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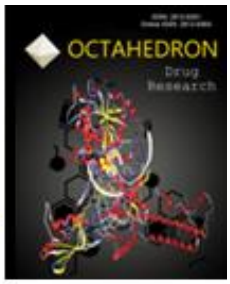

Highly Sensitive green spectrofluorimetric method for determination of metoclopramide via enhancement of its native fluorescence by micellar formation with sodium dodecyl sulfate

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ABSTRACT

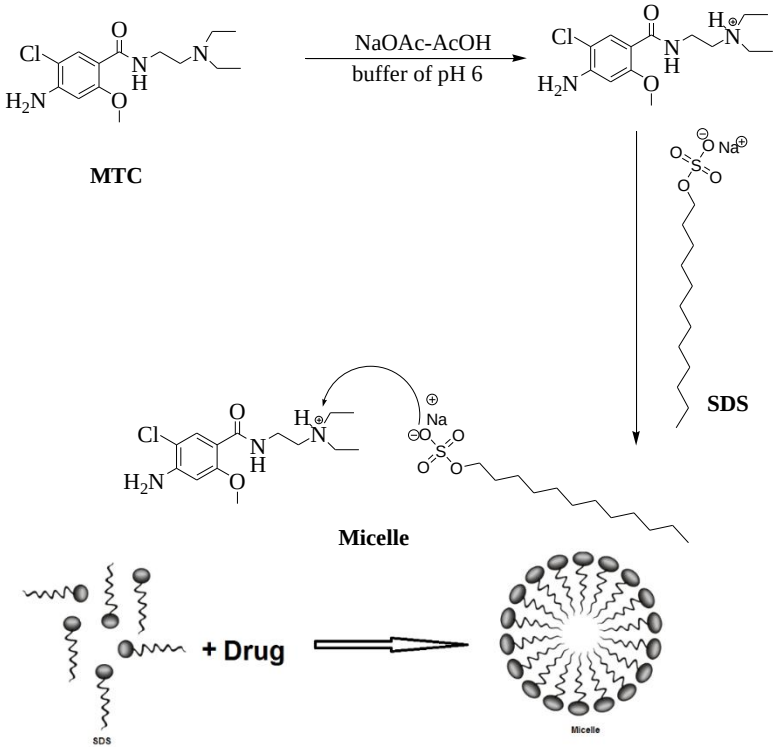
A new simple, accurate, green, a highly sensitive, non-extractable, economic, and rapid spectrofluorimetric method was developed for the determination of metoclopramide hydrochloride (MTC) in its pharmaceutical formulations and spiked human plasma. The method was based on enhancement of the native fluorescence of the studied drug via micellar formation with an anionic surfactant sodium dodecyl sulfate (SDS). The formed micellar fluorescence was measured at 347 nm after excitation at 310 nm. The micellar formation with SDS leads to enhancement of native fluorescence for MTC by about 550%. The fluorescence intensity was directly proportional to the drug concentrations over the concentration range of 25-1500 ng mL^{-1}. The detection limit of 8 ng mL^{-1} and with a quantitation limit of 24 ng mL^{-1} .The proposed analytical method was validated according to ICH guidelines and the results were acceptable. The proposed analytical method has been successfully applied for the determination of the studied drugs in its pharmaceutical formulations as well as spiked human plasma and gives an excellent % recovery. The results show excellent agreement with the reported method with respect to precision and accuracy. The greenness of the proposed method was assessed by GAC principle and AGREE method.

1.Introduction

Metoclopramide, (MTC) is 4-Amino-5-chloro-N-(2-diethylamino-ethyl)-2-methoxy-benzamide,Metoclopramide has dopamine antagonist effect in the central nervous system and other organ systems, its action on the medullary chemoreceptor

trigger zone makes it clinically useful as a routine antiemetic and in preventing vomiting induced by antineoplastic drugs, particularly cisplatin.it is primarily used in adults and children as an antiemetic drug or a gastrointestinal prokinetic drug [1]. It promotes stomach peristalsis, which speeds up gastric emptying, and stimulates the motility of the upper gastrointestinal system without influencing gastric, biliary, or pancreatic output. Additionally, duodenal peristalsis is accelerated, speeding up intestinal transit. The pyloric sphincter is relaxed, and the gastro-esophageal sphincter's resting tone is raised. In addition to being a dopamine-receptor antagonist with a direct impact on the chemoreceptor trigger zone, metoclopramide also exhibits parasympathomimetic action [1]. It might possess 5-HT_3 serotonin receptor antagonist characteristics. Metoclopramide is used to treat nausea and vomiting that are brought on by a variety of gastrointestinal illnesses, migraine, surgery, or cancer treatment. It is also used to treat disorders of gastro-esophageal reflux disease and dyspepsia. Motion sickness cannot be prevented or treated with metoclopramide [2]. Different analytical methods were proposed for the determination of MTC in different solutions, these methods including spectrophotometry [3-5], spectrophotometry [6,7], HPLC[8,9], HPTLC[10], and electrochemical method[11].

