RESEARCH ARTICLE

Simultaneous Determination of Trace Mefenamic Acid in Pharmaceutical Samples via Flow Injection Fluorometry

Maryam Hamed, Mohammad K. Hammood*

University of Baghdad, College of Science, Department of Chemistry, Baghdad, Iraq

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ABSTRACT

Mefenamic acid belongs to non-steroidal anti-inflammatory drugs that are used widely for the treatment of analgesia. Our aim from this study is to establish a new assay for the quantitative determination of mefenamic acid (MFA) in the pharmaceutical sample by two sensitive and rapid flow injection-fluorometric methods. A homemade fluorometer was used in fluorescence measurements, which using solid-state laser diode 405 and 532 nm as a source, combined with a continuous flow injection technique. The first method depends on the effect of MFA on calcein blue (CLB) fluorescence at 405 nm. Another method is a study of rhodamine-6G (Rh-6G) fluorescence after adding MFA, and recording at 532 nm. Optimum parameters as fluorescent dye concentration, basic medium, flow rate, sample volume, purge time, and delay coil have been investigated. The dynamic range of MFA was 0.2 to 2 mmol.L^{-1}; 0.5 to 2.3 mmol.L^{-1} with linearity percentage (% r2) 98.92 and 99.83%, for Rh-6G and CLB, respectively. Limit of detection at a minimum concentration in calibration curve 189.34 and 199.89 ng/sample, for Rh-6G and CLB, respectively. The comparison of developed methods with the classical method (UV-vis spectrophotometry) was achieved. The proposed methods were successfully applied for the determination of MFA in the pharmaceutical samples and can be used as an alternative method.

Keywords: Calcein blue, Flow injection-fluorometric, Laser diode 405 and 532 nm, Mefenamic acid, Rhodamine-6G.

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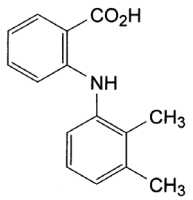
INTRODUCTION

The chemical name of MFA is 2-(2,3-dimethyl phenyl) aminobenzoic acid with molecular weight 241.29 g.mol^{-1} and molecular formula $C_{15}H_{15}NO_2$ (Scheme 1).[1] It is a prevailing non-steroidal anti-inflammatory drug used as a potent analgesic and anti-inflammatory agent in the treatment of several pathologies. MFA is typically prescribed for oral administration, usually available in 100, 250, and 500 mg tablets, or 250 mg capsules.[1,2] Till now, its exact mechanism of action management of pain is still unknown. Studies have ascribed to the ability of MFA to inhibit prostaglandin synthesis. Indeed, some investigations have proposed the mechanism for antipyretic and analgesic effects of MFA via inhibition of prostaglandin synthesis by competitive blocking of the two forms of cyclooxygenase (COX-1 and COX-2).[3,4] In the case of overdosing, MFA accumulates as toxic metabolites in the body, mainly resulting in acute hepatic necrosis, renal failure, hematuria, gastrointestinal bleeding, morbidity, and mortality.[5]

Several analytical methods for the determination of MFA in pure and pharmaceutical samples have already been developed and reported. These analytical methods, include electrochemical analysis,[6] spectrophotometry,[7,8] chromatography,[9,10] atomic absorption spectrometry,[11] fluorescence spectrometry,[12] nuclear magnetic resonance spectroscopy,[13,14] and flow injection analysis.[15,16]

To improve the sensitivity, accuracy, and simplicity of an analytical method, the flow injection technique is combined with a fluorometric method. In this research, the developed methods were dependent on the measurement of fluorescence quenching of Rh-6G and CLB as fluorescent dye via the addition of MFA and distilled water. The intensity of fluorescence and quenching are measured by a locally



Scheme 1: Chemical structure of MFA

*Author for Correspondence: mohki276@sc.uobaghdad.edu.iq

made laser diode fluorometer, combined with a flow injection technique.

