerous metrics have been proposed in order to evaluate the environmental impact as well as health and safety issues associated to the analytical procedures [32]. Some of them are only qualitative and others are semi-quantitative or quantitative tools. The first referenced metrics were defined as a general nature purpose, applicable to any analytical methodology in order to select the appropriate method as well as the optimal parameters. Other metrics are only applicable to a selective group of analytical methods (e.g., liquid chromatography methods), evaluating hazard, toxicity, safety and environmental factors. Moreover, several tools based on multi-criteria approaches have been also used for this purpose [33]. After an extensive overview of the most useful green metrics and taking into account their overall advantages [34–37], Analytical GREEnness metric for sample preparation (AGREEprep) [38], Analytical Eco-Scale [39] and Complementary Green Analytical Procedure Index (ComplexGAPI) [40] have been selected to perform the greenness assessment of EME procedures. In order to study analytical methodologies from a holistic perspective, other metric tools such as RGB model [41] and Blue Applicability Grade Index (BAGI) [42], have been used addressing the sustainability of procedures including, in addition to ecological issues, analytical performance characteristics and practical aspects. All these tools combine a number of versatile features, such as their applicability to different analytical procedures, simplicity and ease of use, as well as the possibility to compare different methodologies.

The aim of this work is to evaluate the importance of the support nature used on both the greenness of the EME procedure and its applicability. For this purpose, the five previously described metrics (AGREEprep, Analytical Eco-Scale, ComplexGAPI, BAGI and RGB model) have been applied to EME methods using different supporting materials. Two non-biodegradable materials such as polymer inclusion membranes (PIMs) and nanostructured tissues (acrylic nanofibers), as well as two biopolymers (agarose and chitosan) have been selected as representative supports. These materials have been developed in our research group, all of them are flat membranes and the determination of the target analytes, after EME, was performed using similar HPLC conditions in all cases. This fact enables controlling different experimental variables of the entire analytical procedure for subsequent comparison purposes.

2. Description of selected metric tools

Taking into account that sample treatment is common in all cases, AGREEprep metric is intended to highlight the importance of the support chemical nature as the main difference between the targeted EME methods.

The next step implies assessing how the nature of the materials affects the greenness of the overall process. This issue is addressed using Analytical Eco-Scale and ComplexGAPI, which have been selected as the most comprehensive and widely used tools for this purpose.

The applicability of the methods is further tested using BAGI to finally assess the importance of all these aspects for sustainability using the RGB model.

2.1. AGREEprep

Wojnowski et al. [38] developed the analytical metric tool known as AGREEprep for the assessment of the environmental impact associated with the sample preparation step due to its influence on the overall analytical methodology. This tool generates a pictogram with qualitative and quantitative information, which is given by a color scale from red to green and a final score between 0 and 1. Fully non-environmentally friendly procedures are assigned a red color and score 0, while the most eco-friendly sample treatment is colored green and has an overall score of 1. The outcome (Fig. 1a) depends directly on the ten principles of green sample preparation [43], evaluating criteria such as sample preparation placement (1), amount of hazardous materials (2), sustainability and renewability of materials (3), waste amount (4), size economy of the sample (5), sample throughput (6), integration and automation (7), energy consumption (8), post-sample preparation configuration for analysis (9) and operator safety (10). Each criterion is additionally assigned a different importance level or weight on the overall score. Thus, the use of safer solvents and reagents (criterion 2) is given the highest weight (weight 5), while favoring *in situ* sample preparation (criterion 1) is given the lowest importance (weight 1). The weights associated with each criterion can be selected individually. In this work, default software weights have been used.

2.2. Analytical Eco-Scale

Analytical Eco-Scale is a semi-quantitative tool introduced by Gałuszka et al. [39] in 2012 as an alternative green chemistry metric to those traditionally used to date, which were mainly focused on organic methods. The application of this tool to assess the greenness of analytical methodologies is based on assigning penalty points to a series of parameters related to the reagents and instruments used. In this regard, three scenarios are considered with respect to the amount of reagents used ($<$10, 10–100 or $>$100 mL or g) and the type of hazard reagents (i.e. none, less severe or more severe). On the other hand, the penalty points associated with the instruments cover energy consumption ($\leq$0.1, $\leq$1.5 or $>$1.5 kWh per sample), occupational risks (analytical process hermitization or emission of vapors and gases to the air) and waste. In the case of waste generated, both the quantity (none, $<$1, 1–10 or $>$10 mL or g) and its treatment (recycling, degradation, passivation or no treatment) are taken into account.

The overall score is calculated by subtracting the total of all penalty points from 100. Accordingly, a score higher than 75 is considered an excellent green analysis, while scores in the range 50–75 and below 50 represent acceptable and inacceptable green analyses, respectively.

