Octahedron Drug Research 6 (2025) 50-57 ISSN: 2812-6351 Online ISSN: 2812-636X

OCTAHEDRON
Drug Research
Vol. 6

Research Article

Highly sensitive green micellar fluorometric method, assed by GABI, for determination of mosapride in pure form, dosage forms, and spiked human plasma

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ARTICLE INFO

Article history :
Received 16 Jan 2025
Received in revised form
19 Jan 2025
Accepted 19 Jan 2025
Available online 19 Januarv 2025

Keywords: Mosapride; micellar; fluorometry; sodium dodecyl sulphate; human plasma; HPTLC

ABSTRACT

The suggested analytical technique uses sensitive spectrofluorimetric method to determine mosapride (MS) in pure form, pharmaceutical dosage forms, and spiked human plasma. MS is selective serotonin 5-HT4 agonist that is used in treatment of gastrointestinal motility impairment. To achieve the highest sensitivity, the method was adjusted for buffer type, pH, surfactant type, concentration, diluting solvent, and time. It relies on the enhancement of MS native fluorescence through micelle formation with anionic surfactant sodium dodecyl sulphate SDS, which increases the native fluorescence by 300%. The results demonstrated that, after a 10-minute reaction, the maximum sensitivity was achieved using SDS (10 mM) in acetate buffer (pH 6). This indicates the highest RFI for MS that can be measured at 352 nm following excitation at 319 nm. With a detection limit of 14.4 ng ml^{-1} and a quantitation limit of 43.2 ng ml^{-1} for MS, the calibration curves were linear spanning the 50–2000 ng ml^{-1} range. The findings of the suggested analytical method's validation in accordance with ICH requirements were deemed acceptable. The suggested approach yields a high recovery rate and has been effectively used to identify the medication under study in both its pharmaceutical forms and in human plasma that has been tampered with. The precision and accuracy of the results were in great accord with the specified approach.

1. *Introduction*

3,4,5-Trimethoxy-benzoic acid 2-dimethylamino-2-phenyl-butyl ester is the formula for Mosapride Citrate (MS). This powerful gastroprokinetic drug, a selective serotonin 5-HT4 agonist, is used to treat esophagitis and non-ulcer dyspepsia-related gastrointestinal motility impairment as well as to enhance esophageal motor performance in patients with chronic gastroesophageal reflux syndrome. [1]. It is used to treat gastritis, gastroesophageal reflux disease, functional dyspepsia, and irritable bowel syndrome. It also speeds up gastric

DOI: 10.21608/odr.2025.351858.1047

emptying throughout the human gastrointestinal tract. It is advised to take it empty-handed at least an hour before or two hours after eating. MS has anti-inflammatory effects on the gastrointestinal [2, 3]. Several analytical methods were proposed for the determination of MS in its different forms, this methods involve spectrophotometric methods[4], spectrofluorometric methods [5], HPLC [4] and HPTLC [6].

This work's primary goal is to develop a straightforward, affordable, sensitive, and accurate green spectrofluorometric technique for the accurate and repeatable measurement of MS in pharmaceutical preparations and human plasma that has been tampered with. As far as we are aware, there are currently very few spectrofluorimetric techniques available for MS analysis. The suggested approach has the benefits of being straightforward, economical, and sensitive. The foundation of this technique was the amplification of the drug's inherent fluorescence when sodium dodecyl sulfate (SDS), an anionic surfactant, was present. At the critical micelle concentration (CMC), the aggregation process between SDS and the medication under study was examined. The suggested technique was applied for the quantitative assessment of the investigated substance in its pure form under stable ideal conditions (scheme.1). Both the pure forms of the drug under study, as well as its pharmaceutical formulations and spiked plasma, were quantitatively determined using the suggested method. The ICH guidelines were followed in the validation of the approach. Many medications can be determined by excellent precision and sensitivity using spectrofluorometers. [5, 7-27]

2. Experimental

2.1. Instrumentation

With a 1 cm quartz cell, grating excitation and emission monochromators with slit widths set at 5 nm, and a PMT voltage of 400 V, the Fluorescence Spectrometer FS-2 (Scinco, Korea) is connected to a Dell PC. Laboratory centrifuge speed of 18,659 g-forces (Bremsen ECCO, Germany); Jenwey PH meter model 350 (E.U.).