MATERIALS AND METHODS

Reagents and Chemicals

All chemicals used in this research were of analytical grade and distilled water was used in all dilution processes. A standard solution of sodium carbonate (Na_2CO_3, 105.99 g.mol^{-1}, 0.5 mol.L^{-1}) and sodium hydroxide (40 g.mol^{-1}, 1 mol.L^{-1}) was prepared by dissolving 10.6 and 8 grams, respectively, in 200 mL distilled water. A stock solution of MFA ($C_{15}H_{15}NO_2$, 124.29 g.mol^{-1}, 0.01 mol.L^{-1}) was prepared by dissolving 0.2412-gram in 10 mL 0.5 M sodium hydroxide, then completed to 100 mL with distilled water and kept the solution in dark container.

CLB stock solution ($C_{15}H_{15}NO_7$, 321.28 g.mol^{-1}, 0.01 mol.L^{-1}) was prepared by dissolving 0.6425-gram in 5 mL of 1 M sodium hydroxide, then completed to 200 mL with distilled water. While, Rh-6G (479.02 g.mol^{-1}, 0.001 mol.L^{-1}) was prepared by dissolving 0.0958-gram in 200 mL distilled water. Standard solution of sodium chloride (NaCl, 58.5 g.mol^{-1}, 0.5 mol.L^{-1}) and potassium bromide (KBr, 119.02 g g.mol^{-1}) prepared, by dissolving 2.93 and 5.95 grams in 100 mL distilled water.

Apparatus

The instrument used in this work is a homemade fluorometer, which is equipped with laser diodes as irradiation sources for excitation. The laser diodes were used with wavelength 405 nm (blue) and 532 nm (green), whereas, at 90º, a photodiode was used as the detector. The newly homemade fluorometer has been produced by Prof. Dr. Issam M. A. Shakir and Prof. Dr. Nagam S. Turkey.

Peristaltic pump with variable speed, Ismatec (ISM796) type was used pump the solutions, 6 port 2 directions injection valve Rheodyne type, with a different sample loop (Teflon 0.5 mm i.d.) used for sample injection. The output signals were recorded by x-t potentiometric recorder Siemens type KOMPENSO C-1032. Peak height was measured for each signal. Shimadzu UV-vis spectrophotometer model UV-1800 (Japan) was used for scanning the absorption spectrum.

Methodology

The design of the manifold system is composed of the carrier stream CLB (0.9 mmol.L^{-1}) or Rh-6G (0.07 mmol.L^{-1}) that gives a constant and continuous emission of fluorescence light at 1.63 mL.min^{-1} flow rate, which leads to injection valve to carry MFA from the sample with a volume of 157 µL. The mixture was then passed through to the measuring cell that gives quenching fluorescence response, which was recorded on x-t potentiometric auto AVO-meter. Figure 1 shows the whole manifold system.

RESULTS AND DISCUSSION

The chemical and physical parameters, such as, Rh-6G and CLB concentrations, and basic medium, as well as, the physical parameters, like delay coil studied, sample volume, and flow rates were examined employing a one-line manifold system as shown in Figure 1.

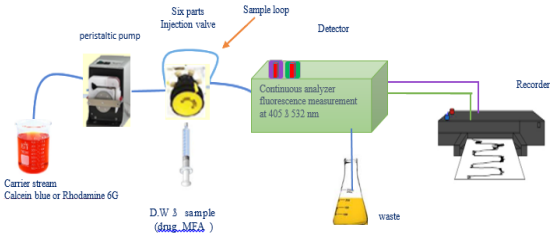


Figure 1: One-line manifold system design for MFA determination as an injected sample