2.3. ComplexGAPI

The ecological features of an analytical procedure can also be assessed both qualitatively and quantitively by using the Green Analytical Procedure Index (GAPI) metric tool, allowing the evaluation of the entire analytical methodology from sampling to instrumental determination [44]. However, Płotka-Wasylka and Wojnowski subsequently developed an improved version of GAPI, named as ComplexGAPI, which also includes aspects related to the processes carried out before the actual analytical procedure [40].

In this case, the result consists in five pentagrams with a graded colored scale, which are combined offering an overall symbol/pictogram. Each of these pentagrams considers one stage of the analytical procedure: sampling, sample treatment, reagents and solvents used in the analysis and instrumental determination (Fig. 1b). Moreover, within each stage or pentagram, different aspects are considered. Similar to the Analytical Eco-Scale, items like amount (9), health (10) and safety (11) hazard of the reagents and solvents used, as well as energy consumption (12), occupational risks (13) and the quantity (14) and treatment (15) of waste are taken into account. Additionally, the evaluation of the sample

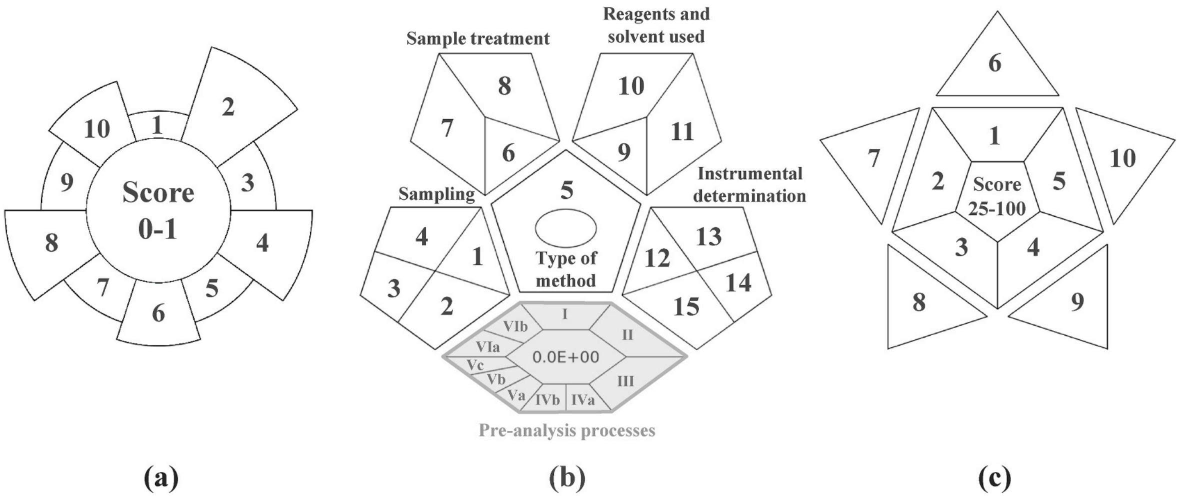

Fig. 1. Criteria distribution for employed pictograms by (a) AGREEprep, (b) ComplexGAPI and c) BAGI.

preparation stage involves parameters such as the sampling mode (1), needing for preservation (2) and transport (3), storage conditions (4), direct/indirect method (5), scale of extraction (if necessary) (6), type of solvents and reagents used (7), and requirement of additional treatments (8).

On the other hand, the pictogram also includes an additional hexagon (highlighted in grey in Fig. 1b) for the evaluation of the steps prior to sample preparation and analysis. Thus, criteria such as yield and conditions (I-II), relation to the green economy (III), reagents and solvents (IVa-IVb), instrumentation (Va-Vc) and workup and purification (VIa-VIb) related to pre-analysis processes are also evaluated. Each of these elements is colored according to its greenness, so that the color scale includes red, yellow and green for high, medium and low environmental impact, respectively. Criteria I and II evaluate both the yield (I) of the product obtained and the temperature and time (II) of the reactions involved, so that the need for heating or cooling for more than 1 h makes these criteria to be colored red. Criterion III is scored according to the number of requirements that are met in terms of design, use and efforts to contribute to process economy. Health (IVa) and safety hazards (IVb) involved in the pre-analysis process are assessed in Criterion IV. The need to use advanced or uncommon (Va), energy-intensive (Vb) and non-hermetic instrumentation (Vc) is also assessed negatively. Finally, the need for treatment and purification of the final product together with the techniques used for this purpose (VIa) as well as the degree of purity achieved (VIb) are also assessable criteria with this metric.

A novelty of the ComplexGAPI is the inclusion in the additional hexagon of a numerical parameter to quantify the amount of waste generated. The value of this parameter, called E-factor, is included by the user, who can calculate it by following some recommended equations. Therefore, the value of this factor is directly proportional to the amount of waste generated and consequently to its negative impact on the environment.