2.2. Materials and reagents

MS was kindly provided by Marcyrl Pharmaceutical Company (El Obour city, Cairo, Egypt). El Nasr Chemical Co. (Abo-Zaabal, Cairo, Egypt) was acquired by SDS. Tween 60 and 80, carboxymethyl cellulose, and cyclodextrin were acquired from El Nasr Chemical Co. (Abo-Zaabal, Cairo, Egypt). El Nasr Chemical Co. (Abo-Zaabal, Cairo, Egypt) provided all other chemicals, such as ethanol, methanol, acetonitrile, diethylformamide phosphoric acid, citric acid, boric acid, acetic acid, sodium acetate, hydrochloric acid, and sodium hydroxide. Distilled water was used to create various buffer solution types with varying pH ranges. The Assiut University Hospital in Assiut, Egypt generously donated human plasma samples, which were then gently thawed and stored at -20°C until the test.

2.3. Pharmaceutical dosage forms.

The following available pharmaceutical products were analyzed Fluxopride® tablets (batch No.1340444), labeled to contain 5mg of mosapride/tablet, produced by Marcryl Pharmaceutical industries, El Obour city, Cairo, Egypt. Mosapride tablets (batch NO.15423) labeled to contain 5mg of mosapride/tablet, produced by western pharmaceutical industries, El Obour city, Cairo, Egypt. All Pharmaceutical dosage forms were purchased from a local pharmacy.

2.4. Preparation of the standard drug solution

A precisely weighed MS salt powder equal to 10 mg MS was transferred into a 100 ml volumetric flask, diluted with distilled water, and thoroughly dissolved before being topped off with distilled water to create stock standard solutions (100-μg ml^{-1}) of MS. For MS, additional dilutions with distilled water were made right before use to get the working solutions. A precise 288 mg of SDS powder was added to a 100 ml volumetric flask, diluted with distilled water, and thoroughly dissolved before being topped off with distilled water to create an SDS 10 mM solution.

2.5. General analytical procedure

Put precisely measured aliquots of the working solutions into a series of 10.0 mL volumetric flasks so that the final concentration is between 0.05 –2 μg/ml for MS. Then, add 1 ml of SDS (10Mm) solution and 1 ml of acetate buffer pH 6 to each flask, and top off the volume with distilled water to reach the 10 ml mark. The fluorescence intensity was measured for MS at λ exc=319 nm, and λ em=352 nm after a portion of the solution was moved to a fluorescence cuvette. 5 nm was chosen as the slit width for the emission and excitation monochromators. Every measurement was taken in a 1 cm quartz cell at room temperature.

2.6. Procedure for pharmaceutical dosage form

Twenty tablets of Fluxopride® and Mosapride were weighed accurately, finely powdered and mixed thoroughly. An accurate amount equivalent to 10 mg of MS was weighed 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.

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

Parameter	MS
λex (nm)	319
λem (nm)	352
Concentration range (ng mL^{-1})	50 - 2000
Correlation coefficient (r)	0.9999
Determination coefficient (r^2)	0.9998
Slope	0.13
intercept	92.9
SD of the intercept (Sa)	0.58
SD of slope (Sb)	0.0006
LOD (ng mL^{-1})	14.4
LOQ (ng mL^{-1})	43.2

LOD: limit of detection, LOQ: limit of quantitation

2.7. Procedure for spiked human plasma

The plasma sample was kindly obtained from normal, healthy, male, human volunteers from Assiut University Hospital, Assiut, Egypt according to institutional guidelines. A sample of 5.0 mL of drug-free human blood sample was taken into a heparinized tube, the tube was vortex-mixed for 60 s at 2000rpm and centrifuged for 30 min at 4000 rpm. Into a 10-mL stoppered calibrated tube, 1.0 mL of the drug-free plasma (supernatant) was spiked with 1ml of stock standard solution. Two milliliters of acetonitrile as a precipitating agent for protein the volume was diluted to the mark with distilled water. And then centrifuged for about 15 min at 3500 rpm. A certain volume of the resulting supernatant was transferred to series of 10ml volumetric flasks to obtain solutions within the concentration range of studied drugs. Then the general analytical procedure was followed. A blank experiment was carried out by treating the drug-free blood sample in the same manner without using the drug.

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

	MS		
Sample number	Taken(ng ml^{-1})	found[a] (ng ml^{-1})	% recovery
1	50	49.8	99.6
2	100	100.1	100.1
3	250	250.3	100.1
4	400	400.7	100.2
5	500	501	100.2
Mean			100
SD		0.25	
RSD		0.25	

SD: Standard deviation; mean of three replicate measurements

3. Results and discussion

In this study, a new, simple, sensitive, green and economic spectrofluorometric method has been developed for analysis of MS. 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 drug and anionic surfactant sodium dodecyl sulfate (SDS), which leads to enhancement of native fluorescence for MS by about 300% (fig.1).