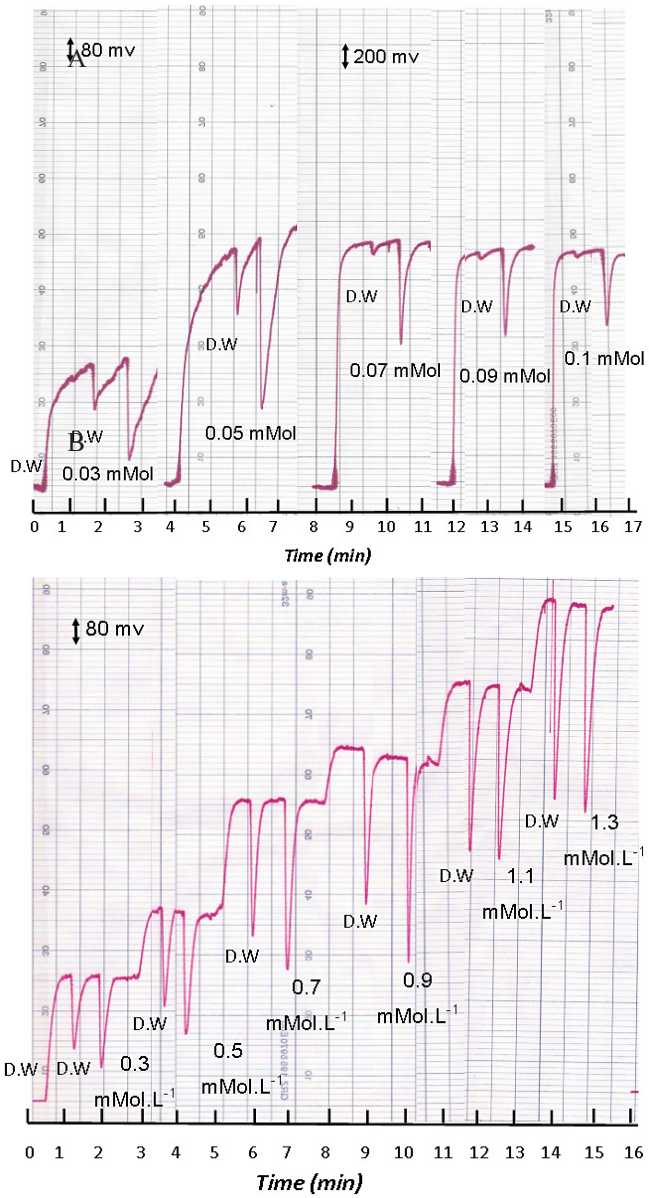


Figure 2: Fluorescence intensity response profile of variation fluorescent dye concentrations; **A:** Rhodamine-6G; **B:** Calcein blue

Chemical Parameters

Fluorescent Dyes Concentrations

Various concentrations of Rh-6G (0.03–0.1 mmol.L^{-1}) and CLB (0.3–1.3 mmol.L^{-1}), as a carrier stream in single line manifold system, were used with flow rate 1.63 mL/min, and 157 µL sample loop with MFA at 2 mmol.L^{-1}. After mixing, the solution arrives at the flow cell, which was radiate by a blue-violet laser diode (405 nm) for calvin blue (CLB) dye, and green laser diode (532 nm) for Rh-6G fluorimeter.

Figure 2 shows the response profile of variation of Rh-6G, CLB, and fluorescence quenching for both distilled water (DW) and MFA. It is noticed that an increase in fluorescent dyes concentrations lead to an increase in the fluorescence intensity. The optimum concentrations of Rh-6G and CLB were chosen as 0.07 and 0.9 mmol.L^{-1}, respectively. The optimum concentrations chosen depend on the greatest difference between the peaks' height of MFA and water.

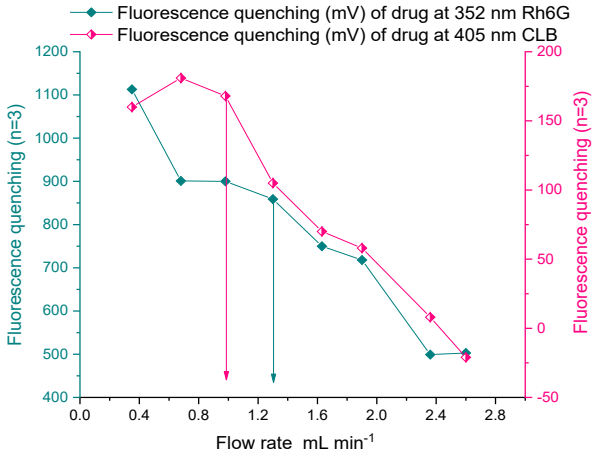


Figure 3: Variation of flow rate on fluorescence quenching for the Rh-6G—MFA system at 532 nm and CLB—MFA at 405 nm

