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Derivatization-free sustainable spectrofluorimetric estimation of antihistamine drug mizolastine in pharmaceutical and biological matrices

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Abstract

Mizolastine is an antihistamine drug that is commonly used for treatment of chronic urticaria and allergic rhinitis. In this study, a facile, rapid, and sustainable fluorimetric method was established for the estimation of mizolastine in pharmaceutical and biological matrices for the first time. The approach methodology relied on the direct assessment of mizolastine's intrinsic fluorescence at 313 nm after excitation at 272 nm. This intrinsic fluorescence, stemming from the benzimidazole fluorophore moiety in mizolastine structure, serves as a distinctive marker for its precise quantification in the spiked human plasma and pharmaceutical formulations with high %recovery. The method exhibits reasonable sensitivity with lower limits of detection and quantification of 5.4 and 16.6 ng mL^{-1}, respectively, across a concentration range of 25.0–2000.0 and 50–1000 ng mL^{-1} for the standard mizolastine analysis and mizolastine assay in the plasma sample, respectively. Moreover, the established method was applied to assess tablet content uniformity and mizolastine assay in plasma samples with high recoveries (98.50–100.20%). Such applications underscore the method's potential applicability within quality control laboratories, preventing the need for sample preparation or laborious extraction steps. Finally, the method's sustainability and practicality were confirmed by applying different greenness and whiteness metrics, yielding excellent results.

Keywords: Mizolastine; Spectrofluorimetry; Sustainability; Pharmaceutical formulations; Human plasma

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1. Introduction

Mizolastine (MST) is an antihistamine agent of the second generation (Figure 1), it is an efficient substitute for other second-class generation antihistamines in the controlling of seasonal rhinitis, idiopathic urticarial, and allergic conjunctivitis [1-4]. It acts via fast blocking of H_1 receptors without prohibiting the production of histamine substance from mast cells but it only prohibits histamine from binding to its receptors [1-4]. It provides symptomatic relief from allergy-related symptoms, including itching of the eyes, nose, and throat, as well as watery eyes and nasal congestion. It helps improve the quality of life for individuals affected by allergic conditions [5, 6]. It has a long period of action, allowing for one-time dosing in most cases. This convenience enhances treatment adherence and patient compliance [7-9]. Overall, MST is an effective and well-tolerated medication for the management of allergic rhinitis and chronic idiopathic urticaria, offering relief from allergy symptoms with minimal sedation and anticholinergic effects. However, as with any medication, it should be used under the guidance of a healthcare professional and according to the prescribed dosage regimen [10, 11]. Even then, the literature survey unveils a few analytical methods that have been designated for the assay of MST comprising; LC with mass spectrometric detection [12], HPLC [13, 14], spectrophotometric [15] and electrophoretic method [16]. Also, MST has been detected by a chemiluminescence method based on using bis(2,4,6-tricholorophenyl) oxalate (TCPO)–H_2O_2 chemiluminescence in the presence of rhodamine 6 G [17].

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Fluorescence spectroscopy is recognized as an appropriate and approved sensing technique, facile, and the usual use of it in most analytical laboratories. It is also a cost-effective technique with high sensitivity and selectivity, making it a viable option for different target detection [18-20]. Indeed, the literature survey did not depict any method adopting a fluorescence mode for detecting MST. From this context, we are dedicated to developing the first spectrofluorimetric approach for the estimation of MST in spiked human plasma and pharmaceutical dosage forms. The designed method used herein relies on the assessment of mizolastine's intrinsic fluorescence in a green solvent (water) at a wavelength of 313 nm. This method has several merits over the reported methods such as greenness, selectivity, simplicity, rapidity, sensitivity, and less time consumption compared with other published methods.

