*Article*

# Green Assessment of Chromatographic Methods Used for the Analysis of Four Methamphetamine Combinations with Commonly Abused Drugs

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**Abstract:** Numerous agents with anxiolytic or stimulant effects have the potential to be overused, and their misuse is associated with serious side effects. In Saudi Arabia, the estimated percentage of Saudis who abuse drugs is around 7–8% and the age range is 12–22 years. Methamphetamine, captagon, tramadol, heroin, and cannabis/cannabinoids have been proven to be the most commonly abused drugs in Saudi Arabia, with methamphetamine being at the top of the list. The present study focuses on the chromatographic analytical methods used for the analysis of methamphetamine in combination with commonly abused drugs, aiming to point out the greenest among them. These mixtures have been chosen as they are analyzed periodically and frequently in criminal evidence and forensic medicine. Therefore, the chances of hazards for analysts and the environment are high if the mixtures are not handled appropriately. This study aims to compare 23 chromatographic methods used for the analysis of methamphetamine mixtures in four major combinations, and to assess their greenness by using three greenness assessment tools, namely, NEMI, ESA and AGREE, to recommend the greenest analytical method. The NEMI results were proven to have low discriminating abilities and, accordingly, the comparisons are based on ESA and AGREE scores. The analysis results show that the safest methods with the most eco-friendly results (based on ESA and AGREE) are the GC-MS method proposed by Mohammed et al. to analyze methamphetamine and captagon mixtures (ESA = 79 and AGREE = 0.57), the UHPLC–MS-MS method proposed by Busardò et al. to analyze methamphetamine and cannabis/cannabinoid mixtures (ESA = 78 and AGREE = 0.57), the LC-MS method proposed by Herrin et al. to analyze methamphetamine and tramadol mixtures (ESA = 81 and AGREE = 0.56), and the LC-MS method proposed by Postigo-et al to analyze methamphetamine and heroin mixtures (ESA = 76 and AGREE = 0.58).

**Keywords:** ESA; AGREE; NEMI; neurotransmitters; green chemistry; methamphetamine; captagon; tramadol; heroin; cannabis/cannabinoids

## 1. Introduction

Drug abuse is the use of excessive amounts of certain drugs, such as anxiolytic or stimulant agents, for the purpose of creating pleasurable effects which eventually result in detrimental disorders [1,2]. The Kingdom of Saudi Arabia is one of the countries that suffers from drug and alcohol addiction, which contradicts the Saudi society, including the traditions and the Islamic religion. In 2017, around 7–8% of Saudis abused drugs, 70% of which were 12–22-year-olds [3]. Methamphetamine is an N-methyl analog of amphetamine, which is considered a sympathomimetic agent [4]. A study in Jeddah/Saudi Arabia demonstrated a huge increase in methamphetamine-related deaths by about 500% between 2016 and 2018, including 61% by accidents, 21% by committed suicides and the rest by homicides [5]. Fenethylline (known as captagon) is an addictive CNS stimulant that is made of a combination of amphetamine and theophylline linked by alkyl chains, which causes irreversible serious effects, including control of judgment and capability of reasonable thinking. Due to these dangerous and adverse effects, it was prohibited worldwide in 1981 [6]. Recently, the attempts to smuggle captagon to Saudi Arabia have statistically elevated, leading to increased captagon abuse [7]. Heroin is a diacetylmorphine analog of morphine. It is an addictive opioid acting as a sympatholytic drug [8]. A study by Osman and his colleague in Jeddah stated that there were 67 serious medical complications due to heroin abuse in a cohort of 48 patients, including multiple sepsis, vein thrombosis and systemic infection [9].