Spectrofluorometric methods as a method of analysis used for determination of different medications in different samples type with high sensitivity and accuracy [12-19]. The main objective of this work is to create a green, simple, economic, accurate, and sensitive spectrofluorometric method for the precise and reproducible determination of the studied drug in different pharmaceutical preparations as well as spiked human plasma. To the best of our knowledge, up till now only a few spectrofluorimetric methods for analysis of MTC. The proposed method has advantages of being simple, sensitive, economic, and environmentally friend. This method was based on enhancement of the native fluorescence of the studied drug in the presence of an anionic surfactant sodium dodecyl sulfate (SDS). The aggregation process of SDS and the studied drugs was investigated at the critical micelle concentration (CMC). Under stable optimal conditions (scheme.1), the proposed method was used for the quantitative determination of the studied drug in its pure forms as well as its pharmaceutical formulations and spiked plasma. The method was validated according to ICH guidelines.



Scheme 1. The suggested mechanism for drug-SDS micelle formation.

2. Experimental

2.1. Instrumentation

Fluorescence spectrometer FS-2 (Scinco, Korea), coupled to a Dell PC, with a 1 cm quartz cell, grating excitation and emission monochromators with slit widths adjusted to 5 nm, and a 400 V PMT voltage. Laboratory centrifuge speed of 18,659 g-forces, Jenwey pH meter type 350 (E.U.), Bremsen ECCO, Germany.

2.2. Materials and reagents

All materials and reagents used in the study were of analytical grade. Metoclopramide hydrochloride was kindly provided by Amoun pharmaceutical company (El Obour city, Cairo, Egypt). SDS was purchased El Nasr Chemical Co., (Abo-Zaabal, Cairo, Egypt). Carboxy methyl cellulose, cyclodextrin, and Tween 60 and 80 were obtained from El Nasr Chemical Co., (Abo-Zaabal, Cairo, Egypt). All other chemicals including ethanol, methanol, dimethylformamide phosphoric acid, citric acid, boric acid, acetic acid, sodium acetate, hydrochloric acid, and sodium hydroxide were obtained from El Nasr Chemical Co., (Abo-Zaabal, Cairo, Egypt). In distilled water, various buffer types with a variety of pH values were created. Assiut University Hospital in Assiut, Egypt generously donated human plasma samples, which were gently thawed before being used for testing.

2.3. Pharmaceutical dosage forms.

The following available pharmaceutical products were analyzed primperan® tablets (batch No. 5EG003), labeled to contain 10 mg of metoclopramide/tablet, produced by Sanofi-Aventis Egypt. Meclopram® tablets (batch No. 3159014), labeled to contain 10 mg of metoclopramide/tablet, produced by Alexandria co. for pharmaceutical industries. Alexandria, Egypt. All Pharmaceutical dosage forms were purchased from a local pharmacy.

2.4. Preparation of the standard drug solution

Stock standard solution (100 μg mL^{-1}) of MTC was prepared by transferring an accurately weighted MTC salt powder equivalent to 10mg MTC into a 100ml volumetric flask, diluted with distilled water, and dissolved well, then completed to the mark with distilled water. The working solution was obtained by further dilutions with distilled water immediately before use. SDS 10 mM solution was obtained by transferring an accurately weighted 288mg of SDS powder into a 100ml volumetric flask, diluted with distilled water, and dissolved well, then completed to the mark with distilled water.

2.5. General analytical procedure

Transfer accurately measured aliquots of the working solutions that gives the final concentration is in the range of 0.025-1.5 μg/ml into a series of 10.0mL volumetric flasks,1ml of SDS (10 mM) solution ,1mL of acetate buffer pH 6 were added to each flask and the volume was completed to 10ml mark with distilled water. A portion of the solution was transferred to a fluorescence cuvette and the fluorescence intensity was measured at λ exc = 310 nm and λ em = 347 nm. The emission and excitation monochromator slit width were set at 5nm. All measurements were performed at room temperature in 1cm quartz cell.