2.4. BAGI

More recently, Manousi et al. [42] introduced BAGI as a new complementary and additional metric tool according to the White Analytical Chemistry (WAC) concept that takes into account additional features of the entire analytical procedure [45]. In this sense, the blue color of this tool refers to the fact that it focuses primarily on the practicality of the analytical method, i.e. productivity and practical/economic efficiency (blueness aspect). The evaluation of an analytical method by using the BAGI metric involves 10 criteria or attributes: 1) type of analysis (quantitative and confirmatory, quantitative, screening or qualitative); 2) number of analytes that are simultaneously determined (multi- or single-element analysis); 3) the analytical technique and instrumentation (portable, simple or advanced instrumentation); 4) the number of samples that can be simultaneously treated; 5) the sample preparation scale; 6) the number of samples that can be analyzed per hour (sample preparation + analysis time); 7) type of reagents and materials; 8) the requirement for preconcentration; 9) the automation degree and 10) sample amount. As a result, an asteroid-shaped pictogram is obtained (Fig. 1c) in which each of the criteria can be colored white, light blue, blue or dark blue to designate non-compliance, low-, medium- or high-compliance with the set criterion, respectively. The pictogram is also accompanied in its center by a numerical value giving the overall method score, which is in the range 25–100. Therefore, a score of 100 is the ideal scenario from the point of view of applicability and performance of the method.

2.5. RGB model

An interesting and original approach was proposed in 2019 by Nowak and Kościelniak [41], who developed a tool to globally evaluate an analytical method using the RGB (Red – Green – Blue) color model. This proposal uses the three primary colors to designate three aspects of an analytical procedure: analytical performance, environmental friendliness and productivity/practical effectiveness, respectively. Each of these aspects is evaluated according to user-selectable criteria, so that the final result provides a color that is the contribution of each of the primary colors. Thus, white is seen as the ideal result, while black is seen as the worst-case scenario. On the other hand, intermediate situations can occur with colors such as yellow, grey or magenta, among others. The evaluation can be easily carried out using an Excel spreadsheet as a template. The evaluable criteria, as well as their importance or weight on the final result, are selected by the user according to the needs. Moreover, together with the color, a numerical value is also obtained, which is defined as the "method brilliance (MB)", so that a quantitative evaluation is also possible. For the sake of clarity, the example used in this work will be used to further explain the assessment using this model. First of all, each main aspect should be weighted according to its importance. In this case, analytical performance (redness) and productivity (blueness) are assigned a weight = 1, while greenness will be assessed with a weight = 2, as it is considered decisive in this work. To evaluate analytical performance, four criteria have been selected: pre-concentration (enrichment factor (EF), weight = 3), accuracy (effective recovery (ER%), weight = 3), precision (%RSD, weight = 2) and LOD (μgL^{-1}, weight = 2). Individual weight values have been established according to the importance given to each criterion and taking into account that the total sum should be 10, as indicated in the model. For the safety and eco-friendliness criteria (greenness), chemicals and waste amounts (mL, weight = 3), chemical safety/hazard pictograms (weight = 3), renewability/reusability (weight = 2) and energy consumption (kW h, weight = 2) are selected as evaluable parameters. On the other hand, the number of samples that can be prepared in 1 h (weight = 3), the number of target analytes (weight = 3), sample amount (mL, weight = 2) and total analysis time per sample (min, weight = 2) are the criteria considered for the assessment of productivity/practical effectiveness (blueness). Once all criteria have been established, the lowest acceptable value (LAV) and the lowest satisfactory value (LSV) have to be defined for each criterion, which are assigned a score of 33.3 and 66.6 out of 100, respectively (see supplementary material for more details). Thus, the final result provided by the assessed method (color and %MB) is automatically scored according to these values as well as to the importance (weight) of each criterion. This tool, although different from the metrics usually used to evaluate an analytical method, can be very useful as it facilitates the modification and selection of criteria to be considered according to each situation.

3. Description of the targeted supports

In this section, a detailed description of the employed supports: polymer inclusion membranes (PIMs) [46], nanostructured tissues (acrylic nanofibers (Tiss®-OH)) [47], agarose films [23] and chitosan membranes [25–28] is presented for comparison.

3.1. Polymer inclusion membranes (PIMs)

PIMs membranes have a polymer basis (mainly cellulose triacetate (CTA) or polyvinyl chloride (PVC)), a carrier acting as an extracting compound and a plasticizer component in different rates. This composition confers PIMs good features, such as high diffusive resistance and optimal mechanical strength, which turn into an excellent self-supporting membrane and, consequently, a good alternative as supports in EME procedures [48,49].