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 factors studied 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.

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 drugs in micellar medium with SDS was acetate buffer at pH 6 which gives higher RFI than Theorell 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. 3, so 1ml 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.4.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. 5. 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[28] regarding linearity, limit of detection (LOD), limit of quantification (LOQ), precision, accuracy, robustness and selectivity.

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

		MS	
Precision level	Conc (ng ml^{-1})	% Recovery[a] ± SD	RSD
Intraday	50	99.9 ± 1.4	1.4
	100	100.4 ± 0.44	0.44
	250	99.95 ± 0.35	0.35
Interday	50	100.2 ± 1.11	1.11
	100	100.5 ± 1.12	1.12
	250	100.1 ± 0.5	0.5

SD: standard deviation, RSD: relative standard deviation.

[a] Mean of three replicate measurements

3.2.1. Linearity and range

The linearity of the proposed fluorometric method was evaluated by analyzing a serious concentration of the standard drug solutions, ranging between 50 ng ml^{-1}to 2000ng ml^{-1} for MS. 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 drug 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.

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

Variation	MS %Recovery[a] ± SD
Optimum condition	100.4 ± 0.44
Effect of pH (acetate buffer)	
pH = 5.5	98.7 ± 0.71
pH =6.5	99.1 ± 0.4
SDS volume	
0.75 ml	98.4 ± 0.31
1.25 ml	100 ± 0.26
Effect of time	
5min	98 ± 0.46
15 min	100 ± 0.36

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

3.2.2. Accuracy and precision

Five concentration levels within the designated range of the substance under study were used to assess the accuracy of the suggested fluorometric approach. Three duplicates of each concentration were made. The three measurements' mean was determined as follows. Table 2 displayed the measurement results as a percentage recovery ± standard deviation. The acquired findings demonstrate the excellent accuracy of the suggested method by demonstrating a close agreement between the measured and real values.

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

Dosage form	%Recovery[a] ± SD		*t*-value[b]	*F*-value[b]
	Proposed	reported[c]		
Fluxopride®tablet 10mg MS/tab	99.6 ± 0.4	99.2 ± 0.36	1.7	1.19
Mosabride®tablet 10mg MS/tab	99.5 ± 0.43	99.0 ± 0.39	1.6	1.23

[a] Values are the mean of five determinations.

[b] Tabulated t- and F-values at 95% confidence limit are 2.78 and 6.39, respect, [c] Reported method [5].

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

	MS	
Added conc	Found conc[a]	% Recovery ± SD
50	49.1	98.2 ± 1.24
75	73.6	98.2 ± 0.9
100	79.8	97.8 ± 0.8

[a] Mean of five determination

Three concentrations of each drug were analyzed three times in succession to assess intra-day precision. Three concentrations of each drug were replicated over three consecutive days to assess the inter-day precision. Table 3 provides a summary of the intra-day and inter-day precision outcomes. The calculated relative standard deviations of different measurements were below 2%, indicating the excellent precision of the proposed procedure at both levels of repeatability and intermediate precision.

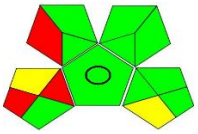
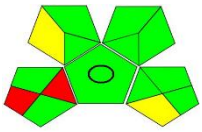
3.2.3. Limit of detection (LOD) and limit of quantitation (LOQ)[28]

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 results obtained were presented in Table 1. The limit of quantitation was 52.47 ng ml^{-1} for MS. This indicates a high sensitivity of the proposed spectrofluorometric method compared with the reported spectrophotometric methods.

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

Table 7: Greenness assessment of the proposed method for determination of MS under different applications

	Proposed method	
Technique*	Spectrofluorimetry	
Application	Plasma samples	Pharmaceutical products
Organic Solvents	ACN for plasma sample preparation	Totally Free
Conditions	Enhancement of native fluorescence of MS in Prescence of SDS using acetate buffer pH 6	
Range	50.0 - 2000.0 ng mL^{-1}	
GAPI assessment		
AGREE assessment		

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 the 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 [5] 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 results obtained were presented in Table.6. The mean percent of recoveries of three drugs concentration in plasma were found to range from97.2 to 98.5 with standard deviation ranges from 0.19 to 0.93. this indicates that the studied drugs 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 drug in real human plasma samples after oral administration without significant matrix-related interference