2.6. Procedure for pharmaceutical dosage form

Twenty tablets of primperan®, and Meclopram® were weighted accurately, finely powdered, and mixed thoroughly. An accurate amount equivalent to 10 mg of MTC was weighted and transferred into a 100-mL volumetric flask, dissolved in about 50ml of methanol. The contents of the flask were swirled, sonicated for 5 min, and then completed to volume with methanol to the mark. The contents were mixed well and filtered the first portion of the filtrate was rejected. The prepared solution was further diluted quantitatively to obtain final concentration within the concentration range of the calibration, and then the general analytical procedure was followed.

2.7. Procedure for spiked human plasma

According to institutional procedures, the plasma sample was graciously collected from healthy, human male volunteers at Assiut University Hospital in Assiut, Egypt. In a heparinized tube, 5.0 mL of drug-free human blood was drawn, the tube was vortexed for 60 seconds at 2000 rpm, and it was centrifuged for 30 minutes at 4000 rpm. One milliliter of the drug-free plasma (supernatant) was spiked with one milliliter of stock standard solution and placed into a 10-mL stoppered calibrated tube. Two milliliters of methanol

were diluted with distilled water to the proper concentration before being used as a protein precipitator. and then spun at 3500 rpm for roughly 15 min. To obtain solutions within the concentration range of the investigated medicines, a specific volume of the resultant supernatant was transferred to a series of 10ml volumetric flasks. The general analytical process was then carried out. The drug-free blood sample was treated the same way as the drug-treated blood sample to conduct a blank experiment.

3. Results and discussion

In this study, a new, green, simple, sensitive, and economic spectrofluorometric method has been developed for analysis of MTC This method of analysis depends on enhancement of the native fluorescence of the studied drug in the presence of sodium dodecyl sulfate (SDS), through micelle formation between studied drugs and anionic surfactant sodium dodecyl sulfate (SDS), which leads to enhancement of native fluorescence for MTC by about 550%, (**Fig.1**).

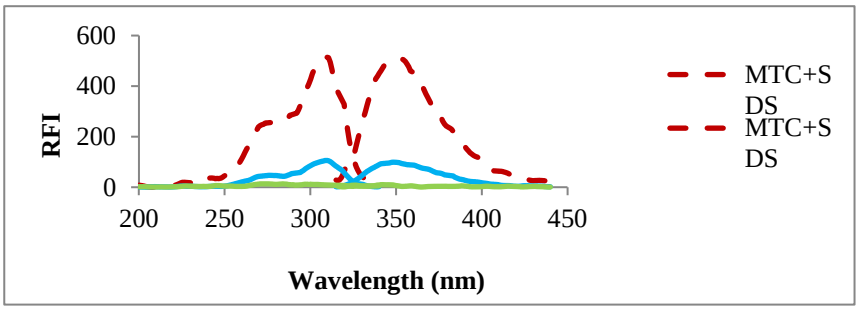


Fig. 1. Fluorescence spectra of MTC,500ng ml^{-1} in the optimal working conditions(Acetate buffer, pH 6 and SDS 10 mM.

3.1. Optimization of variables

The different experimental parameters affecting formation and stability of the micelle between the studied drug and SDS. These factors were changed individually while the others were kept unchanged. The studied factors included buffer type and pH, SDS volume, diluting solvent, reaction time and effect of another surfactant.

3.1.1. Effect of buffer type and pH.

In order to select the optimum buffer type and pH for the micelle formation, different types of buffers with different pH ranges were studied. As shown in **Fig. 2,** it was found that the most Suitable for the fluorescence enhancement of these drug in micellar medium with SDS was acetate buffer at pH 6 which gives higher RFI than Teorell and Stenhang buffer and phosphate buffer at the same pH.

3.1.2. Effect of SDS volume

To select the optimum SDS volume for the micelle formation, different volumes of SDS (10 mM) were taken, it was observed that a gradual increase in the fluorescence intensity by increasing SDS volume until 1ml of SDS after that insignificant increase in the fluorescence intensity was observed (**Fig. 2**) so, 1 mL of SDS (10 mM) was chosen for the general analytical procedure.

