Original Article

Micellar Enhanced Spectrofluorimetric Quantification of Gemifloxacin Mesylate in Pharmaceuticals and Bio-fluids

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ABSTRACT

Introduction: Gemifloxacin mesylate (GFX) is one of the most potential anti-infective agents with broad spectrum and influential activity. **Objectives:** The current study described a fast and precise spectrofluorometric probe for GFX quantification in authentic drug, commercial tablets and bio-samples. **Materials and Methods:** The suggested technique was conducted by complexing GFX with Al ions in the presence of alkaline buffer of pH 8. **Results:** The FI was enhanced by adding sodium dodecyl sulfate (SDS). Rectilinear relationship was achieved over (0.05-100 ng mL^{-1}) drug samples. The fluorescence spectra were recorded at λ_{ex} at 268 nm and λ_{em} 400 nm. The lowest quantification and detection values were 0.049 ng mL^{-1} and 0.05-100 ng mL^{-1}, respectively. The suggested probe was employed to determine the investigated drug in its Factive® tablets with percentage recovery 99.85±0.7 %. In addition, the selected drug was also quantified in human serum and urine with percentage recovery 99.4 %. The outcome data were statistically treated and validated. **Conclusion:** The obtained results confirmed the suitability of this probe for the quantification of the drug in bio-fluids and commercial tablets.

Key words: Complexation, Gemifloxacin mesylate, Spectrofluorimetry, Pharmaceutical formulations, Bio-samples.

INTRODUCTION

Fluoroquinolones are one of the most potential anti-infective agents with broad spectrum and influential activity. Due to their simple molecular nucleus, they are amenable to form many modified structures. They, also have several beneficial properties such as good tissue penetrability, low toxic and adverse effects and magnificent bioavailability.

Gemifloxacin (GFX) is a member of fluoroquinolone antibacterial compounds (Figure 1) with a wide antibacterial activity.[1-6] It displays four-fold higher activity against Gram positive microorganisms than that of moxifloxacin against *Streptococcus pneumoniae*.[5,7]

By increasing the attention to use more sensitive reagents the attempts have been focused on using a third component like surfactants to convert the binary complexes of metal ions to ternary complex.[8] In the field of inorganic analysis, many previously addressed articles extensively discussed the mode of formation, the sensitivity and selectivity improvement of both ternary complex types.[9,10] However, to enhance the sensitivity of organic complex system, a binary ion-pair complex was formed by producing organic compound-organic dye interaction,[11,12] but this method is convoluted and requires an extraction procedure.

The previously documented methods for the determination of GFX included different spectroscopic and separation techniques. Among these are, spectrophotometry,[13-15] spectrofluorimetry,[16,17] chemiluminescence,[18] many separation techniques have been reported for its estimation and

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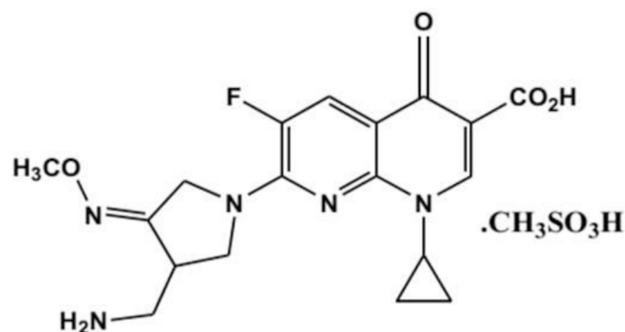

Figure 1: Chemical structure of gemifloxacin mesylate.

quantification,[19-27] voltammetry,[28,29] and ion selective electrode.[30-32]

Although the above reported separation techniques provide an automated, fast separation and accurate estimation of analytical substances, they still have many limitations, such as the requirement to huge amounts of reagents and solvents which are costly and require high technical skills. Additionally, potentiometric and voltametric techniques can also perform very fast, recorded signals may showed some analytical errors, requiring environmental protection to minimize the toxicity. Meanwhile, spectrofluorimetry as on of spectroscopic techniques still possessed much opportunity and attention, due to its sensitivity, cost effective, stability and high throughput.[33,34]

Bahia *et al*., (2014),[35] described two different spectrofluorimetric methods based on the reactions of GFX with n-electron donor and - electron acceptor reagents providing a charge transfer complex. The detection limits of the previously described studies were 7.38 and 22.37 ng mL^{-1} of the two methods, respectively. These studies gave satisfactory results, but still have certain drawbacks such as high detection limit and carried out using pharmaceutical formulation. Therefore, the suggestion of more sensitive, simple and precise spectrofluorimetric method to quantify the GFX in bio-fluids is still in concern. This approach aimed to suggest a new simple and fast spectrofluorimetric method to determine the GFX in its bulk powder, tablets and in bio-fluids. Further study was carried out to match between the outcomes of the current probe and the previously published techniques to ensure the sensitivity of the suggested method.