Effect of Reaction Mediums

The study of reaction medium effect on the fluorescence quenching of the optimum concentration (0.07 mmol.L^{-1}) Rh-6G and (0.9 mmol.L^{-1}) CLB, with preliminary concentration 2 mmol.L^{-1} of MFA, was carried with different base and salts. Variable concentrations of sodium hydroxide (0.02–0.06 mmol.L^{-1}) and sodium carbonate (0.01–0.05 mmol.L^{-1}), while, 0.1 mmol.L^{-1} of NaCl and 0.1 mmol.L^{-1} KBr were used as a preparation medium of the fluorescent dyes, and it is used as a carrier stream. The whole obtained results are shown in Table 1. These variations show a decrease in peak height response of fluorescence quenching at different concentrations of salts and bases. Therefore, the optimum and suitable media for the preparation of CLB and Rh-6G dyes are distilled water, to give the best response.

Physical Parameters

Effect of Flow Rate

The study was carried out for the preferred flow rate of fluorescent dyes (0.07 mmol.L^{-1} for Rh-6G and 0.9 mmol.L^{-1} for CLB) within the range of 0.35 to 2.6 mL.min^{-1}, using the preliminary concentration of MFA at 2 mmol.L^{-1}. The obtained results of the quenched fluorescence response are shown in Figure 3. It was noticed that at a low flow rate, there was an increase in peak base width (Δt_B), and peak height; the broadening at the peak maxima might be due to the dispersion and dilution leading to an irregular response profile.[18] While, at high flow rate influence led to a decrease in the peak base width and sharp maxima with regular peak profile. Therefore, 1.3 mL.min^{-1} of the Rh-6G—MFA system, and 0.98 mL.min^{-1} of the CLB—MFA system were chosen as optimum flow rates for the carrier stream.

Sample Volume

Using the whole optimum condition in previous studies, such as, the flow rate of 1.3 mL.min^{-1} for (0.09 mmol.L^{-1}) Rh-6G

Table 1: Effect of salts and basic medium on Rh-6G—MFA system for estimation of MFA

Salts and bases type	*Concentration of salts or bases (mmol.L^{-1})*	*Continuous of fluorescence response $\bar{Y}$ (mV)*	*Total fluorescence quenching $\bar{Y}$ (mV)*	*S.D.*	*% RSD*	*Confidence interval at 95% $\bar{y}_i \pm t_{(\alpha=0.05/2)} \frac{\sigma_{n-1}}{\sqrt{n}}$*	*Fluorescence quenching by DW $\bar{Y}$ (mV)*	*Fluorescence quenching of MFA $\bar{Y}$ (mV)*	*Fluorescence remaining $\bar{Y}$ (mV)*
Rhodamine-6G—MFA system									
NaOH	0.02	1,780	311	2	1.48	311 ± 5.74	60	251	1,469
	0.04	1,600	240	0	0	240 ± 0	60	180	1,360
Na_2CO_3	0.01	1,960	599	2.3	0.39	599 ± 5.74	120	480	1,360
	0.03	1,920	540	0	0	540 ± 0	100	440	1,380
NaCl	0.1	1,980	320	0	0	320 ± 0	80	240	1,660
KBr	0.1	2,010	442	3.4	1.57	442 ± 8.61	80	362	1,568
Calcein Blue—MFA system									
NaOH	0.02	800	390	2	0.52	390 ± 5	304	86	410
	0.04	728	295	1.8	0.63	295 ± 4.59	240	55	433
Na_2CO_3	0.01	776	304	0	0.15	304 ± 1.15	256	48	472
	0.03	816	252	4	1.59	252 ± 9.94	224	28	564