3.1.3. Effect of diluting solvent.

To select the most appropriate solvent for dilution, different solvents were evaluated, such as water, methanol, ethanol, acetonitrile, and dimethylformamide. Water was the best solvent for dilution as it gives the higher RFI value between the evaluated solvents (**Fig.2)** .so water was selected as the diluting solvent for the general analytical procedure.

3.1.4. Effect of time.

To select the suitable time for the micelle formation the fluorescence intensity was measured continually for 60 min the maximum fluorescence intensity was

measured after 10 min and remains constant for 60 min **(Fig. 2).** So, the fluorescence intensity was measured after 10 min after mixing the reactants.

3.2. Validation of the proposed method

The proposed analytical method was validated according to ICH guidelines[20] regarding linearity, limit of detection (LOD), limit of quantification (LOQ), precision, accuracy, robustness and selectivity.

3.2.1. Linearity and range

The linearity of the proposed fluorometric method was evaluated by analyzing a serious concentration of the standard drug solution, ranging between 25 ng ml^{-1} to 1000 ng mL^{-1} for under the above-described experimental conditions, the Calibration curves of the studied drugs were obtained by plotting RFI of the micellular system against the concentrations of the drugs within the specific range. Each concentration was repeated three times. Statistical treatment of the data was carried out using linear regression Analysis and the analytical parameters were calculated (**Table 1**). The correlation coefficients (r) for the studied drugs were 0.9999 indicating excellent linearity.

3.2.2. Accuracy and precision

The accuracy of the proposed fluorometric method was evaluated at five concentration levels within the specified range of the studied drug. Each concentration was replicated three times. The mean of the three measurements was calculated as found. The results of measurements were presented as percent recovery ± standard deviation, (**Table 2)**. The obtained results show the close agreement between the measured and true values indicating a high accuracy of the proposed method. The intra-day precision was evaluated through replicate analysis of three concentrations of the drug on three successive times. The inter-day precision was also evaluated through replicate analysis of three concentrations of the drug over a period of 3 successive days. The results of intra-day and inter-day precision are summarized in **Table 3**. The calculated relative standard deviations of different measurements were below2% indicating the excellent precision of the proposed procedure at both levels of repeatability and intermediate precision.

3.2.3. Limit of detection (LOD) and limit of quantitation (LOQ)[20]

The limits of quantification (LOQ) and limits of detection (LOD) were determined based on standard deviation of response and the slope of calibration curve using the equations; LOD=3.3 σ/S and LOQ=10 σ/S, where S is the slope of the calibration curve and σ is the standard deviation of intercept. The obtained results were presented in **Table 1**. The limit of quantitation was 24.1ng mL^{-1} for MTC. This indicates a high sensitivity of the proposed spectrofluorometric method compared with the reported spectrophotometric methods.

Table 1: Analytical parameters for the analysis of MTC by the proposed spectrofluorimetric method with SDS.

Parameter	MTC
λex (nm)	310
λem (nm)	347
Concentration range (ng mL^{-1})	25 -1500
Correlation coefficient (r)	0.9999
Determination coefficient (r^2)	0.9998
Slope	0.66
intercept	48.18
SD of the intercept (Sa)	1.6
SD of slope (Sb)	0.0029
LOD (ng mL^{-1})	8
LOQ (ng mL^{-1})	24

LOD: limit of detection, LOQ: limit of quantitation

Table 2: Evaluation of the accuracy of the proposed analytical procedure for determination of MTC with SDS at five concentration levels within the specified range.

Sample number	Take(ng mL^{-1})	found[a] (ng mL^{-1})	% recovery
1	25	24.9	99.6
2	100	99.9	99.9
3	250	249.8	99.9
4	400	400.3	100.1
5	500	500.4	100.1
Mean			99.9
SD			0.2
RSD			0.2