MATERIALS AND METHODS

Chemicals and Reagents

Pure grade GFX ($C_{19}H_{24}FN_5O_7S$, 485.5 g/mol, and 98%) and its product (Factive® 320 mg/tablet) were provided from Tabuk pharmaceutical Co. (Tabuk, Saudi Arabia). Sigma Aldrich (Hamburg, Germany) supplied various kinds of surface-active agents such as Sodium dodecyl sulfate (SDS, $CH_3(CH_2)_{11}OSO_3Na$, 288.38 g/mol, and 95%), cetyltrimethyl ammonium bromide (CTAB, 99 %), tween 80 (Polysorbate 80, $C_{64}H_{124}O_{26}$, 1.310 g/mol, and 10% solution), cetylpyridinium chloride (CPC, $C_{21}H_{38}ClN$, 339.99 g/mol, and 98%), glycerol ($C_3H_8O_3$, 92.09382 g/mol) and triton-X100 ($C_{14}H_{22}O(C_2H_4O)_n$ (n=9-10), 647 g/mol). Aluminum chloride ($AlCl_3$, 133.34 g/mol, and 99.9%) was obtained from BDH, Pool, UK). Boric acid (H_3BO_3, 61.83 g/mol, and 99.5%) and sodium hydroxide (NaOH, 40.0 g/mol, and 99.9%) were purchased from Winlab (East Midland, UK). Biological samples such as human urine was provided from healthy volunteers. Normal Serum (HUMATROL N Control, Germany) was used in spiked serum analysis.

Instruments

All analytical measurements were conducted using Perkin-Elmer luminescence spectrometer (Waltham, Massachusetts, USA). The pH of the analytical samples was controlled using HANNA pH-meter (HANNA instruments, Romania). The experimental studies were carried out using distilled water GFL Water distillation unit 2004 Lab Unlimited (Carl Stuart, UK).

General procedure

Production of GFX standard solution

A stock solution (100 μgmL^{-1}) of GFX was obtained by liquefying accurate amount of 0.01 g GFX in 100 mL distilled water and kept in amber glass bottle. The analytical samples (0.05-100 ng mL^{-1}) were resulted by carrying out sequential dilution using distilled water.

Typical calibration graph of GFX

To plot the calibration graph of the suggested method, the final GFX (0.05-100 ng mL^{-1}) was prepared. Approximately, 1.5 mL of $AlCl_3$ solution (1.0×10^{-3} mol L^{-1}), 2.0 mL of SDS (1.0 %) followed by 2.0 mL of alkaline buffer solution (borate buffer pH 8) were added in a 10-mL measuring flask. The FI of each sample was determined at 268 and 400 nm excitation and emission wavelengths, respectively.

Tablet sample preparation and assay procedure

The average weight of 10 tablets was calculated. The weighed tablets were finely powdered and homogenized. A required standard GFX solution (100 μgmL^{-1}) was prepared in 100 mL distilled water under sonication for 25 min. The resulted solution was filtered using filter paper (Schleicher and Schuell, 595 Ø 150 mm) and the desired volume was adjusted to 100 mL with distilled water. The analytical solutions (0.05-100 ng mL^{-1}) were

analyzed as previously mentioned in calibration graph procedure.

Analysis of GFX in serum and urine

In spiked human urine

The collected urine samples were filtered using Schleicher and Schuell, 595 Ø 150 mm and the spiked sample was obtained by taking 1.0 mL of the previously filtered urine in 100-mL measuring flask and spiked with the required drug concentrations, then diluted with distilled water. The analytical samples (0.05-100 ng mL^{-1}) were tested as previously mentioned in calibration graph procedure.