3.4. Assessment of the greenness of the proposed method

Several assessment tools have been recently reported for evaluation of the ecological impacts of the analytical methodologies. The assessment of analytical methods helps in the reduction of environmental pollution generated by such processes. For instance, an average of 0.5L of organic waste can be generated daily from conventional HPLC systems. The Green Analytical Procedure Index (GAPI) was introduced in 2018 [29]. GAPI presents 15 pictograms, each representing a step within 5 main pentagrams corresponding to an analytical process. The color code applied in GAPI indicates red, yellow, and green colors. The red and green colors indicate the highest and lowest ecological impacts, respectively. As shown in table 7, only 2 red pictograms are presented in GAPI assessment for pharmaceutical dosage form analysis. The two red pictograms are presented in the sample handling pentagram which corresponds to the off-line sampling. The off-line sampling which in turn require sample transportation occurs due to the regulations forcing the segregation between sites of pharmaceutical production and/or clinical observation, and the quality control (QC) laboratories. Although pharmaceutical dosage forms require no special preservation, however if the proposed method was applied to plasma sample, there are 3 red pictograms, two of them as the application to the dosage forms, The third red pictogram is found in the sample preparation pentagram which represents the use of small volume of non-green solvent, acetonitrile (ACN). The other main steps defined in the proposed method, concerning instrumentation, reagents or generated waste, are ecologically safe and green.

AGREE [30] is another assessment tool that has been recently introduced on the color code based in GAPI. The main difference from GAPI is that it was based on the

twelve green analytical chemistry (GAC) principles [31]. AGREE shows a clock shaped pictogram, which perimeter is divided into 12 sections, each corresponding to a GAC principle. The center of the pictogram shows a numerical value estimating the ecological impact, where the closer to 1, the better impact. As shown in table 7, AGREE shows low ecological impact as expressed by the numerical 0.86, and 0.92 values for plasma samples and dosage form samples. The perimeter is almost greener, except for the third GAC principle concerned with off-line sampling which is un-avoidable as clarified in GAPI pictogram discussion. The slight ecological impact seen in the 10th, 11th, and 12th principles of AGREE assessment arise from the use of ACN in plasma samples for protein precipitation before analysis. In case of using the proposed method for pharmaceutical dosage form analysis, 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.

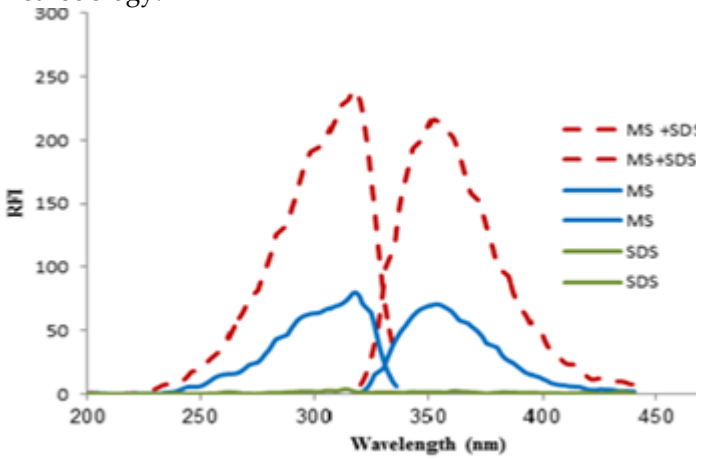


Fig. 1. Fluorescence spectra of MS,1µg ml^{-1} in the optimal working conditions (Acetate buffer, pH 6 and SDS 10 mM).

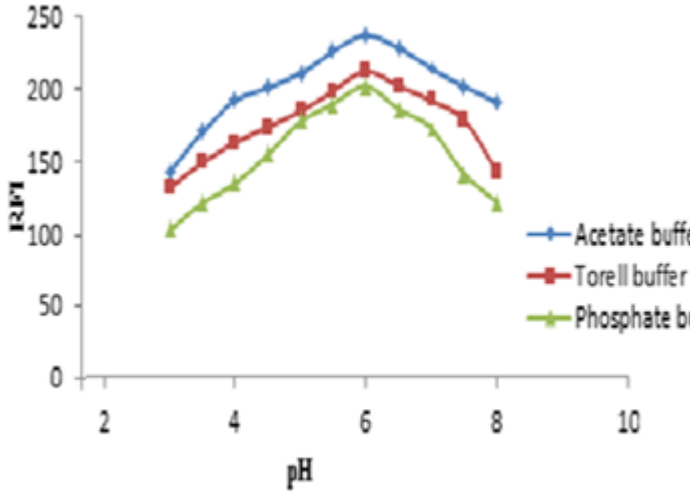


Fig. 2. Effect of buffer and pH on RFI of MS,1µg ml^{-1}.