SD: Standard deviation, [a]: mean of three replicate measurements

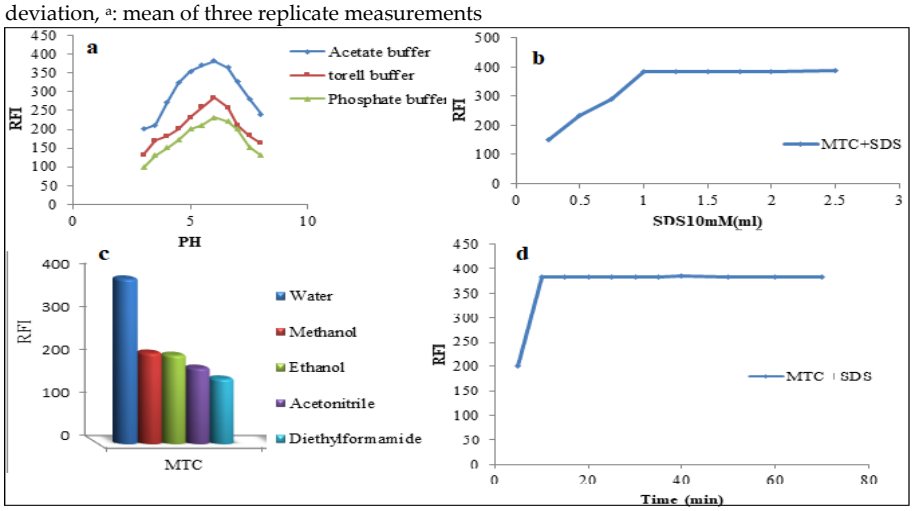


Fig.2. Effect of (a) buffer and pH, (b) SDS Volume, (c) diluting solvent, and (d) Time on RFI of MTC,500ng mL^{-1}

Table 3: Evaluation of the intraday and interday precision of the proposed spectrofluorimetric method for determination of MTC in pure form.

Precision level	Conc (ng mL^{-1})	% Recovery[a] ± SD	RSD
Intraday	50	99.8 ± 0.2	0.2
	100	100 ± 0.62	0.62
	250	100.1 ±0.3	0.3
Interday	50	99.5 ± 1.1	1.1
	100	100.1 ±0.85	0.85
	250	100.2 ± 0.4	0.4

SD: standard deviation, RSD: relative standard deviation. [a] Mean of three replicate measurements.

3.2.4. Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters. To test the robustness of the proposed spectrofluorimetric method, one experimental variable was varied while keeping all the others constant. The studied variables

included pH of buffer solution, the volume of SDS, and time. The results presented in **Table 4** indicated that small variations in any of these variables did not significantly affect the performance of the suggested procedure. This gave an indication of the reliability of the proposed method.

3.3.1. Application to pharmaceutical dosage forms

The proposed method was successfully applied to the determination of the studied drug in its pharmaceutical dosage forms. The selectivity of the method was studied by observing any interference results from tablet excipients.it were shown that there is no interference from tablet excipient with the proposed method. The results obtained from this proposed method were compared with those obtained from reported method using Student's *t*-test and *F*-test with respect to accuracy and precision. The results presented in **Table 5.** It is clear from the table that there is no significant difference between the results from the proposed method and reported method as indicated by Student's *t*-test and *F*-test, as the calculated values did not exceed the theoretical values at 95% confidence level. This indicates high accuracy and precision of the proposed method.

3.3.2. Application to spiked human plasma.

The proposed analytical method was successfully applied for the determination of the studied drug in spiked human plasma. The concentration of each drug was computed from its corresponding regression equation. The studied drugs standard solutions were spiked to the plasma to gives a final concentration of 60, 75, and 100ng. The obtained results were presented in **Table.6**. The mean percent of recoveries of three drugs concentration in plasma were found to range from98.1to 98.5 with standard deviation ranges from 0.4 to 0.7 .this indicates that the studied drug can be successfully determined in spiked human plasma with a high degree of accuracy and precision without interference. These results suggest the possibility this proposed analytical method to determine the concentration of studied drugs in real human plasma samples after oral administration without significant matrix-related interference.

Table 4: Robustness study of the proposed spectrofluorimetric method for determination of MTC(100 ng mL^{-1}) in pure form.

Variation	%Recovery[a] ± SD
Optimum condition	100 ± 0.62
Effect of PH (acetate buffer)	
PH = 5.5	98.8 ± 0.6
PH =6.5	98.7 ± 0.58
SDS volume	
0.75 ml	98.3 ± 0.8
1.25 ml	100.1 ± 0.61
Effect of time	
5min	98.9 ± 0.75
15 min	100 ± 0.72

SD: standard deviation. [a] Mean of three replicate measurements

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3.3.2. Application to spiked human plasma

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Table 5: Comparison between the proposed spectrofluorimetric and reported methods for determination of MTC in its pharmaceutical dosage forms.