2. Experimental

2.1 Reagents and Materials

MST sample was delivered by Medizen Pharmaceutical Industries (4th Industrial Zone, Alexandria, Egypt) and utilized as received. Lastlerge® tablets (10.0 mg MST/tablet, Batch No. 0240–02) were gotten from local pharmacies. All chemicals were of analytical grade; methanol, ethanol, acetonitrile, sodium acetate trihydrate, NaOH, HCl, H_2SO_4, CH_3COOH, Sodium lauryl sulfate, Beta-Cyclodextrin (β-CD), Cetrimonium bromide (CTAB) and Tween-80 were brought from El-NasrCompany for Chemicals (Cairo, Egypt). Acetate buffer solution (pH 3.6 – 6) was also used in our experiments. Human plasma samples were obtained from Blood banking (Luxor, Egypt), and they were kept frozen at -20 °C till they were used.

2.2 Instruments

A fluorescence spectrometer with monochromators (10 nm as a slit width) was applied in our assay. Additionally, a pH meter (METTLER TOLEDO, Switzerland) and a centrifuge operating at 5000 rpm (HERLME, Germany) were employed.

2.3 MST standard solution

A stock ethanolic MST standard solution of 50.0 μg mL^{-1} was prepared by accurately weighing and dissolving 5.0 mg of MST in 100 mL of ethanol with sonication for 30 min. This solution was further diluted with ethanol and the diluted solution was used for preparation of the working solutions which are directly analysed by spectrofluorimetry.

2.4 Procedures

2.4.1 MST Assay Procedure

Different aliquotes of MST standard solution were inserted into a series of 10-mL measuring flasks for preparation of MST working solutions within the concentration range (25 – 2000 ng mL^{-1}). After that, the volume in the flasks was accomplished to the mark (10 mL) using dist. water as the diluting solvent. The flasks were then mixed well, and analysed fluorometrically at 313 nm after excitation at 272 nm.

2.4.2. General procedures for tablets assay

Five Lastlerge® tablets were crushed, and an accurate weight, corresponding to 10.0 mg of MST was conveyed to a 100-mL volumetric tube. Then, a concentration of 100.0 μg mL^{-1} was obtained by dissolving a powder of 10.0 mg in 80 mL ethanol, then the solution was accomplished to the mark with ethanol and finally, the solution was filtered. Later, different aliquots within the linearity were investigated following the MST assay procedures.

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2.2. 3 Spiked plasma samples analysis

Different aliquotes of MST authentic solutions were added to plasma samples (1.0 mL each) to obtain MST-spiked plasma samples over the measurement range. The mixtures were vortexed and then diluted with methanol for protein precipitation. After centrifugation and filtration, the clear supernatants were collected for assay. The fluorescence of the spiked plasma samples was then monitored at 313 nm after excitation at 272 nm.

3. Results and discussion

3.1 Development of fluorescence

Spectrofluorimetry emerged as a potent analytical implement in chemical as well as pharmaceutical investigations [21]. Its utility spans various domains, prominently in detecting and quantifying an array of analytes and medicinal substances [22-33]. A key strength lies in its innate sensitivity, permitting the detection of small substance amounts in intricate matrices. Alongside sensitivity, spectrofluorimetry offers high selectivity, ensuring accurate identification within intricate mixtures [34]. Furthermore, this technique delivers speed and ease, often demanding minimal sample preparation while delivering prompt outcomes [35]. Its versatility across diverse compounds and the capacity for precise quantification at low amounts make it indispensable in pharmaceutical exploration, quality assurance, and clinical diagnostics. The inherent fluorescence of MST was ascribed to benzimidazole fluorophore moiety which acts as a fingerprint for MST, enabling its selective determination at λ_{em} 313 nm after excitation at λ_{ex} 272 nm (Figure 2). Figure 2 shows the emission spectra of different concentrations of MST. Notably, the effect of pH and different surfactans have no effect on the the fluorescence intensity of MST and we will disscuse these effects and their reasons indeatils later.

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3.2. Method optimization

Experimental conditions which affect the fluorescence intensity of MST were checked and optimized. These factors include the effects of pH, organized media, and diluting solvents.

3.2.1. Effect of pH

In this work, diversified acids such as HCl, $HClO_4$, CH_3COOH, H_2SO_4, H_3PO_4 (1.0 M) and acetate buffer (0.1 M, pH 3.6 – 6) were utilized to study their effect on the fluorescence of MST. By the addition of acids or acetate buffer, a decrease in the intensity of fluorescence (FI) of MST was observed (Figure. 3). As yet the pH did not affect the fluorescence of MST. Also, we have checked the effect of different pH values of acetate buffer solution on the fluorescence intensity of MST and we found that acetate buffer with different pH values does not affect the fluorescence intensity of MST (Figure S1).