In particular, for this work, a flat PIM (25 μm thickness, 6 mm diameter) as support in the EME procedure described by Román-Hidalgo et al. [46] will be studied. The composition of this PIM was 29 % (w/w) of CTA as base polymer and 71 % (w/w) of Aliquat®336 as both plasticizer and cationic carrier. In this work, the simultaneous extraction of four non-steroidal anti-inflammatory drugs (NSAIDs), such as salicylic acid (SAL), ketoprofen (KTP), naproxen (NAX) and ibuprofen (IBU), together with four highly polar acidic drugs (anthranilic acid (ANT), nicotinic acid (NIC), amoxicillin (AMX) and hippuric acid (HIP)) was successfully carried out. The addition of 1-octanol as a liquid membrane was required for the compounds to be extracted. The EME device by using PIMs is described schematically in Fig. 2a.

3.2. Nanostructured tissues Tiss®-OH

Nanostructured tissues, commercially named Tiss®-OH, have also been selected for this assessment. This material is an electrospinning-manufactured sheet membrane composed of acrylic nanofibers functionalized with hydroxyl groups. It belongs to a family of polymeric nonwoven series of nanofibers membranes developed by nanoMyP® (Granada, Spain). Specially, this nanostructured tissue is 100 μm thickness with a variable pore size ranging from 800 nm for dry nanofibers to 1–3 μm for wet nanofibers. Tiss®-OH have been successfully used in EME for extracting high polarity acidic compounds (NIC, AMX, HIP and SAL) [47]. The EME device is similar to that used with PIMs, with minor modifications, as can be seen in Fig. 2a. In this work, the

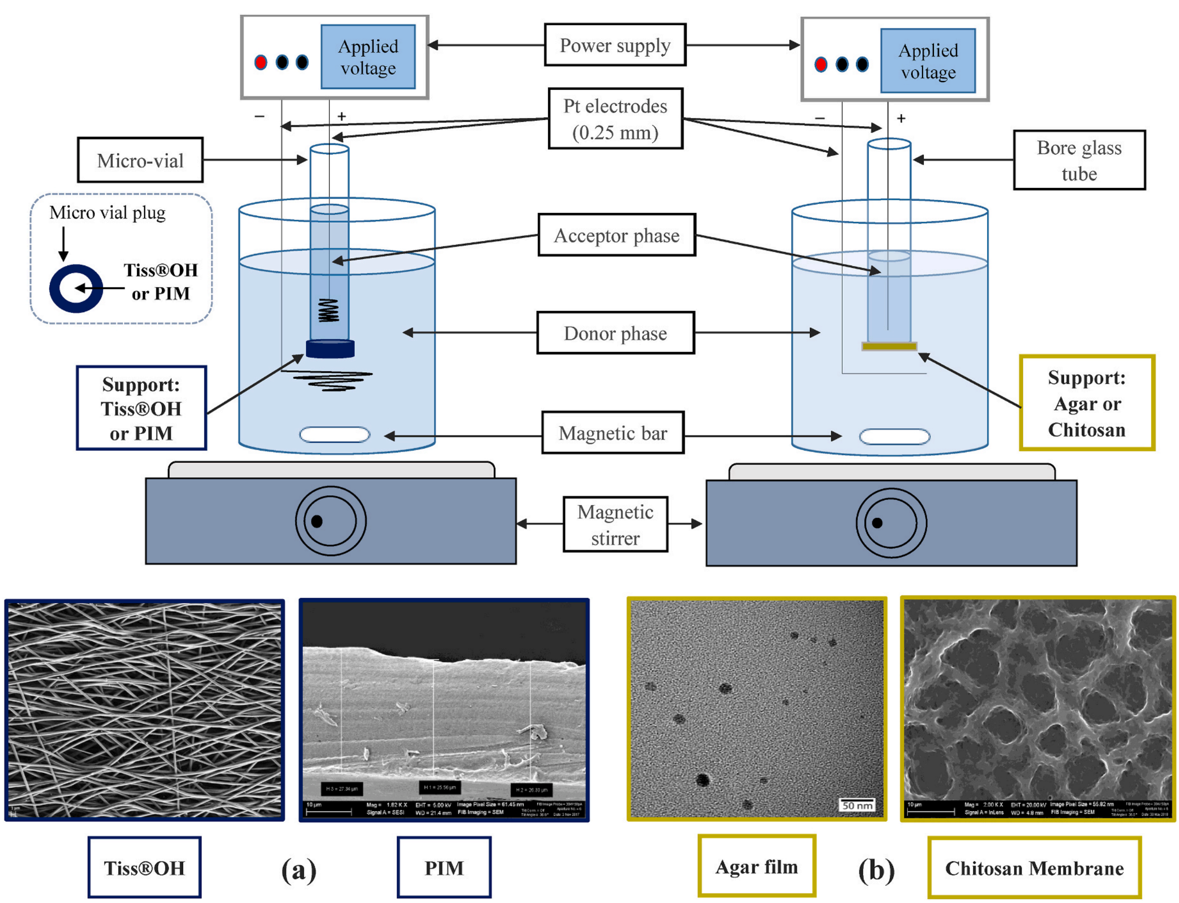

Fig. 2. Comparative EME devices developed with supports of different nature: (a) PIMs and Tiss®OH, (b) Agar films and chitosan membranes.

active role of the membrane during the extraction process was demonstrated. Moreover, 1-octanol as a liquid membrane was required.