Tramadol is an opioid analgesic with a chemical structure like morphine. It is a mu-receptor agonist that works by mediating neuronal excitability by gamma-aminobutyric acid (GABA) release inhibition [10]. A study in Egypt demonstrated that there was an association between tramadol abuse and cognitive impairment, especially memory impairment. Tramadol is remarkably linked to polysubstance abuse, mostly with cannabis [11]. The herbal cannabis has more than 400 components; more than 60 of them are cannabinoids known as aryl-substituted meroterpenes [12]. A retrospective study in Aseer region, Saudi Arabia, reported that 4101 and 4649 out of 8750 people had committed narcotic crimes and were job applicants, respectively. A total of 852 people (18.33%) in the narcotic group and 16 people (0.34%) in the job applicant group tested positive in the cannabis test [13]. According to a literature review and the Criminal Evidence Section—Ministry of Interior—Jeddah, KSA, methamphetamine, captagon, tramadol, heroin, cannabis, and cannabinoids proved to be the most common drugs of abuse in Saudi Arabia, where methamphetamine is considered to be at the top of the list. Accordingly, the current study is focused on the analytical methods used for the analysis of methamphetamine in combination with these commonly abused drugs. These mixtures have been chosen as they are analyzed periodically and frequently in criminal evidence and forensic medicine departments, and, accordingly, a high potential of health and environmental risks may emerge when using non-green analytical methods for such combinations.

Accordingly, the aim of this study is to compare the chromatographic analytical methods of these combinations to identify and recommend the greenest method for each combination, to reduce the risk of certain analytical activities to the environment and operators. Green analytical chemistry (GAC) was introduced in 2000 to reduce the hazardous effects that can be caused by analytical procedures [14]. As these effects may cause damage to the environment and analysts [15], it is important for chemical analysts to consider the greenness of the analytical chemical methods they work on for their health and safety and the environment, as there is increasing concern about the environmental state [16]. In GAC, it is necessary to establish a balance between achieving high-quality findings and reducing the environmental risks of analytical procedures [17]. The principles of GAC are important for achieving this balance [17]. The chromatographic methods are more common, highly precise, reproducible, and applicable to all greenness assessment tools. The literature survey indicates that there are 23 chromatographic methods for the analysis of the combinations of methamphetamine with captagon, heroin, tramadol and cannabis and/or cannabinoids. In this study, the assessment is conducted by using three assessment

tools, which are the National Environmental Method Index (NEMI), Analytical eco-Scale assessment (ESA) and Analytical Greenness metric (AGREE). NEMI is basic, uncomplicated and the oldest qualitative tool used to assess the greenness of analytical processes (by using a circle consisting of four quadrants). ESA calculates numerical values and produces a final number that reveals the greenness of the system, where 100 represents the optimal green procedure. AGREE is a new greenness assessment tool characterized by comprehensiveness, input flexibility and simple output [18,19]. The present study aims to compare the different analytical chromatographic methods and to assess their greenness by using three greenness assessment tools, to recommend the greenest chromatographic method for each combination.

## 2. Methodology

The literature review reported three chromatographic methods for the analysis of methamphetamine and fenethylline (captagon) [20–22]. While methamphetamine with cannabis or cannabinoids has six analytical methods [20,23–27], there are six analytical methods for methamphetamine and tramadol [22,28–32], and eight analytical methods for methamphetamine and heroin [20,22,33–38].

The National Environmental Method Index (NEMI) [39], introduced by the Methods and Data Comparability Board (MDCB), is the oldest and widest greenness assessment tool. NEMI is based on four quadrants that represent persistent, bio-accumulative and toxic (PBT), corrosive, hazardous and waste, as shown in Figure 1, and gives an environmental/safety profile of reagents used in chromatographic analysis. Each quadrant is colored white, which indicates less greenness of the analytical method, or green, which indicates more greenness of the analytical method. Therefore, green quadrants indicate a more eco-friendly and safe analytical method. For a hazardous quadrant, each chemical in the analytical methods is checked on the Toxics Release Inventory (TRI) chemical list [40], and if it is listed on TRI, the quadrant will be colored white, otherwise the quadrant will be green. As for PBT, searching for each chemical in its MSDS (material safety data sheet) and TRI list needs to be performed to find out which chemical is considered PBT and, hence, to color the quadrant appropriately. A corrosive quadrant depends on the pH of the chemicals used in the analytical methods, and if any mobile phase/solvent has a pH lower than 2 or more than 12, this means that the method has a corrosive impact on the environment; consequently, the corrosive quadrant will be colored white. If the amount of waste for each analytical method is more than 50 g/mL, this indicates a large waste amount, and the waste quadrant will be colored white.
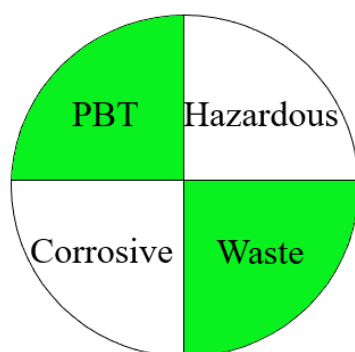