3.2.2. Effect of organized media

Different types of surfactants were added above their critical concentrations such as Tween 80 (0.2 % v/v), SLS (0.2 % w/v), CTAB (0.2 % w/v), and β-CD (0.2 % w/v) to see their effects on the fluorescence behavior of MST. Notably, there was no effect of these surfactants on the fluorescence of MST (Figure 4). In some cases, micelles enhance the fluorescence intensity of certain drugs to a high extent [36, 37]. However, in our case, none of the investigated micelles improved the fluorescence intensity of the studied analytes and this could be attributed to photophysical properties of MST, complex dynamics of drug-micelle interaction, incompatibility of the investigated surfactants with the analyte, or FRET quenching.

3.2.3. Effect of solvent for dilution

To select the best diluting solvent, various types of solvents were tested such as distilled water, methanol, ethanol, acetone, and acetonitrile. The results indicated that distilled H_2O was the best

diluting solvent, as it achieved the maximum light emission. This adds a valuable advantage to the developed method in terms of method greenness (Figure 5).

3.3 Method validation

The developed spectrofluorimetric method was validated according to ICH validation for analytical procedures guidelines [38].

3.3.1 Calibration Curve

Numerous concentrations of MST solutions as well as spiked human plasma samples were effectively prepared. The relative fluorescence intensity (RFI) was then plotted against the above-prepared MST solutions to create calibration plots for both MST standards and spiked human plasma samples. For the standard MST solutions, the concentration range studied was 25-2000 ng mL^{-1}, and the calibration plot was found to be linear over this range (Table 1). In contrast, the calibration graph for spiked plasma samples was ranging from 50 to 1000 ng mL^{-1}.

3.3.2 Limits of Detection (LOD) and Quantitation (LOQ)

We evaluated the sensitivity of the introduced method by computing the LOD and LOQ. Following the ICH guidelines [39], we utilized the recommended equations:

LOD= 3.3 σ/S & LOQ= 10 σ/S

(where "σ" refers to the standard deviation of the blank and "S" to the slope of the OLP calibration graph). As depicted in Table 1, the LOD as well as LOQ values were 5.40 and 16.60 ng mL^{-1}, respectively. Furthermore, a comparison of the developed method with other reported methods was carried out. Table S1 shows that the low detection limit of the proposed method indicates the high sensitivity in comparison to the previous reports.

3.3.3 Accuracy and precision

For the accuracy evaluation, a standard addition methodology was utilized. The high recoveries, (98.70 ± 0.60 to 100.10 ± 0.50 %), which are illustrated in Table 2 affirm the elevated accuracy

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of our new fluorimetric method. The reproducibility of the established approach was checked by calculating the relative standard deviation values at distinct concentrations (50, 500, and 2000 ng mL^{-1}). The outcomes obtained are presented in Table 3, revealing that the estimated %RSDs were very small and fewer than 2.0 %, specifying the acceptable precision of our proposed approach.

3.4. Estimation of MST in Commercial Dosage Form

To evaluate the real implementation of our new approach in real sample analysis, a comparison was made between the results obtained from our newly introduced strategy and those derived from a formerly reported spectrophotometric procedure [15]. The results acquired from both strategies for the detection of MST in the dosage form were subjected to statistical analysis, employing t- and F-tests (95% confidence level). Inspection of the outcomes, as presented in Table 4, indicated no significant alterations between the outcomes of the two methods. This statistical analysis affirms the method's accuracy and precision, highlighting its reliability and suitability for pharmaceutical quality control purposes. Furthermore, the selectivity of the developed method was evaluated by investigating the interference probability from the excipients that might be added during pharmaceutical formulation. Hence, samples were prepared by mixing a known amount of (10 mg MST) with different quantities of the common excipients, for example, mannitol (5 mg), microcrystalline cellulose (10 mg) and magnesium stearate (10 mg). Then the suggested method is applied for the analysis of laboratory-prepared samples using the general described procedure. The recovery values were found to be in the range of 100.00 ±1.50 to 101.30 ± 0.20 % (Table S2). The attained results confirmed the high selectivity of the developed method for the detection of MST in commercial dosage forms in the presence of common excipients.