3.3. Agarose films

Among the different formats of agarose supports, a 20 µm thickness agarose film (<0.1 µm pore size) has been selected for this study. This agarose-based film contains metallic nanoparticles in order to favour the EME procedure. Specifically, spherical silver nanoparticles of 20–30 nm diameter synthetized *in situ* in the polymeric film, resulting in a homogeneously distributed film of 107.9 mg Ag/g agar [23]. In this work, the use of dihexyl ether was required as a liquid membrane for carrying out the EME procedure. Five NSAIDs (SAL, KTP, NAX, IBU and diclofenac (DIC)) were successfully extracted by using the EME device depicted in Fig. 2b.

3.4. Chitosan membranes

In addition, chitosan-based membranes used as support in EME methodology have been selected. The composition of the membrane consists of 60 % (w/w) chitosan and 40 % (w/w) Aliquat®336, having a variable thickness (30–35 µm and 10–11 µm). This biopolymeric membrane has proven to be very versatile in EME procedures, playing an active role in the extraction process as mentioned in section 1. Numerous compounds belonging to different families, such as NSAIDs, polar compounds, parabens, fluoroquinolones and polyphenols have been simultaneously or selectively extracted using similar devices (Fig. 2b) from complex matrices (urine, food and environmental water samples) [25–28]. From a GAC point of view, an important and favorable feature of this biopolymeric material is that it allows the elimination of organic solvent to carry out the extraction.

4. Comparative results from the metrics implementation

The EME supports described above (Tiss®OH, PIMs, agar films and chitosan membranes) were evaluated for comparative purposes by applying the five analytical metric tools defined in section 2. Table 1 shows the results obtained from AGREEprep. It should be mentioned that, as they are all EME procedures coupled to subsequent HPLC determination criteria 1, 7 and 9 in AGREEprep pictograms are equal in all cases, being therefore assigned the same score and/or color. Thus, criterion 1 is represented in red, as the sample is collected in off-line mode and its transport to the laboratory is required to perform the EME procedure as a sample treatment. Additionally, non-automation and the use of liquid chromatography are scaled to orange (criteria 7 and 9). On the other hand, being a miniaturized technique, the required amount of sample is minimal, so this aspect is scaled to green for all methods (criterion 5).

As can be seen, Tiss®OH and PIMs EME methods have similar final scores of 0.47 and 0.41, respectively. This slight difference lies only in criteria 6 and 8 which, in the case of PIMs, score lower due to longer extraction time, leading to higher energy consumption. In contrast, the use of biodegradable materials (criterion 3) such as agar films and chitosan membranes turns into an improved environmental performance. Furthermore, these procedures also use greener solvents and even the active role of the support in the extraction process enables the practice of solvent-free methods, which reduces waste generation (criterion 4) as well as health hazard to operator (criterion 10). Therefore, these characteristics lead to an increase in the overall score towards values in the range 0.62–0.73, which is mainly conditioned by a greener attribution of the criteria 2–4 and 10.

According to the results obtained, the most environmentally friendly EME procedure involves the use of biodegradable chitosan membranes as a self-supporting material in the extraction without the need for organic solvent as SLM. Additional criteria, such as sample throughput (criterion 6) or energy consumption (criterion 8) also contribute to this result by reducing the extraction time and consequently increasing the number of samples that can be prepared in 1 h.

When studying the greenness of the whole analytical procedure, a similar trend is observed. Accordingly, reagents penalty points obtained from Analytical Eco-Scale (Table 2) are mainly controlled by the support nature, decreasing as biodegradable material is employed. Instruments penalty points are nearly constant and they have not an important influence since the analytical determination remains invariable (HPLC) in

Table 1
Greenness assessment of EME procedures by AGREEprep metric tool.

