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A total scoring system and software for complex modified GAPI (ComplexMoGAPI) application in the assessment of method greenness

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ABSTRACT

Evaluating analytical methods with innovative metrics is essential to ensure the effectiveness of analytical procedures. Various approaches have been proposed to assess the performance of an analytical method and its environmental consequences, as sustainable environment and green chemistry ideology are of high importance nowadays. Considering greenness evaluation of developed analytical procedures, Green Analytical Procedure Index (GAPI), one of these metrics, utilizes five distinct colored pentagons to evaluate the environmental footprint of the analytical process at different stages. An additional tool named Complementary Green Analytical Procedure Index (ComplexGAPI) was introduced to expand on GAPI by adding additional fields pertaining to the processes performed prior to the analytical procedure itself. Nevertheless, the existing ComplexGAPI lacks a comprehensive scoring system for individual methods, which would allow for even easier comparison of procedures using this tool. In response to queries from ComplexGAPI users, this study introduces a refined tool named ComplexMoGAPI, merging the visual appeal of ComplexGAPI with precise total scores. The accompanying software streamlines the application, facilitating quicker and simpler evaluations. This software is available as an open source on bit.ly/ComplexMoGAPI. We believe that, following ComplexGAPI success, this ComplexMoGAPI tool will also gain attention and eventually trust and acceptance from the chemical community.

1. Introduction

Assessing analytical methods using novel metrics is crucial for ensuring the reliability, robustness, and efficiency of analytical processes [1]. Numerous methodologies have been suggested for evaluating the efficiency of an analytical process and its subsequent environmental impact [2]. White Analytical Chemistry (WAC) was first introduced by Nowak et al. to assess methods based on ecological, analytical, and practical criteria using the red-green-blue (RGB) model [3]. Shortly after, Manousi et al. introduced the blue applicability grade index (BAGI) as a swift and straightforward tool to evaluate the practicality of any analytical method [4]. Both WAC and BAGI were inspired from various pre-existing tools such as the National Environmental Method Index (NEMI) [5], analytical eco-scale [6], green analytical procedure index (GAPI) [7], analytical greenness calculator (AGREE) [8], and analytical greenness metric for sample preparation (AGREEprep) [9] for assessing method greenness. Other tools have been recently introduced such as modified NEMI [10], RGB model [11], and ChlorTox Scale [12].

GAPI, among these metrics, employs five colored pentagrams to assess the environmental impacts of the analytical process across different steps [13–16]. It takes into account various factors such as sampling, method type, sample preparation, solvent/reagent use, and energy consumption. This quick evaluation aids in identifying and improving methods to reduce their environmental footprint. The color code in GAPI provides a visual representation of the ecological impact of analytical procedures. It uses a color scale where green represents methods with low environmental impact (high sustainability), orange indicates moderate impact, and red signifies procedures with a high environmental impact (low sustainability). This color-coding system allows users to quickly assess the greenness of different analytical methods and make informed decisions when selecting procedures based on their environmental considerations [17–19].

In 2021, a complementary tool called ComplexGAPI was introduced to further enhance the evaluation process [20]. In ComplexGAPI, an additional hexagonal segment has been incorporated into the original GAPI diagram to represent the activities carried out before sample

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Table 1
The points system of the proposed ComplexMoGAPI (Modified with permission from [20]).