Dosage form	%Recovery[a] ± SD		*t*-test[b]	*F*-ratio[b]
	Proposed	reported[c]		
Primpran®tablet 10mg MTC/tab	100.1±0.5	99.4 ± 0.68	1.95	1.8
meclopram®tablet 10mg MTC/tab	99.6±0.29	99.2 ± 0.47	1.3	2.7

[a] The values are the mean of five determinations. [b] The tabulated *t*- and *F*-values at 95% confidence limit are 2.78 and 6.39, respect

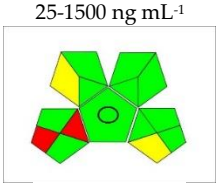
[c] Reported method [7].

Table 6: Application of the proposed spectrofluorimetric method for determination of MTC in spiked human plasma.

Added conc	Found conc[a]	% Recovery ± SD
50	49.05	98.1 ± 0.4
75	73.6	98.1 ± 0.7
100	98.5	98.5 ± 0.56

[a] Mean of five determination

Table7: assessment of greenness of the proposed analytical method.

	Proposed method
Technique*	Spectrofluorimetry
Application	Pharmaceutical products and Plasma
Organic Solvents	Methanol for Pharmaceutical products and Plasma preparation
Conditions	Fluorometric estimation of MTC via micelle formation with SDS
range	25-1500 ng mL^{-1}
GAPI assessment	
AGREE assessment	

3.4. Assessment of the greenness of the proposed method

Recently, several assessment techniques for assessing the ecological effects of the analytical methodologies have been revealed. The evaluation of analytical techniques aids in reducing the environmental damage that these activities produce. For instance, typical HPLC systems can produce 0.5L of organic waste on a daily average[21-23]. In 2018 [24]. the Green Analytical Procedure Index (GAPI) was released. Each of the 15 pictograms in the GAPI are a stage inside one of the five primary pentagrams that correlate to an analytical process. Red, yellow, and green colors serve as indicators for the color codes used in GAPI. Highest and lowest ecological consequences are shown by the red and green colors, accordingly. **Table 7** demonstrates that there are only two red zones in the sampling pentagram for our method's GAPI pictograms, which correlate to off-line sampling. The regulations requiring the separation between locations of pharmaceutical manufacture and/or clinical observation, and the quality control (QC) laboratories, result in off-line sampling which in turn necessitates sample transportation. The application of our suggested method to pharmaceutical dosage forms and human plasma, as shown in **Table 7**, does not necessitate the use of acetonitrile (ACN), an essential organic solvent for the preparation of plasma samples. Instead, we employed methanol for protein precipitation. The remaining key steps outlined in the suggested procedure, which deal with instruments, reagents, or created waste, demonstrate its superiority to other approaches that have been published in the same category of application. Another assessment instrument that utilizes the GAPI color coding system is called AGREE [25] has just been released. The fundamental distinction between it and GAPI is that it was founded on the 12 GAC (green analytical chemistry) principles[23, 26-28]. A clock-shaped symbol with 12 pieces along its perimeter—each representing a GAC principle—is displayed in the AGREE statement. The ecological impact is represented by a numerical value in the pictogram's center; the closer it is to 1, the greater the ecological impact. As shown in **Table 7**, AGREE pictograms show the lowest ecological impact, as expressed by the numerical evaluation, when compared to the other published method within the same application. The perimeter of the proposed method is almost greener, except for the third GAC principle concerned with off-line sampling which is un-avoidable as pointed out in GAPI pictogram discussion. When using the proposed method for pharmaceutical dosage form analysis and plasma samples, the method would be totally green due to absence of any required organic solvents. The use of low energy spectrofluorometric equipment, its higher throughput, and simple sample preparation procedures without need for derivatizing agents account for the better environmentally friendly behavior of the proposed methodology.

4. Conclusion

The present study described a simple, economic, highly sensitive, rapid, less tedious and doesn't require any pretreatment of studied drugs before analysis than many reported spectrofluorometric methods for determination of metoclopramide hydrochloride in its pharmaceutical dosage forms and spiked human plasma. The present study does not require tedious liquid-liquid extraction and there is not depends on expensive or critical chemical reagent or expensive instrumentation this makes it more economic and simpler these advantages make the possibility of the proposed method to applied to routine quality control analysis of these drugs owing to save money and time.in addition, the proposed method can determine the studied drugs in nanograms per milliliters. So, it can be used for determination of the studied drugs in real human plasma samples after oral administration without significant matrix-related interference.

Ethical consideration: All the participants in this study gave their informed permission.

Conflicts of Interest: No conflicts of interest are disclosed by the authors.

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