In spiked human serum

The analytical serum sample was prepared by spiking 1.0 mL serum with 1.5 µg mL^{-1} GFX solution. The resulted solution was deproteinated following the previous literature.[33] briefly, in centrifuged tubes, aliquots of GFX standard aqueous solution were added to 1.0 mL serum and the final concentration was adjusted to be 1.5 µg mL^{-1}. The solution was shaken well for 3 min, and then deproteinated by adding 0.8 mL of acetonitrile. The mixture was shaken on a vortex mixer for 30 s, and centrifuged for 5 min at 1500 rpm. Then, the protein free supernatant was transferred into a 10.00 mL standard flask and analyzed.

The protein free serum sample was analyzed using the suggested analytical method.

RESULTS AND DISCUSSION

In the current study, the fluorescence spectrum of GFX was determined using its highly stable complex with aluminum (III) chloride. It can be clearly observed that the excitation and emission spectra for aqueous solutions of GFX-Al^{3+} complex was recorded at λ_{ex} 268 nm and λ_{em} at 400 nm (Figure 2). The surfactants effect on the FL properties of GFX-Al^{3+} complex was screened using various micellar media, including triton X 100, tween-80 and glycerol (non-ionic), anionic surfactant such as SDS and cationic surfactants such as (CTAB) and CPC. All studied organized media such as nonionic and cationic surfactants caused a decrease in a fluorescence of the complex system or even have no significant effect or small enhancement effect, while SDS exhibited a high FI enhancement of a complex system (Figures 3a). The decrease in the FI of the complex system by adding nonionic and cationic surfactants indicated that these agents have some quenching effect on GFX-Al^{3+} complex system. This can be related to the nature of interaction between the complex system and the tested

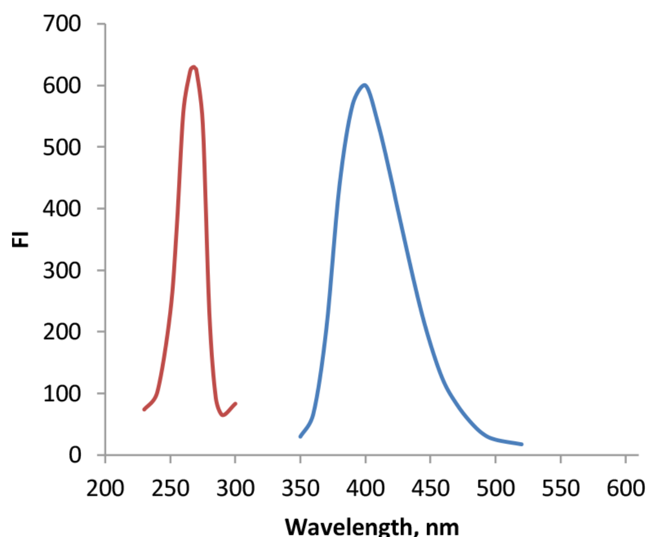

Figure 2: Excitation and emission absorption maxima of aqueous solution of GFX-Al^{3+} complex: GFX (60 ng mL^{-1}), $AlCl_3$ (1.0x10-3 mol L^{-1}), SDS (1.0 % w/v) and borate buffer of pH 8.

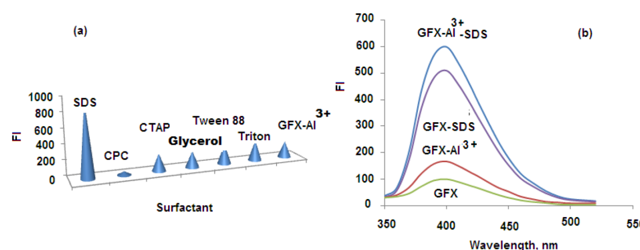

Figure 3: (a) Effect of type of surfactants (1.0 % w/v), 100 ng mL^{-1} of GFX and $AlCl_3$ (1.0×10^{-3} mol L^{-1}), (b) Comparison between the current method, GFX (60 ng mL^{-1}), $AlCl_3$ (1.0×10^{-3} mol L^{-1}), SDS (1.0 % w/v) and borate buffer of pH 8.

complex. While, using SDS, the molar absorptivity and fluorescence quantum efficiency were changed with an important improvement in FI. The increase in the fluorescence can also be due to the stabilization of GFX-Al^{3+} complex by the monomers of SDS. The previous reported studies revealed the enhancement of surfactants on the fluorescence signals appears to be due to increasing the hydrophobic species solubility, provide the protection of the fluorescence system from quenching in the bulk solvent.[36] Furthermore, the FI of GFX, GFX-Al^{3+}, GFX-SDS and GFX-Al^{3+}-SDS was studied (Figure 3b). It was noticed that the native FI of GFX was lesser than those of GFX-Al^{3+}, GFX-SDS. However, the formation of ternary complex GFX-Al^{3+}-SDS gave a significant increase in the FI. Therefore, this system was suggested to quantify GFX in different pharmaceutical and biofluids media.