Category	Color (points)		
	Green (3)	Yellow (2)	Red (1)
Pre-analysis processes			
Yield/selectivity and conditions			
Yield (I)	>89 %	70–89 %	<70 %
Temperature/ time (II)	Room temperature, <1 h	Room temperature, >1 h	Heating, >1 h
		Heating, <1 h Cooling to 0 °C	Cooling <0 °C
Relation to the green economy			
Number of rules met	5–6	3–4	1–2
Reagents and solvents			
Health hazard (IVa)	Slightly toxic, slightly irritant; NFPA health hazard score is 0 or 1	Moderately toxic; could cause temporary incapacitation; NFPA = 2 or 3	Serious injury on short-term exposure; known or suspected small animal carcinogen; NFPA = 4
Safety hazard (IVb)	Highest NFPA flammability, instability score of 0 or 1. No special hazards	Highest NFPA flammability or instability score is 2 or 3, or a special hazard is involved	Highest NFPA flammability or instability score is 4
Instrumentation			
Technical setup (Va)	Common setup	Additional setups/ semi-advanced instruments used	Pressure equipment >1 atm; glove box
Energy (Vb)	≤0.1 kW h per sample	≤1.5 kW h per sample	>1.5 kW h per sample
Occupational hazard (Vc)	Hermetization of the analytical process	—	Emission of vapours to the atmosphere
Workup and purification			
Workup and purification of the end product (VI a)	None or simple processes	Application of standard purification techniques	Application of advanced purification techniques
Purity (VIb)	>98 %	97–98 %	<97 %
ADDITIONAL FIELD: E-factor			
$E\text{-}factor = \frac{total\ mass\ of\ waste\ from\ process}{total\ mass\ of\ product}$	Eq. 1 [21]		
Sample preparation and analysis			
Sample preparation			
Collection (1)	In-line	On-line or at-line	Off-line
Preservation (2)	None	Chemical or physical	Physicochemical
Transport (3)	None	Required	—
Storage (4)	None	Under normal conditions	Under special conditions
Type of method: direct or indirect (5)	None sample preparation	Simple procedures, *e.g.*, filtration and decantation	Extraction required
Scale of extraction (6)	Nanoextraction	Microextraction	Macroextraction
Solvents/ reagents used (7)	Solvent-free methods	Green solvents/ reagents used	Non-green solvents/reagents used
Additional treatments (8)	None	Simple treatments (extract clean up, solvent removal, *etc.*)	Advanced treatments (derivatization, mineralization, *etc.*)
Reagents and solvents			
Amount (9)	<10 mL (<10 g)	10–100 mL (10–100 g)	>100 mL (>100 g)
Health hazard (10)	Slightly toxic, slightly irritant; NFPA health hazard score is 0 or 1	Moderately toxic; could cause temporary incapacitation; NFPA = 2 or 3	Serious injury on short-term exposure; known or suspected small animal carcinogen; NFPA = 4
Safety hazard (11)	Highest NFPA flammability, instability score of 0 or 1. No special hazards.	Highest NFPA flammability or instability score is 2 or 3, or a special hazard is used.	Highest NFPA flammability or instability score is 4
Instrumentation			
Energy (12)	≤0.1 kW h per sample	≤1.5 kW h per sample	>1.5 kW h per sample
Occupational hazard (13)	Hermetization of the analytical process	—	Emission of vapours to the atmosphere
Waste (14)	<1 mL (<1 g)	1–10 mL (1–10 g)	>10 mL (<10 g)
Waste treatment (15)	Recycling	Degradation, passivation	No treatment
ADDITIONAL MARK: QUANTIFICATION			
Oval in the middle of GAPI: *Procedure for qualification and quantification (5)*		No oval in the middle of GAPI: *Procedure only for qualification (1)*	

preparation and the final analysis. This extra hexagon supports the assessment of sustainability across various parameters, including production yields and conditions, choice of reagents and solvents, utilization of instrumentation and techniques, as well as purification methods. These criteria are applicable for evaluating the eco-friendliness of processes involved in the synthesis of organic compounds, solvents, nanomaterials, or stationary phases [20]. The key benefit of the ComplexGAPI tool lies in its comprehensive approach and the provision of software tools to streamline its application. By employing ComplexGAPI to assess the environmental impact of the entire procedure, users can quickly identify disparities in methods and areas requiring attention to mitigate potential issues. Although, ComplexGAPI is very popular and often used by chemical community, users asked ask for an additional option indicating the points awarded to a given procedure, which could help in the direct method comparisons. To meet the expectations of ComplexGAPI users, this work introduces a modified tool called ComplexMoGAPI, which combines the visual appeal of ComplexGAPI with precise total scores. ComplexMoGAPI allows for more accurate and objective method comparisons, providing a comprehensive evaluation of method eco-friendliness. The accompanying software simplifies application, making assessments faster and more straightforward. We hope, that this new generation of ComplexGAPI will gain attention, trust and acceptance from the chemical community.

2. Scoring system in ComplexMoGAPI

MoGAPI offers more than just the familiar red/green/yellow icons found in ComplexGAPI. It additionally evaluates the overall environmental sustainability of a method by generating a cumulative score. This scoring system considers the range of choices within each category. For instance, in the Yield category, options include >89 %, 70–89 %, or <70 %. The highest score is awarded to yields >89 % (3 points), and the lowest score goes to yields >70 % (1 point). The total points are aggregated and divided by the maximum achievable points to determine the percentage score. The details of the categories, the choices, the color code and the points system are summarized in Table 1.

3. Case studies

The advancement in pictogram representation in the ComplexMoGAPI tool allows for a comprehensive evaluation of the environmental impact of analytical methods, rather than assessing each step in isolation. The ComplexMoGAPI tool was utilized to assess four methods