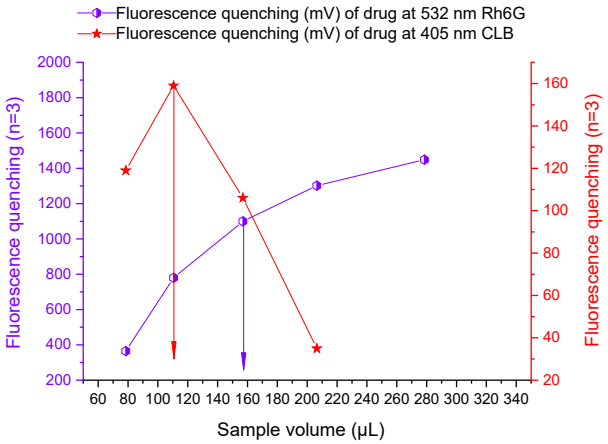


Figure 4: Effect of sample volume variation on fluorescence quenching of the Rh-6G-MFA system and CLB-MFA system

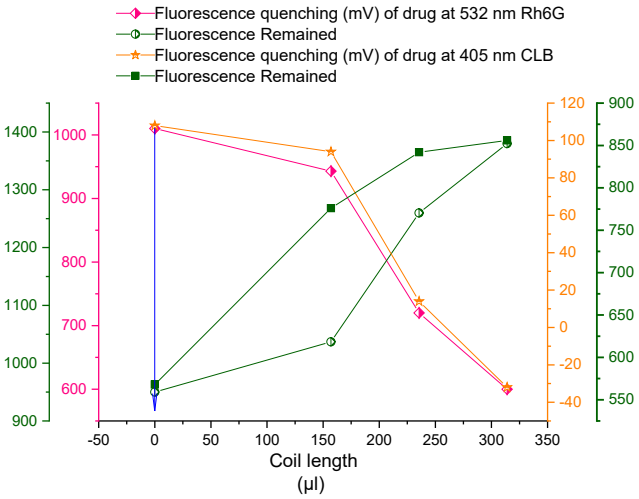


Figure 5: Effect of reaction coil for the determination of MFA using laser diode fluorimeter

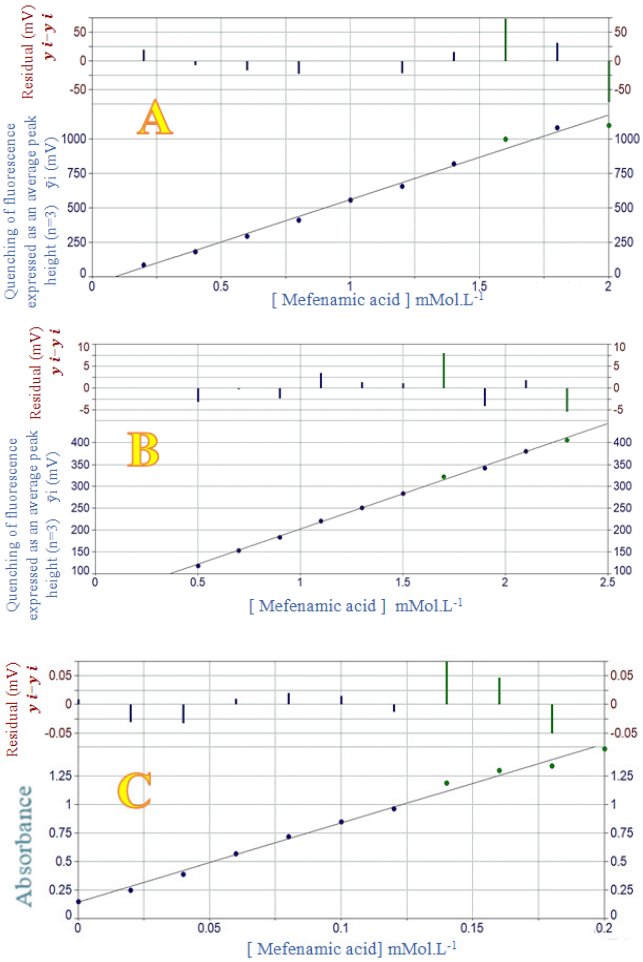


Figure 6: Calibration graph for variation of MFA concentration expressed by the linear equation; **A:** Rh-6G-MFA; **B:** CLB-MFA using homemade laser diode fluorometer, combined with flow injection; **C:** Absorption determination method of MFA; Residual ($\bar{y}_i$–$\hat{y}_i$); $\bar{y}_i$: practical value; $\hat{y}_i$: estimate value