**Figure 1.** NEMI pictogram example.

Analytical Eco-Scale Assessments (ESA) [14] are based on a total score that is calculated by certain criteria, in which every analytical method is assumed to have a score of 100 and the analytical method is assessed by adding penalty points (PPs). These penalty points are subtracted from 100 to give a total score (out of 100) to indicate the safety and ecological profile of the analytical method. Penalty points count hazards, reagents, energy and waste for each analytical method. A total score of 75 or above indicates a green analytical method,

50–74 indicates an acceptable green method, and less than 50 indicates an inadequate green method. Details of ESA calculations that have been carried out are written in the Supplementary File S1.

The analytical greenness metric (AGREE) tool is a new downloadable application proposed by Pererira et al. [19]. It is based on the 12 principles of green analytical chemistry (GAC), as shown in Figures 2 and 3. Basically, it is a scoring system that has 12 sections, with each section representing one of the GAC principles. The data of each analytical method are assessed and put into the system to give a score for every section between 0 and 1, and the scores are calculated systemically to give a final score between 0 and 1, where 1 is green (eco-friendlier and safer) and 0 is red (less eco-friendly and risky). The weight or width of each section can be changed to increase the impact of some principles to the final score, depending on their importance. In the present study, the weights of Sections 7, 8, 11 and 12 were modified and increased.
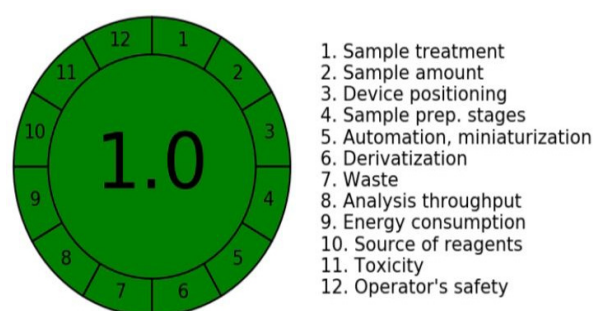


**Figure 2.** AGREE pictogram before weight modification.
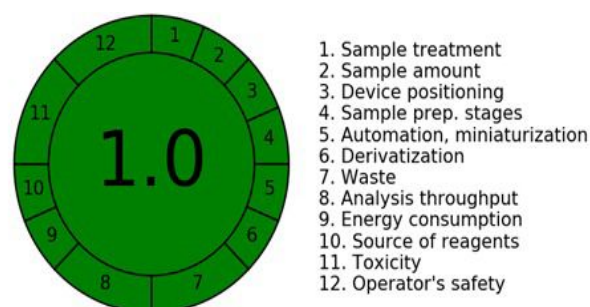


**Figure 3.** AGREE pictogram after weight modification.

The greenness assessment of all 23 chromatographic methods was carried out by applying the three greenness assessment tools, namely, NEMI, ESA and AGREE, to compare the ecological and safety profile in order to recommend the safest and most eco-friendly analytical method for each methamphetamine mixture.
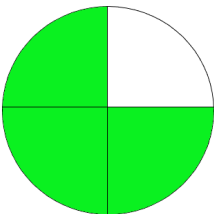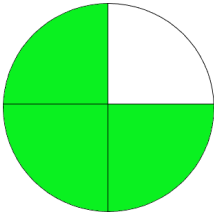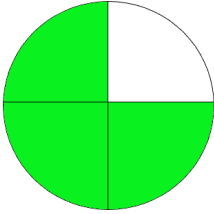
## 3. Results and Discussion