Optimization of the analytical conditions

The results of analysis indicated that the buffer had a large effect on the FI of the system. The following

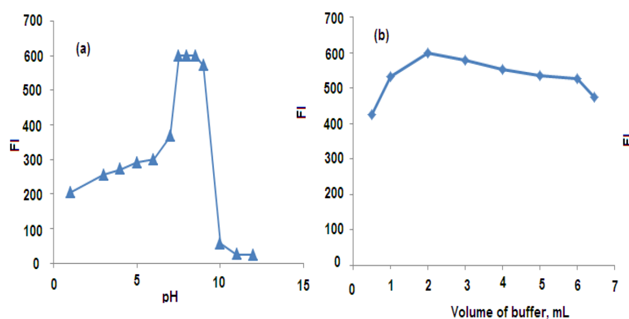

Figure 4: (a) Effect of pH on GFX-Al^{3+}, GFX (60 ng mL^{-1}), $AlCl_3$ (1.0×10^{-3} mol L^{-1}) in the presence of 2.0 mL of SDS (1.0 %), (b) The selection of suitable added volume of borate buffer, 60 ng mL^{-1} GFX-Al^{3+}-SDS.

buffers were examined: Clarck and Lubs, Britton Robinson, phosphate and borate buffer. The recorded FI signals were found to be 421, 520, zero and 600 for the above-mentioned buffers. It was found that borate buffer was the most suitable buffer.

The effect of pH FI of GFX-Al^{3+}-SDS complex can be observed in Figure 4a. A maximum FI was observed within a pH range 7.5-8.5. At higher pH more than 8.5 a sharp decrease in the FI was observed due to the weak fluorescent emission body in basic media; on the other hand, the presence of SDS enhanced the stability constant of the reaction system,[37] and facilitate the formation of strong hexagonal alumina complex with GFX which prevent the hydrolysis of GFX-Al^{3+}-SDS complex at pH 8. Therefore, a borate buffer of pH 8.0 was chosen for the spectrofluorimetric determination of GFX-Al^{3+}-SDS complex.

The effect of the amount of added buffer was investigated and the maximum FI was obtained when 2.0 mL of borate buffer at pH 8 was added. The flask was diluted with distilled water (Figure 4b).

To study the effect of added $AlCl_3$ volume on FI, different volumes (0.25-3) mL of 1.0×10^{-3} mol L^{-1}) $AlCl_3$ solution were tested. Maximum FI was achieved by adding 1.5 mL of $AlCl_3$ (Figure 5a). Moreover, micelle enhanced fluorescence of GFX was determined, by increasing the concentrations of SDS solution. It was noticed that by adding 2.0 mL of 1.0 % SDS (Critical micelle concentration, c.m.c), the FI increased and then decreased at high concentration of SDS (Figure 5b).

Stability test

The stability of the suggested system was studied, the maximum fluorescence intensity was recorded after 5 min and the experiments revealed excellent stability in the fluorescence intensity for three weeks when kept

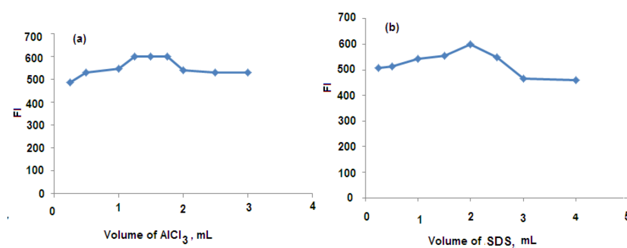

Figure 5: Effect of added volumes of (a) $AlCl_3$ and (b) SDS: The conditions: 60 ng mL^{-1} GFX-Al^{3+}-SDS, 1.0 % w/v SDS.