3.5. Content uniformity

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The analytical protocol introduced in this study not only demonstrates remarkable sensitivity but also exhibits consistent repeatability, enabling the precise determination of MST content in individual tablets. By analyzing a sample size of ten tablets, the results reveal that the acceptance record (AV) consistently falls below the highest allowed acceptance record (L1) when adhering to the content uniformity procedure as outlined in the United States Pharmacopeia (USP) guidelines [40] (Table 5). This underscores the method's effectiveness in ensuring the uniform distribution of MST content among multiple tablets, thereby meeting stringent pharmaceutical quality standards.

3.6. Application to spiked human plasma

Table 6 spectacles high extraction recovery rates (98.50 ± 1.30 to 100.20 ± 0.50%) for MST analysis in spiked plasma samples, signifying the proposed method's high accuracy. The developed fluorimetric strategy effectively detects MST in spiked plasma samples. Our work found that the concentration of MST in plasma samples may be determined by a linear regression equation (RFI = 0.318 × $Conc_{(ng/mL)}$ - 0.83) relying on the obtained spiking calibration plot.

3.7. Greenness and whiteness assessment of the developed method

Greenness and whiteness evaluation of the developed approach were accomplished to check the eco-friendliness, analytical performance, and practical effectiveness of the proposed spectrofluorimetric method. For the greenness evaluation, two metric systems, named Analytical Eco-Scale [41, 42] and Analytical GREEnness (AGREE) were employed to estimate the greenness step of our established fluorimetric strategy. Analytical Eco-Scale involved the assessment of the twelve principles of green analytical chemistry and the assignment of penalty points to each aspect. Toxic reagent points, waste generation, or high energetic demand were subtracted from base 100 and the number of remaining points; the analyst could decide whether

the procedure is ideally green, acceptable, or not. AGREE [42] is a comprehensive, adaptable, and facile evaluation approach that yields easily interpretable and meaningful outcomes. It has been widely employed to inspect the greenness of numerous analytical techniques with high efficiency [43-48]. In brief, the AGREE software can determine the color and a scale in 0–1 range for each principle of the twelve principles, which depicts its degree of greenness. The AGREE pictogram shows the output as a clock-like graph, with the total score and color representation in the middle. Table 7 and Figure 6 reveal that the established fluorimetric strategy has an Eco-scale adjacent to 100, with an overall AGREE score of 0.86 and a core green color, indicating its greenness.

For the whiteness evaluation, the RGB-12 model was used to demonstrate how the analytical performance (represented in red color), safety and eco-friendliness (represented in green color), and practicality (represented in blue color) of the developed method were covered [49-51]. This model was designed to be a comparative tool for evaluation of up to 10 methods and comparison between them regarding the Green Analytical Chemistry (GAC) and White Analytical Chemistry (WAC) merits [49, 50]. Therefore, we employed this model to compare the whiteness of the developed method with five reported methods [12, 13, 15-17] employed for the assay of MST in various matrices. The results illustrated in Figures 7 and S2 indicate the whiteness of the developed method since it produced a 97.5% score for the methods's analytical performance, 95.8% score for the method's eco-friendliness (green), 92.3% score for the method's practicality (blue), and an overall score of 95.2% (white). Although the liquid chromatography-electrospray ionization-mass spectrometric (LC-ESI-MS) method produced higher sensitivity, the instrumentation cost and the high volume of hazardous organic solvent in the mobile phase resulted in low scores of greenness and practicality.