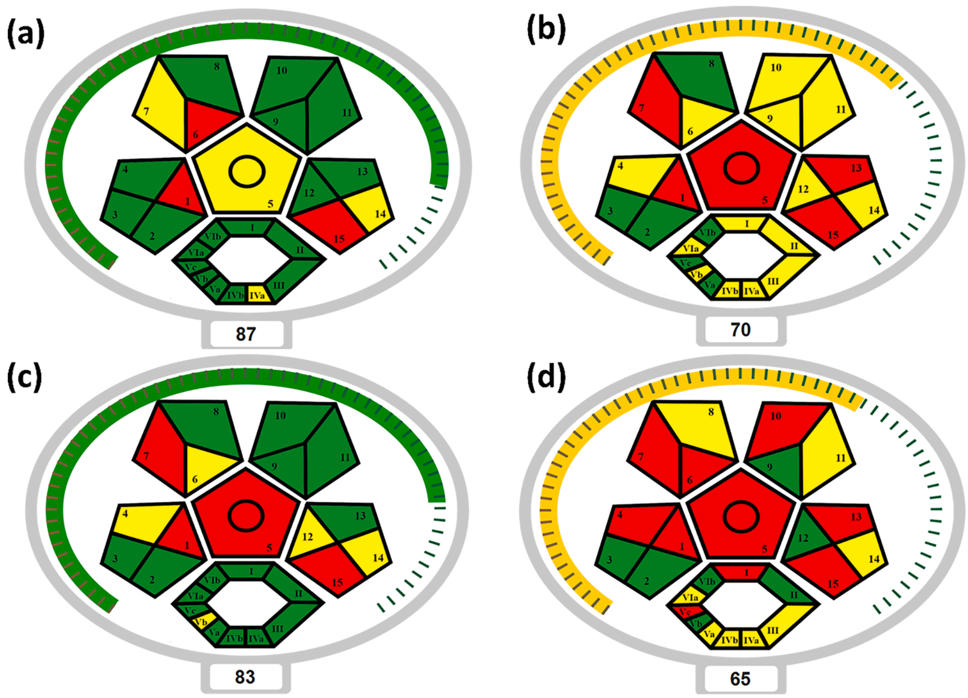

Fig. 1. ComplexMoGAPI scores of four methods used for the determination of molnupiravir (a), ritonavir (b), favipiravir (c), and polidocanol (d).

for quantifying different substances: molnupiravir in hard gelatin capsules [22], ritonavir in human plasma [23], favipiravir in human plasma [24], and polidocanol in commercial ampoules [25].

In the first method (Fig. 1a), researchers developed a novel method for detecting molnupiravir by creating fluorescent probes using carbon quantum dots (CQDs) derived from eggshell biomass waste. By employing a swift microwave heating process lasting only 90 s, researchers successfully synthesized CQDs that emitted bluish fluorescence at 408 nm when excited at 340 nm. The study demonstrated that molnupiravir could quench the fluorescence of the CQDs, indicating the formation of a non-emissive complex. This innovative approach allowed for the reliable determination of molnupiravir levels in hard capsules, achieving satisfactory percent recoveries and repeatability.

In the second method (Fig. 1b), a hybrid material composed of microcrystalline cellulose (MCC) and a metal-organic framework (MOF) was employed for efficient dispersive solid phase microextraction (dSPME) for ritonavir from human plasma. Through a series of chemical treatments involving CaCl2, soda water, and 1,3,5-benzenetricarboxylic acid, white MCC/MOF composites were prepared. These composites served as effective sorbent materials, enabling the extraction of ritonavir from human plasma for subsequent determination using high-performance liquid chromatography with UV detection.

The third method (Fig. 1c) utilized menthol-assisted homogenous liquid-liquid microextraction to analyze favipiravir in human plasma in conjunction with HPLC/UV. Optimal extraction conditions included the utilization of tetrahydrofuran as the extractant, menthol, and vortexing before centrifugation to induce phase separation and facilitate the extraction of favipiravir molecules. This method was successfully applied in a bioequivalence study involving two different formulations of favipiravir.

Lastly, the fourth method (Fig. 1d) incorporated spectrophotometry for the determination of polidocanol, a challenging non-chromophoric pharmaceutical product. The assay principle relied on the formation of a ternary complex between polidocanol and a cobalt(II)-thiocyanate complex, which could be extracted into a dichloromethane layer. By measuring the absorbance at 320 nm, researchers were able to quantify the concentration of polidocanol accurately. This approach demonstrated maximum sensitivity when utilizing dichloromethane as the extractant and specific extraction conditions involving ammonium thiocyanate mixed with polidocanol.

4. Conclusion

A new tool called ComplexMoGAPI has been created and effectively utilized to evaluate the sustainability of analytical methodologies. This enhancement to the ComplexGAPI framework allows for a comprehensive visual assessment of the method's environmental impact and safety, along with the assignment of a total score to each method. In contrast to other greenness metrics, ComplexMoGAPI presents a visual presentation that illustrates each phase of the analysis process. Furthermore, it improves the ability to compare methods based on their total scores, especially when steps vary significantly. Additionally, the software streamlines the application of ComplexMoGAPI, making it faster and more user-friendly. Our upcoming research will focus on applying this metric to practical scenarios and comparing methods in more detail.

CRediT authorship contribution statement

Fotouh R. Mansour: Writing – review & editing, Writing – original draft, Project administration, Supervision, Resources, Investigation, Conceptualization. **Khalid M. Omer:** Writing – review & editing, Writing – original draft, Project administration, Supervision, Resources, Investigation, Conceptualization. **Justyna Płotka-Wasylka:** Writing – review & editing, Writing – original draft, Project administration, Supervision, Resources, Investigation, 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

Data will be made available on request.

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