and 0.98 mL.min^{-1} for (0.9 mmol.L^{-1}) CLB, with 2 mmol.L^{-1} of MFA concentration. Variable sample volumes (78.5–314.5 µL) have been injected using open valve mode. The change in fluorescence quenching *vs.* sample volumes and DtB is shown in Figure 4. It was noticed that an increase of sample volume for Rh-6G up to 157 mL, leads to an increase in response height, but at a larger than 157 mL, give a slightly higher response with wider in DtB. While, for the CLB-MFA system, the response height is increased with increasing sample volume up to 110 mL, characterized by the sharpness and regular response profile. Larger volume more than 110 µL, the response height is slightly decreased and broadening at the peak maxima, and an increase in the base width (Δt_B), which was most probably attributed to the continuous long time duration of the segment in front of the detector.

Purge Time Effect

The study of injection time duration (permit allowable time for a purging of the sample from the injection valve unit) was carried out with whole previous optimum parameters and used 2 mmol.L^{-1} of MFA as sample segment. The using 5 to 25 seconds, also, to open valve mode as purge time. The optimum allowed time was open valve mode, the response height is increased with an increase in the allowed time to purging the sample from the injection valve.

Reaction Coil Length

The effect of the reaction coil on the response profile was studied. Using variable coil length (0, 157, 235, 314) microliter (µL), which connected after the injection valve directly to mix the solutions after that the solution passing through the flow cell.

The studies have been performed using optimum concentration for fluorescent dyes (Rh-6G and CLB), preliminary concentration MFA 2 mmol.L^{-1} with optimum physical parameters in previous studies. The results obtained are present in Figure 5. A decrease can be seen in the fluorescence quenching effect with the increase of coil length.

Table 2: Summary of calibration curve results for determination of MFA drug, using developed and classical methods

Measured (MFA) mmol.L^{-1}	*Linear dynamic range mmol.L^{-1}*	*Type of measured*	*$\hat{Y}i$ (mV) = a ± Sa t + b ± Sb t [Am] mmol.L^{-1} at confidence level 95%, n - 2*	*r r^2 r^2%*	*t_{tab} at 95% confidence level, n - 2*	*Calculated t-value = $\frac{/r/\sqrt{n-2}}{\sqrt{1-r^2}}$*
0.2–2.6 with Rh-6G at 532 nm	0.2–2 n = 10	Quenching of fluorescence	52 ± 64.45 + 611.54 ± 51.93	0.9945 0.9892 98.92	2.603 << 30.29	
0.3–2.5 with CLB at 405 nm	0.5–2.3 n = 10	Quenching of fluorescence	41.866 ± 8.153 + 160.66 ± 5.387	0.9991 0.9983 99.83	2.306 << 68.53	
0.01–0.2 n = 11		Absorbance	0.145 ± 0.0527 + 6.918 ± 0.445	0.9963 0.9927 99.27	2.262 << 34.99	

ŷ: estimated response (mV) for (n = 3) expressed as average peak heights of the linear equation of the form ŷ = a + bx; r: correlation coefficient; r^2: coefficient of determination; r^2%: linearity percentage

Table 3: LoD calculation summary for proposed different approaches

Minimum concentration of MFA (mmol.L^{-1})	*Practically based on gradual dilution for the minimum concentration*	*Theoretical based on the volume of slope X = 3S_B/slope*	*Theoretical based on the linear equation $\bar{Y} = Y_b + 3Sb$*
0.2 mmol.L^{-1} with Rh-6G at 532 nm	189.34 ng/157 µL sample	5.015 ng/157 µL sample	0.760 µg/157 µL sample
0.3 mmol.L^{-1} with CLB at 405 nm	199.89 ng/110 µL sample	17.92 ng/110 µL sample	0.211 µg/110 µL sample