4. Conclusion

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In this work, a green and facile fluorescence strategy for the assay of MST was conducted for the first attempt. The designed method presented numerous valuable merits, for instance, greenness, accuracy, simplicity, selectivity, and convenience. The LOD and LOQ were estimated to be 5.4 and 16.60 ng mL^{-1}, respectively, with a linearity of 25–2000 ng mL^{-1}. Our results showed that the linearity range of MST in human plasma was 50 – 1000 ng mL^{-1}, with percentage recovery ranging from 98.50 ± 1.30 to 100.20 ± 0.50 % for the MST analysis in plasma samples. The greenness, as well as whiteness of the described strategy, were efficiently evaluated using diverse metrics, indicating its excellent greenness and whiteness. The greenness, selectivity, sensitivity, and accuracy of the introduced fluorimetric strategy tolerate its implementation in quality control laboratories replacing more complicated and time-consuming chromatographic methods for MST quantification.

Conflict of Interest

The authors declare no conflicts of interest.

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Figure Legends:

Figure 1. Chemical structure of mizolastine (MST).

Figure 2. Emission spectra of MST at λ_{em}= 313 nm and λ_{ex}= 272 nm.

Figure 3. Effect of different types of acids on RFI of MST (200.0 ng mL^{-1}).

Figure 4. Effect of different organized media; β-CD (0.2 % w/v), SDS (0.2 % w/v), CTAB (0.2 % w/v) and Tween-80 (0.2 % v/v) on RFI of MST (200.0 ng mL^{-1}).

Figure 5. Effect of diluting solvents on RFI of MST (200.0 ng mL^{-1}).

Figure 6. Greenness evaluation of the developed method using Analytical GREEnness (AGREE) metric approach.

Figure 7. Comparison of five reported methods for determination of mizolastine in different matrices with our method (spectrofluorimetry) using the RGB-12 model.

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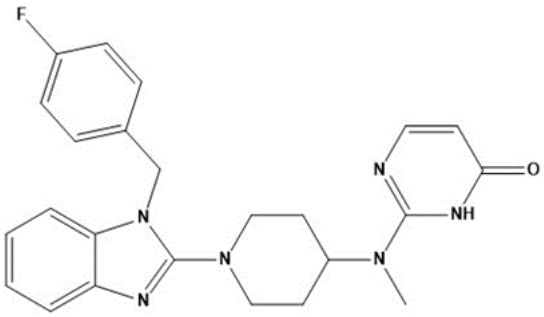


Fig. 1.tif

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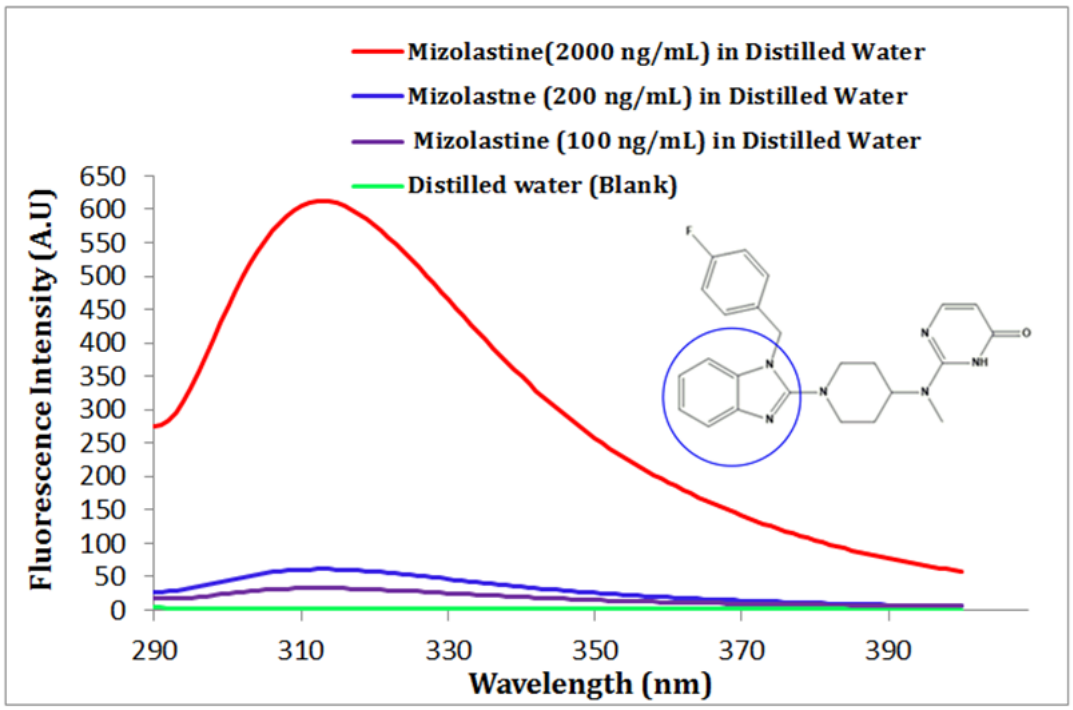