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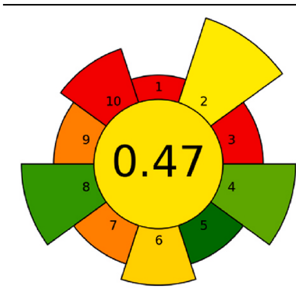
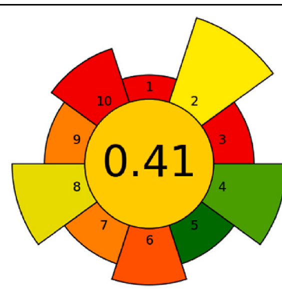
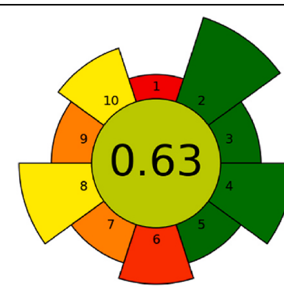
<tr><td>
</td><td>
</td><td>
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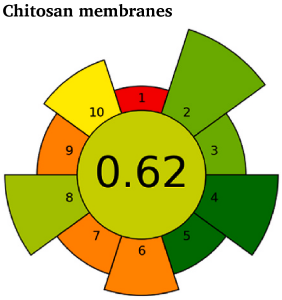
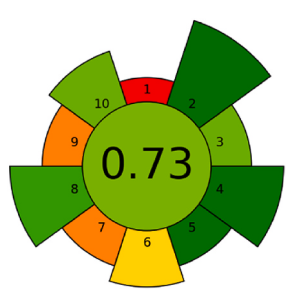
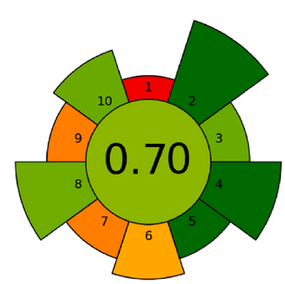
<tr><td>
</td><td>
</td><td>
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<tr><td>[26]</td><td>[25]</td><td>[27,28]</td></tr>
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Table 2
Analytical Eco-Scale scores for the assessed procedures.

EME support	Reagents Penalty Points	Instruments Penalty Points	Total penalty points	Analytical Eco-Scale total score	Ref.
Tiss®OH	14	8	22	78	[47]
PIMs	11	8	19	81	[46]
Agar films	4	6	10	90	[23]
Chitosan	4	6	10	90	[26]
	2	6	8	92	[25,27,28]

all cases. As can be noted, nanostructured tissues and PIMs supports provide the procedures leading to most total penalty points, resulting in a lower final score (78 and 81, respectively), mainly due to their plastic nature and the use of hazardous reagents (such as 1-octanol or ammonia). On the other hand, the reduction/removal of reagents and organic solvents, as well as the use of biodegradable materials such as agar or chitosan, lead to a better Analytical Eco-Scale total score (90–92).

These results are in accordance with those obtained by performing ComplexGAPI (Table 3). As can be seen from the pentagrams obtained, criteria 1, 3 and 5 are scaled to red due to off-line sampling, transport and sample preparation. Since sample storage is required, criterion 4 is yellow, while lack of preservation leads to a green assignment (criterion 2). In the same way, criteria related to the pre-analytical processes evaluable in ComplexGAPI concerning yield (I), safety hazard (IVb), workup/purification (VIa) and purity (VIb) are scored equally in all cases. Thus, all the EME procedures investigated in this work provide a yield above 89 %, the highest NFPA (National Fire Protection Association) flammability or instability score is 2 or 3, no purification of the final product is necessary and a degree of purity above 98 % can be considered. Criterion II (temperature/time) is colored yellow in all cases except in the case of the procedure based on the use of agar films, which is scored red, as their synthesis involves reflux heating for 2 h at 90 °C. Therefore, the final score of each assessed procedure differs as a consequence of the other items. Methods based on PIMs and Tiss®OH have virtually the same ComplexGAPI symbol (Table 3), where parameters such as type of reagents and solvents used (7), health hazard (10) and waste treatment (15) are colored in red. An intermediate-yellow score is attributed to the micro-scale of the extraction (6) and to safety hazard (11) due to the flammability of the reagents used. Concerning the additional hexagon, both procedures (Tiss®OH and PIMs) mostly match. In addition to the above-mentioned aspects of health and occupational hazards, criterion III (relation to the green economy) stands out negatively, as in both cases is colored red because only the requirements related to the micro-scale and the consequent reduction of chemicals are fulfilled. The only difference between the two procedures lies in the technical setup required for the preparation of the support, as electrospinning is performed in the case of Tiss®OH, which implies the use of advanced instrumentation (criterion Va) and, therefore, higher energy consumption (criterion Vb). On the other hand, in the case of PIMs, synthesis is carried out by mixing of reagents and ultrasound-assisted dissolving, resulting in yellow-colored fields. Therefore, the values of E-factor, estimated from the amount of waste generated, are $4.0 \cdot 10^{-1}$ and $3.0 \cdot 10^{-1}$, respectively, so they are in the same order of magnitude.