S_B: standard deviation of blank solution; X = value of LoD based on slope; Y_b: average response for the blank solution (equivalent to intercept in straight line equation)

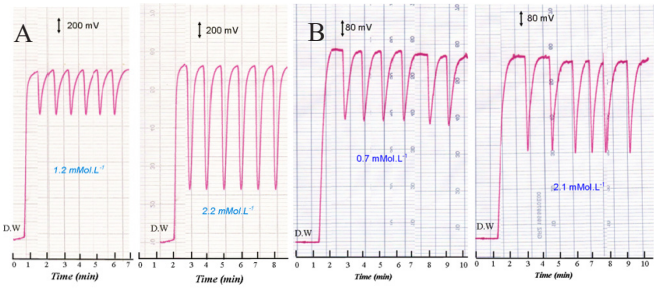


Figure 7: Profile of successive repeatability measurements; **A:** MFA with Rh-6G measured at 532 nm; **B:** MFA with CLB measured at 405 nm

This study indicates that no reaction coil is necessary for the determination of drugs by quenching of fluorescence with one line manifold design system.

Linear Calibration Plot of MFA

The calibration curves of MFA were evaluated by using a homemade laser diode fluorometer. A series of solutions of MFA ranging between 0.2 and 2 mmol.L^{-1} were papered and tested with fluorescent dye Rh-6G, and green laser at 532 nm as a source. While, for another method 0.3 to 2.3 mmol.L^{-1} of MFA was papered that tested with CLB and used blue laser at 405 nm as a source. Straight lines using linear regression analysis of MFA for two different methods were recorded in Figure 6. The methods achieved in this work were compared with the classical method (spectrophotometric methods)[19] via the measurement of the absorbance spectrum at λ_{max} = 286 nm of MFA, and the linear calibration graph of the classical spectrophotometric method was shown in Figure 6 C.

Table 2 illustrates the results of the determination of the MFA using a homemade fluorometer combined with flow injection and classical spectrophotometer method. The values of the correlation coefficient, linear percentage, straight-line equation, and the calculated t-value at 95% confidence.

Limit of Detection (LoD)

The LoD for the determination of MFA depended on developed methods (fluorescence quenching) and were calculated by three different approaches as tabulated in Table 3.

Repeatability

The efficiency and repeatability of the proposed method were studied at a selected concentration of MFA 1.2 and 2.2 mmol.L^{-1} with Rh-6G fluorescent dye, while 0.7 and 1.2 mmol.L^{-1} with CLB fluorescent dye. Repeat measurements for six successive injections were recorded and obtained peak profiles are shown in Figure 7. The % RSD is less than 1%, exhibits the trustiness of the new methodology.

Application

The analysis measurements of MFA were conducted by development two methods using Laser diode fluorometer at 532 nm with Rh-6G; while at 405 nm with calcein blue and the third method was used the classical spectrophotometric method[19] that measuring at λmax = 286 nm. The standard addition method was applied to three proposed methods. A series of

Table 4: Analysis results of MFA in pharmaceutical preparation using standard addition, with two developed methods and UV-Vis spectrophotometric method