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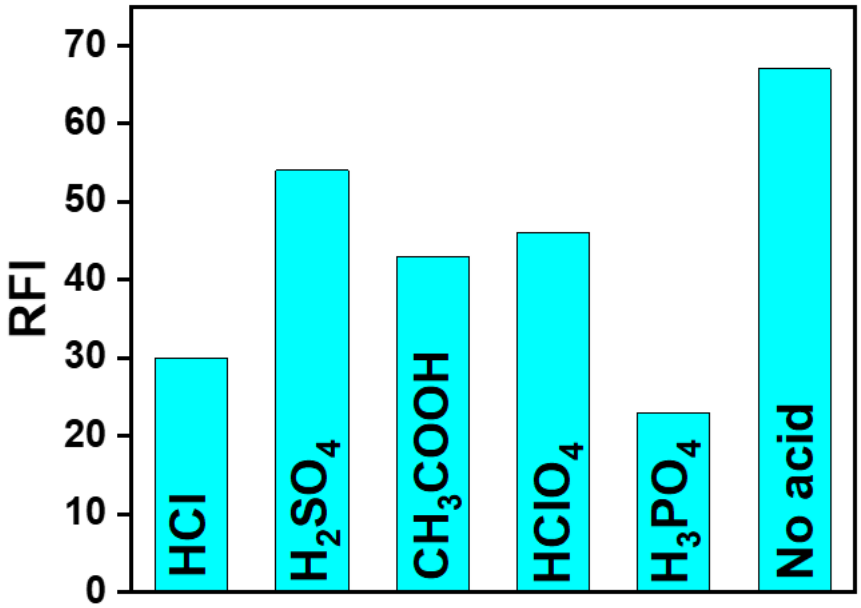


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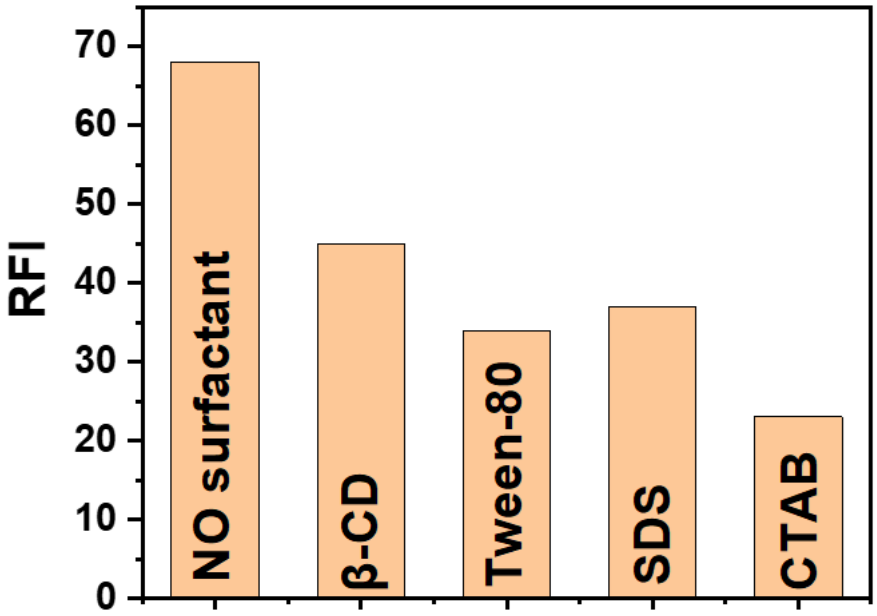