On the contrary, procedures involving the use of biomembranes (agar- and chitosan-based membranes) provide a more favorable scenario from an ecological point of view. Thus, criterion 7 change from red to yellow using greener reagents and from red to green by applying solvent-free methods [27,28], also influencing criterion 10 which responds in a similar way. Moreover, due to their nature, agar- and chitosan-based materials can be easily degraded, so waste treatment is accomplished, providing a yellow-score for this criterion (15). Moreover, the additional ComplexGAPI hexagon is greener when using chitosan because a large number of rules are met in terms of design, use and effort (criterion III) and a common instrument configuration is used (criterion Va), which reduces energy consumption (criterion Vb) and occupational hazards (criterion Vc).

Therefore, there is clearly a trend towards more environmentally friendly analytical procedures by simply varying the nature of the EME support for sample preparation, i.e., replacing plastic materials with biodegradable alternatives that reduce or even eliminate the use of hazardous reagents and solvents.

With regard to the application of the selected procedures, in terms of BAGI results (Table 4), all of them score above 50, so that they can

Table 3
ComplexGAPI pictograms obtained for the analytical procedures evaluated.

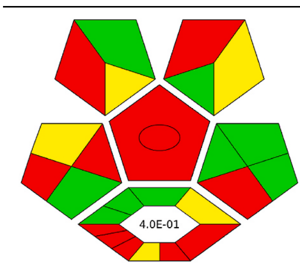
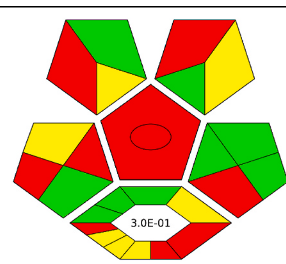
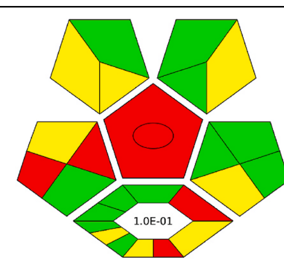
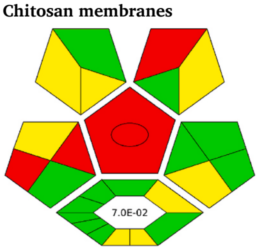
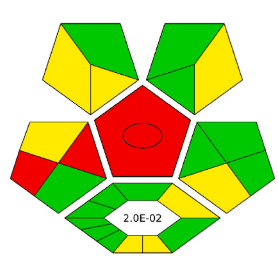
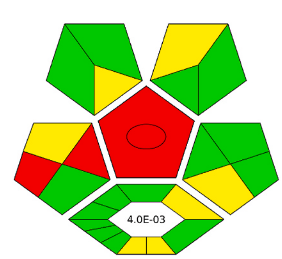
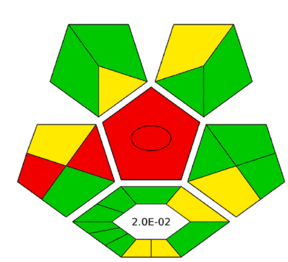
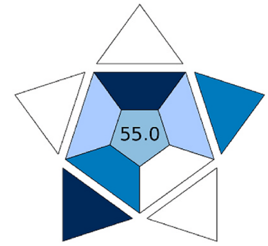
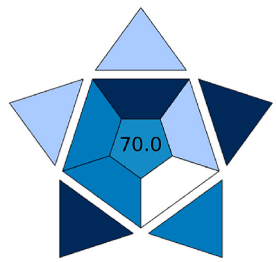
Tiss®OH	PIMs	Agar films	
			
[47]	[46]	[23]	
Chitosan membranes			
			
[26]	[25]	[27]	[28]

Table 4
Evaluation of selected procedures using the BAGI tool.

Tiss®OH	PIMs	Agar films
		
[47]	[46]	[23]
Chitosan membranes		
		
[26]	[25,27,28]	

generally be accepted from the point of view of their blueness. Particularly, the analysis of NSAIDs by agar-based EME method coupled to subsequent HPLC-DAD determination, with lower scoring, requires some improvements to make it practical in routine laboratories. On the other hand, the use of chitosan membranes in the sample preparation stage [25,27,28] overcomes these limitations, thus demonstrating their practicability and applicability not only for NSAIDs, but also for the determination of other families of compounds such as high polarity compounds, polyphenols or parabens in various matrices (biological, food and environmental). The overall scores of all procedures differ, however, only very slightly, so no further conclusions can be drawn.

Looking at sustainability and focusing (besides greenness) also on aspects such as analytical performance (redness) and productivity (blueness) of analytical methods, a holistic perspective of the evaluated procedures can be achieved. In this regard, the results of performing the RGB model (Table 5) show that the %MB values increase with the use of biomembrane-based supports in the sample treatment. Thus, procedures employing Tiss®OH and PIMs score the lowest with 31.8 and 41.2 %, respectively, followed by the procedure involving agar films with 57.3 %, while the methodologies based on chitosan membranes have values in the range 73.2–90.4 %. Among chitosan-based EME procedures, the method brilliance is increased by eliminating the organic supported liquid membrane and, consequently, chemical safety/hazards and reusability [27,28].