Three greenness assessment tools, NEMI, ESA and AGREE, were used separately to evaluate the greenness of all 23 chromatographic methods reported for the analysis of methamphetamine combinations. All chromatographic methods are listed in four separate tables. Each table contains the chromatographic methods of one mixture with proper references and results. The NEMI results are represented in a pictogram with four quadrants of a circle in a white–green model, where green indicates the safety and eco-friendliness of the method. The ESA results are represented as a numerical value out of 100, where higher values indicate higher safety and eco-friendliness of the analytical method. The AGREE results are represented in a pictogram colored by red, yellow and green. All 12 sections in the periphery of the circle and the inner circle represent the overall greenness with varying intensities of color and a score between 0 and 1, where 1 is the highest and 0 is the lowest score for the greenness, eco-friendliness and safety of the method.

### 3.1. Methamphetamine and Captagon

As for NEMI, all three methods have the same results in three green quadrants (PBT, corrosive and waste) and a white hazard quadrant. Accordingly, the greenest analytical method cannot be discriminated. However, the ESA and AGREE results can be used to determine the greenest method, and according to ESA and AGREE, the greenest method among the three methods is the analytical method 1.2 [21], having ESA = 79 and AGREE = 0.57, where both are higher than the other analytical methods, as shown in Table 1. As per the AGREE tool in all methods, device positioning and energy consumption have the least contribution to the greenness, whereas derivatization and analysis throughput are green in all methods. The greenness analysis results are in congruence with the earlier reports by Gamal et al. [17].
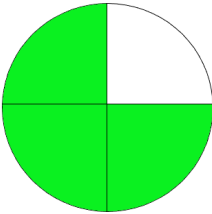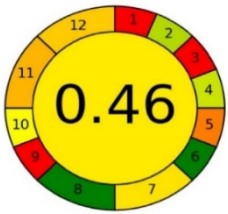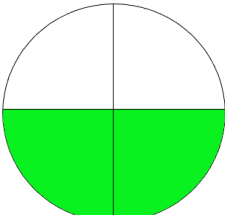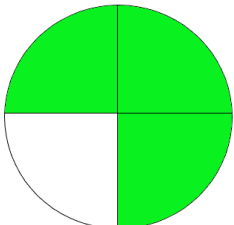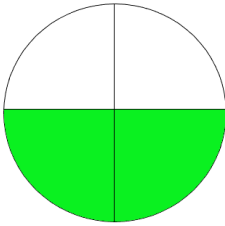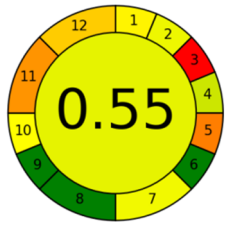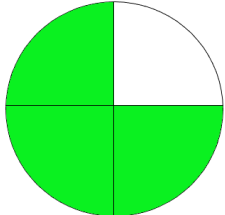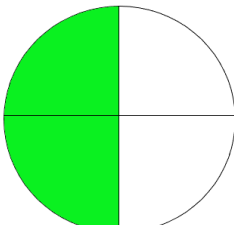
**Table 1.** Greenness assessment results of methamphetamine and captagon analytical procedures.

| Analytical Method | ESA [14] | NEMI Pictogram [39] | AGREE Pictogram [19] |
|---|---|---|---|
| Method 1.1 [20] | 69 | | |
| Method 1.2 [21] | 79 | | |
| Method 1.3 [22] | 51 | | |

### 3.2. Methamphetamine and Cannabis/Cannabinoids

The NEMI results of methods 2.1 and 2.5 are the same with three green quadrants (PBT, corrosive and waste) and a white hazardous quadrant. Method 2.3 has three green quadrants (PBT, hazardous and waste) and a white corrosive quadrant. Methods 2.2 and 2.4 are less green than the other methods, with two white quadrants for each. Therefore, the greenest method is more likely to be one of the 2.1, 2.3 and 2.5 methods, as all of them share three green quadrants. According to ESA and AGREE, the greenest method is 2.3 [24], with ESA = 78 and AGREE = 0.57, which are higher than methods 2.1 and 2.7, as shown in Table 2. As per the AGREE tool sample amount, derivatization and analysis throughput contribute to greenness in all methods, whereas device positioning and energy consumption are the least green in most of the methods. The findings are in agreement with the earlier reports [17].