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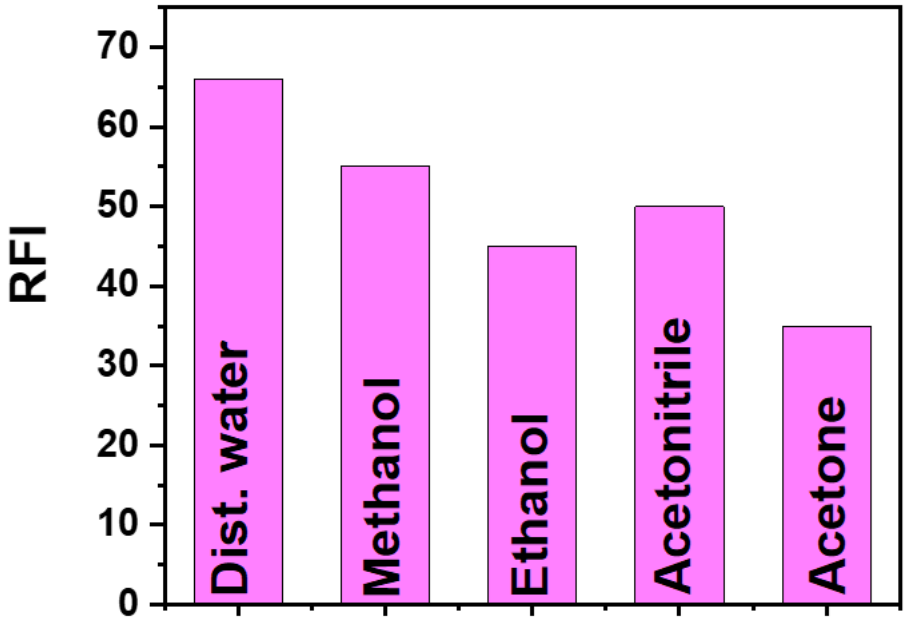


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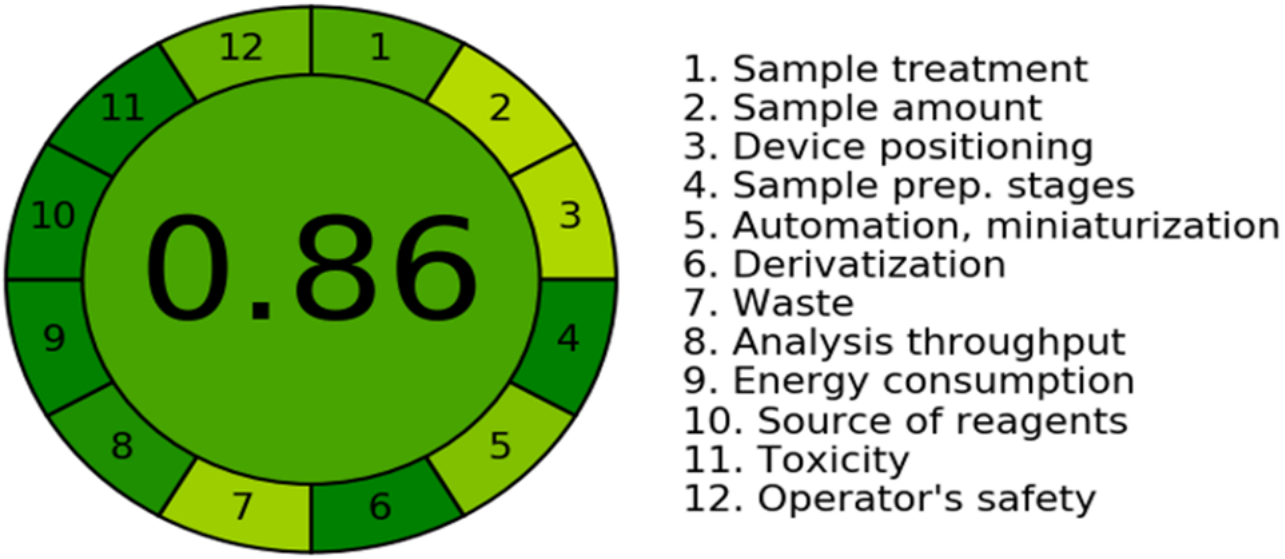