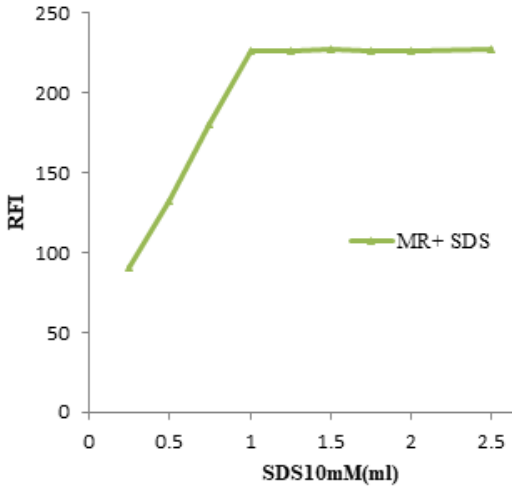


Fig. 3. Effect of SDS Volume on RFI of MS, (1µg ml^{-1}).

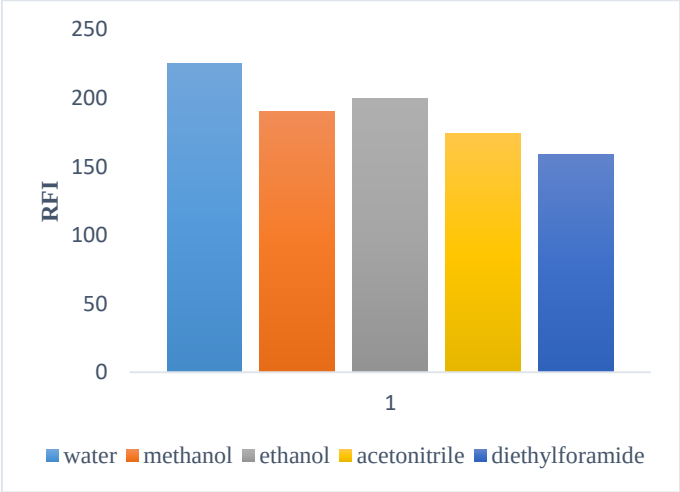


Fig. 4. Effect of diluting solvent on RFI of MS, (1µg ml^{-1}).

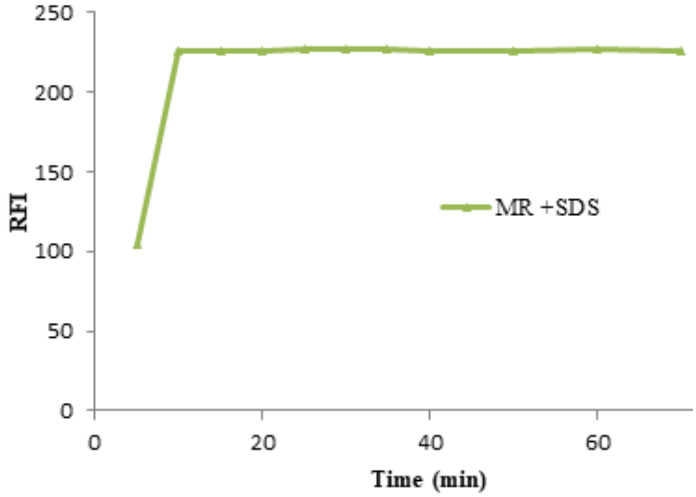


Fig. 5. Effect of time on RFI of MS, (1µg ml^{-1}).

4. Conclusion

Unlike several previously published spectrofluorometric procedures for determining MS in its pharmaceutical dose forms and spiking human plasma, the current study revealed a straightforward, cost-effective, highly sensitive, quick, and less laborious, and does not require any preparation of MS before analysis. The current study is more cost-effective and straightforward because it does

not necessitate laborious liquid-liquid extraction or rely on costly or essential chemical reagents or expensive equipment. These benefits also make it possible for the suggested method to be used for routine quality control analysis of these medications because it saves time and money. Furthermore, the suggested approach can measure the substance under study in nanograms per milliliter. Therefore, it can be utilized to identify the medications under study in actual human plasma samples.

Conflict of interest

The authors declare that there is no conflict of interest.

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