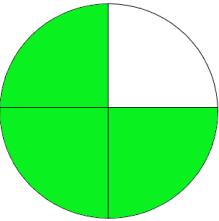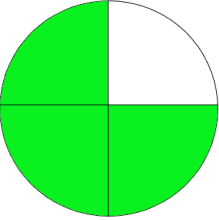**Table 2.** Greenness assessment results of methamphetamine and cannabis/cannabinoid analytical procedures.
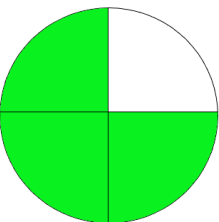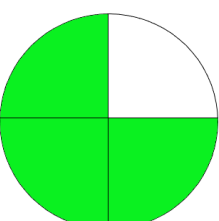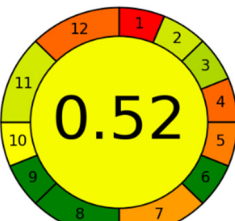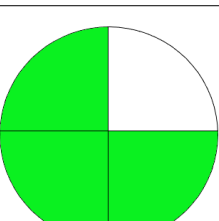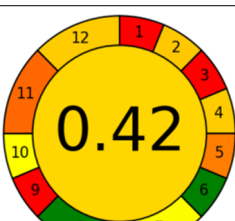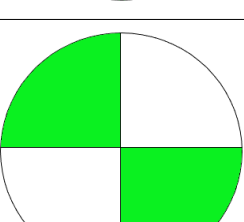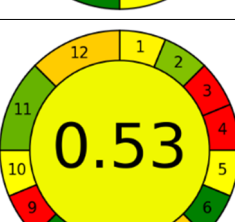
| Analytical Method | ESA [14] | NEMI Pictogram [39] | AGREE Pictogram [19] |
|---|---|---|---|
| Method 2.1 [20] | 69 | | |
| Method 2.2 [23] | 70 | | |
| Method 2.3 [24] | 78 | | |
| Method 2.4 [25] | 69 | | |
| Method 2.5 [26] | 70 | | |
| Method 2.6 [27] | 74 | | |

*3.3. Methamphetamine and Tramadol*

In the NEMI assessment tool, the analytical methods (3.1, 3.2, 3.3, 3.4 and 3.5) have the same results with three green quadrants (PBT, corrosive and waste) and a white hazardous quadrant. Method 3.6 has two green quadrants (PBT and waste) and two white quadrants (corrosive and hazardous). With these results, the greenest method cannot be decided because five methods have three green quadrants. Based on ESA and AGREE, method

3.3 [30] was found to be the greenest with an ESA score of 81 and AGREE score of 0.56, as shown in Table 3. As per the AGREE tool, sample amount, derivatization and analysis throughput contribute to greenness in all methods, whereas device positioning (except method 3.4) and energy consumption are the least green in most of the methods. The results are similar to the earlier reports of greenness analysis using the NEMI, ESA and AGREE tools [17].

**Table 3.** Greenness assessment results of methamphetamine and tramadol analytical procedures.

| Analytical Method | ESA [14] | NEMI Pictogram [39] | AGREE Pictogram [19] |
|---|---|---|---|
| Method 3.1 [28] | 78 | | |
| Method 3.2 [29] | 72 | | |
| Method 3.3 [30] | 81 | | |
| Method 3.4 [31] | 70 | | |
| Method 3.5 [22] | 51 | | |
| Method 3.6 [32] | 68 | | |