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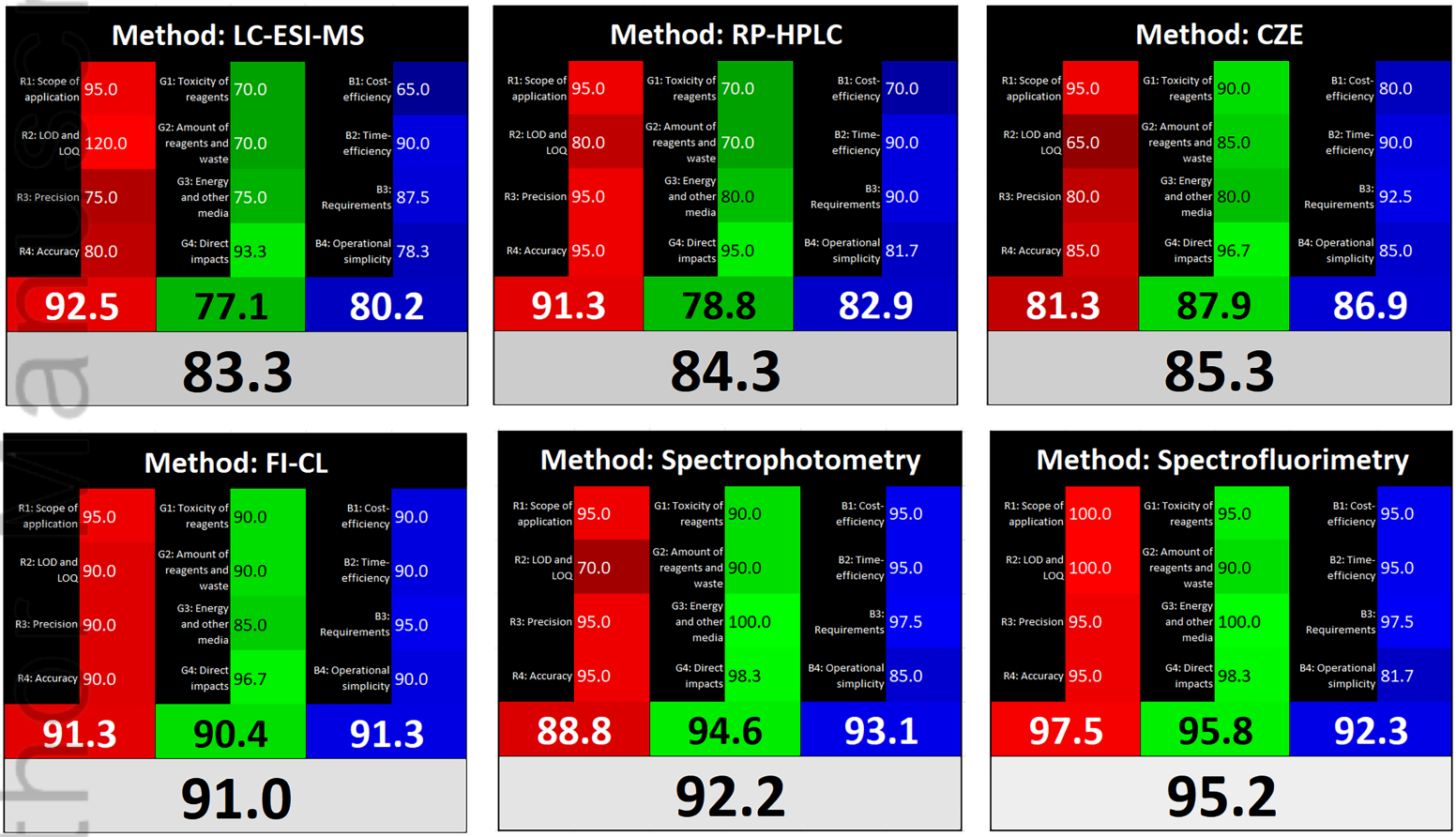


Fig. 7.tif

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