Regarding the redness, agar films procedure has the lowest score (38.7 %) mainly because the preconcentration is lower in this case (EF = 2.5–15.3). Methods based on the use of Tiss®OH and PIMs follow in score (61.0 and 69.4 %, respectively), as the EF values are higher and in the case of PIMs, better sensitivity (LOD) is also obtained. Precision and accuracy are virtually the same in all cases. However, procedures based on chitosan membranes score higher on this attribute due to higher preconcentration (EFs up to 195) and better sensitivity (LOD = 0.2–37.1 μgL^{-1}).

Table 5
RGB results in the evaluation of selected analytical procedures.

EME support	Redness (%) (W = 1)	Greenness (%) (W = 2)	Blueness (%) (W = 1)	Final color	Method Brilliance (%MB)	Ref.
Tiss®OH	61.0	20.0	80.8	black	31.8	[47]
PIMs	69.4	31.5	70.8	black	41.2	[46]
Agar films	38.7	56.4	59.1	grey	57.3	[23]
Chitosan	80.2	76.8	66.6	yellow	73.2	[26]
	73.6	87.0	90.5	white	88.2	[25]
	80.4	91.5	83.5	white	88.7	[28]
	80.7	92.9	85.5	white	90.4	[27]

With respect to blueness, the scores are closer, which is in line with previous BAGI results. Agar films procedure is the lowest scoring due to the analysis time (40 min EME+12 min HPLC), although this is compensated to some extent by the multi-elemental analysis (5 target analytes). This is also the case for the other methods, e.g. procedures based on the use of Tiss®OH for the determination of polar compounds and the determination of FQs by means of chitosan membranes [26] score very close but for different reasons. In the first case, due to short analysis time (10 min EME+12 min HPLC) and thus sample throughput, and the number of target analytes, whereas these aspects are less favorable in the case of FQs determination (3 target analytes and total analysis time of 43 min). On the other hand, the sample amount is smaller in the latter case and, therefore, the overall blueness score is compensated.

Consequently, methodologies involving the employment of Tiss®OH and PIMs have a final black colour, which means, according to the authors [41], that the proper use of the method is doubtful as it is defective because of one or more primary attributes and, therefore lacks acceptance. The use of agar film in the procedure can be considered in the absence of a better alternative, as it is colourless (grey). On the other hand, the method for the determination of FQs with chitosan membranes [26] is acceptable (yellow colour) for a relatively low number of analyses. The other processes based on chitosan membranes [25,27,28] provide the ideal situation with a white colour, so that those methods are suitable for all applications.

Based on the results of the tests applied, it can be affirmed that biodegradable supports represent a great improvement in the application of new materials for the development of more environmentally friendly analytical technologies. At the same time, high figure of merits (LOD, LOQ, linear range, linearity, recovery and enrichment factor) are obtained for the different families of investigated analytes (NSAIDs, acidic polar drugs, fluoroquinolones, polyphenols, parabens [25–28]) when these biopolymers have been used making them sustainable alternatives.

5. Conclusions and future perspectives

The application of different green metric tools such as AGREEprep, Analytical Eco-Scale, and ComplexGAPI confirm that the evolution towards biopolymeric materials as supports in EME procedures is a key factor in obtaining an improved ecological assessment.

In addition to the ecological improvement, figure of merits and analytical application of these procedures using biopolymeric materials are enhanced, as demonstrated by the results obtained with BAGI and RGB model.

The use of different metrics is recommended in order to manage comprehensive information of the global analytical procedure from diverse points of view, i. e., greenness, analytical performance and feasibility.

Among all the investigated materials, the lowest results correspond to nanostructured tissues and PIMs for all the applied metrics, having a high number of penalty points mainly due to the necessity of using organic solvents as well as because of the plastic nature of these materials. In contrast, agar and chitosan membranes lead to most eco-friendly methodologies.

Additionally, new approaches for analytical methodologies might be considered, especially in those aspects leading to low scores. Sustainable energy sources could be a further improvement for penalty points, as well as the automation of all steps involved in the entire analytical process. Regarding analytical separation techniques, the use of capillary electrophoresis instead of HPLC can be an important improvement for a greener overall procedure. Moreover, simple and rapid instrumentation requiring less organic solvents and analysis time, such as the use of portable devices or even smartphones for colored analytes detection, could enhance the environmental profile of these methods.

CRediT authorship contribution statement

Cristina Román-Hidalgo: Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation. **Mercedes Villar-Navarro:** Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis. **María Jesús Martín-Valero:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Funding acquisition. **Germán López-Pérez:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization.

Declaration of competing interest

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.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aca.2024.342868.

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