### 3.4. Methamphetamine and Heroin

Among the eight methods, methods 4.2, 4.3, 4.4, 4.6, 4.7 and 4.8 have the same result in NEMI, with three green quadrants (PBT, corrosive and waste) and a white hazardous quadrant. Method 4.1 has two white quadrants (PBT and hazardous) and two green quadrants (corrosive and waste), while method 4.5 has two white quadrants (corrosive and hazardous) and two green quadrants (PBT and waste). According to the NEMI results, the greenest analytical method cannot be discriminated because six methods share three green quadrants. On the other hand, the ESA and AGREE results can be used to determine the greenest method, and, accordingly, the greenest method among the eight methods is method 4.4 [35], with ESA = 76 and AGREE = 0.58, which are higher than the other methods, as shown in Table 4. As per the AGREE tool, the analysis throughput is green in all methods, whereas the energy consumption is the least green. The results are similar to the earlier reports [17].

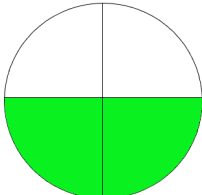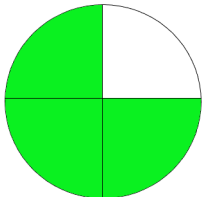**Table 4.** Greenness assessment results of methamphetamine and heroin analytical procedures.
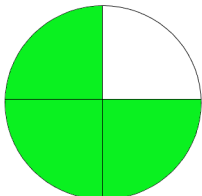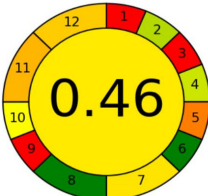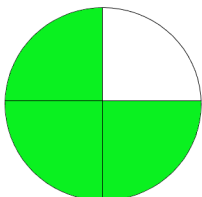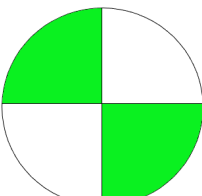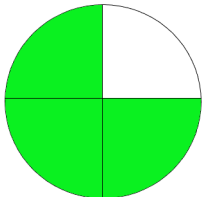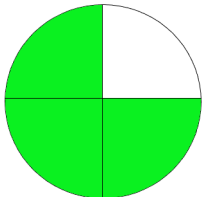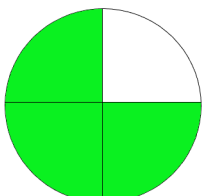
| Analytical Method | ESA [14] | NEMI Pictogram [39] | AGREE Pictogram [19] |
|---|---|---|---|
| Method 4.1 [33] | 69 |  |  |
| Method 4.2 [34] | 70 |  |  |
| Method 4.3 [20] | 69 |  |  |
| Method 4.4 [35] | 76 |  |  |
| Method 4.5 [36] | 73 |  |  |

**Table 4.** *Cont.*

| Analytical Method | ESA [14] | NEMI Pictogram [39] | AGREE Pictogram [19] |
|---|---|---|---|
| Method 4.6 [37] | 67 | | 0.46 |
| Method 4.7 [22] | 51 | | 0.42 |
| Method 4.8 [38] | 65 | | 0.48 |

## 4. Conclusions

The GC-MS method proposed by Mohammed et al. [21] is a safe method and is considered to be the most eco-friendly method to analyze methamphetamine and captagon combinations, with ESA = 79 and AGREE = 0.57. The UHPLC–MS-MS method proposed by Busardò et al. [24] is safe and the most co-friendly method to analyze methamphetamine and cannabis/cannabinoid combinations, with ESA = 78 and AGREE = 0.57. The LC-MS method proposed by Herrin et al. [30] is safe and the most eco-friendly method to analyze methamphetamine and tramadol combinations, with ESA = 81 and AGREE = 0.56. The LC-MS method proposed by Postigo et al. [35] is safe and is considered the most eco-friendly method to analyze methamphetamine and heroin combinations, with ESA = 76 and AGREE = 0.58.

NEMI, as a greenness assessment tool, proved to be inefficient in discriminating the greenness of methods; other numerical tools, such as ESA and AGREE, showed more distinct results. AGREE proved to be the best, owing to its qualitative and quantitative greenness assessment features that are presented in the graphs, and, therefore, it would be the most recommended tool for comparisons.

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