Practical concentration mMol.L^{-1} in 25 mL and 50 mL	*$r_{,}^{2}$ r^2 %*	*Laser diode-Fluorometer at 532 nm with Rh-6G* *Laser diode-Fluorometer at 405 nm with CLB* *UV – Vis spectrophotometer method at 286 nm* *Equation of standard addition curve at 95% for n-2* $\hat{Y}i = a \pm Sat + b \pm Sbt$ *[MFA] mMol.L^{-1}*	*Theoretical content for the active ingredient* $W \pm 1.96\frac{\sigma_{n-1}}{\sqrt{n}}$ *at 95% (g)*	*Weight of sample equivalent to 0.1206g 10 mMol.L^{-1} of active ingredient*	*Confidence interval for average weight* $\bar{W} \pm 1.96\frac{\sigma_{n-1}}{\sqrt{n}}$ *at 95% (g)*	*Commercial nam, content company, country,*
0.576mMol.L^{-1} 9.612mMol.L^{-1}	0.9978 0.9957 99.57	$\bar{y}\ i(mV)$ =376.38 ± 35.69+652..57 ± 58.94				
0.492mMol.L^{-1} 9.831mMol.L^{-1}	0.9984 0.9969 99.69	$y\ \hat{i}\ (mV)$ =150.61 ± 14.27+306.42 ± 23.57	0.5 ± 0.0024	0.1731	0.7177 ± 0.0035	Iraq Content o.5g pioneer
0.020 mMol.L^{-1} 9.786mMol.L^{-1}	0.9982 0.9966 99.66	$\bar{y}\ i$=0.243 ± 0.063+12.38 ± 1.088				
0.611mMol.L^{-1} 10.192mMol.L^{-1}	0.9946 0.9893 98.93	$\bar{y}\ i(mV)$=406.57 ± 58.01+664.85 ± 95.81				
0.511mMol.L^{-1} 10.220mMol.L^{-1}	0.9954 0.9909 99.09	$y\ \hat{i}\ (mV)$ =169.57 ± 26.67+331.85 ± 44.05	0.5 ± 0.0033	0.2066	0.8570 ± 0.0025	India Content 0.5g Micro
0.021 mMol.L^{-1} 10.576mMol.L^{-1}	0.9950 0.9902 99.02	$\bar{y}\ i$=0.264 ± 0.109+12.50 ± 1.718				
0.566mMol.L^{1-} 9.441mMol.L^{-1}	0.9976 0.9953 99.53	$\bar{y}\ i(mV)$ =361.71 ± 36.75+638.57 ± 60.69				
0.508mMol.L^{1-} 10.158mMol.L^{-1}	0.9980 0.9961 99.61	$y\ \hat{i}\ (mV)$=165.28 ± 16.96 +325.42 ± 28.02	0.5 ± 0.0018	0.1892	0.7842 ± 0.0029	Jordan Content o.5g Pfizer
0.019mMol.L^{-1} 9.670mMol.L^{-1}	0.9985 0.9971 99.71	$\bar{y}\ i$=0.213 ± 0.049+11.05 ± 0.813				

$\hat{Y}i$ = estimated value for energy transducer response (mV) or absorbance, $t_{0.025,\infty}$ = 1.96 at 95%, r = Correlation coefficient , Coefficient of determination, r2% = Linearity percentage

MFA drug solutions were prepared by transferring 0.6 mL of 10 mMol.L^{-1} with Rh-6G system and 0.5 mL (10 mMol.L^{-1}) with calcein blue, followed by the addition 0, 0.2, 0.4, 0.6, 0.8, 0 1 mMol.L^{-1} from 10 mMol.L^{-1} of standard solution of MFA, the preparations achieved in six 10 mL volumetric flask. While classical method, the solutions of 10 mMol.L^{-1} were prepared from the previous samples by transferred 0.02 mL to each six 10 ml volumetric flasks, followed by the addition (0, 0.02, 0.04, 0.06, 0.08, 0.1 mMol.L^{-1}) of 10 mMol.L^{-1} standard MFA. The obtained results for the analysis of mefenamic acid (MFA) in three different samples at a 95% confidence interval were tabulated in Table 4.

CONCLUSION

The proposed two methods for MFA analysis were characterized by sensitivity, accuracy, and speedy methods. The developed methods depend upon the interaction of MFA with fluorescent dyes (Rh-6G or CLB) that quench of fluorescein solutions (continuous fluorescence of Rh-6G or CLB). The % RSD values of new methods are found to be less than 1%, which indicates a good precision of the proposed method. The matrix effects were canceled using the standard addition method in analysis. The statistical analysis of fluorescence methods is in good agreement with the spectrophotometric method that shows no doubt that the newly developed methods can be considered as alternative methods for the determination of MFA in pharmaceutical preparations.

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