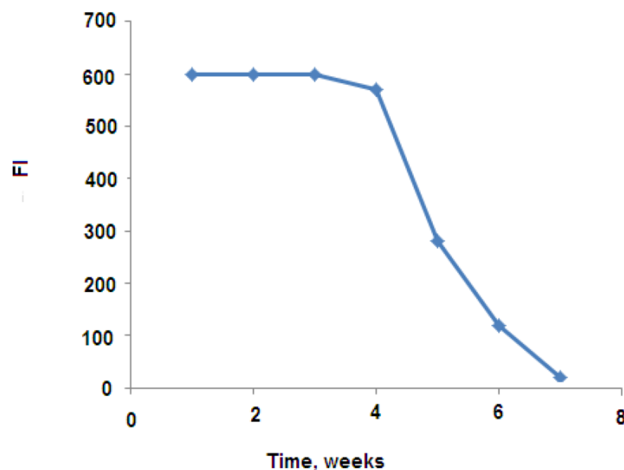

Figure 6: The time effect (in weeks) on the system stability of GFX-Al^{3+}-SDS system using GFX (60 ng mL^{-1}), $AlCl_3$ (1.0×10^{-3} mol L^{-1}) and 1.0 % w/v SDS.

in refrigerator. After three weeks, the FI was sharply lowered as a result of the decay of the investigated complex (Figure 6).

Stoichiometry of reaction

The stoichiometry of the formed complex was investigated to complete the understanding of complexation of the selected drug with metal ions. The molar ratio method was employed to study the stoichiometry of reaction and it was found that the formed complex is 1:3 [Al^{3+}: GFX] as indicated in Figure 7.

Method validation

The suggested method was validated according to ICH guidelines,[38] to ensure the suitability of the method to quantify GFX in different analytical matrices.

Under adjusted conditions, the calibration graph of the studied drug was plotted. The enhanced FI of the system was linear over 0.05 - 100 ng mL^{-1} GFX solutions, with a regression equation $FI = 9.363C+34.72$, (n=6) and correlation coefficient of r = 0.999.

The lower limits of detection and quantification (LOD) and (LOQ) of the investigateddrug was calculated by the equations at 3.3 σ/s and 10 σ/s, respectively, where σrepresents the standard deviation of the response and s is the slope of calibration graph. The current probe displayed high sensitivity with LOD 0.016 ng mL^{-1} and LOQ 0.049 ng mL^{-1}. As presented in Table 1, the suggested method showed a higher sensitivity and lower detection limit rather than other analytical techniques. Student's *t*-test and F-test,[39] were used to evaluate the accuracy of the suggested analytical technique. The results are matched and in good acceptance with others previously reported (Table 2). The intra-day and inter-day precision were estimated by analyzing three concentrations of complex (Table 3). The calculated RSD% for the three testes GFX concentrations was found to be 1.25%, 1.00% and 1.44% for intra-day assay. However, for inter-day assay the RSD % were 0.73%, 0.59% and 1.27%. The current results were less than 2% revealing that the suggested probe is highly precise for the analysis of GFX.

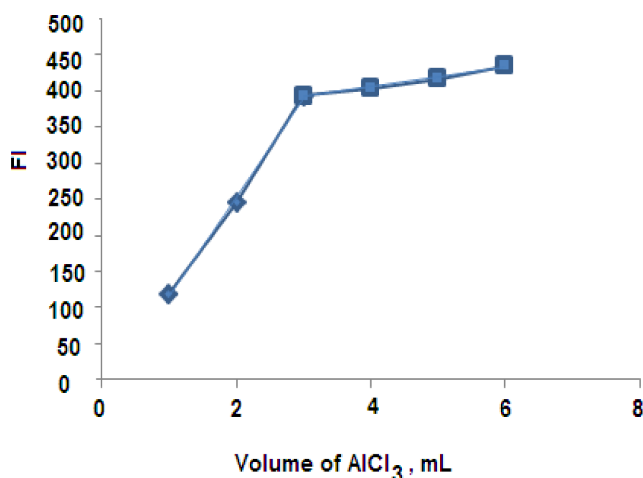

Figure 7: Determination of molar reactivity of GFX-Al^{3+}, GFX (1.0 mL, 1.0×10^{-6} mol L^{-1}), $AlCl_3$ (1.0 ×10^{-6} mol L^{-1}) and 1.0 % w/v SDS.

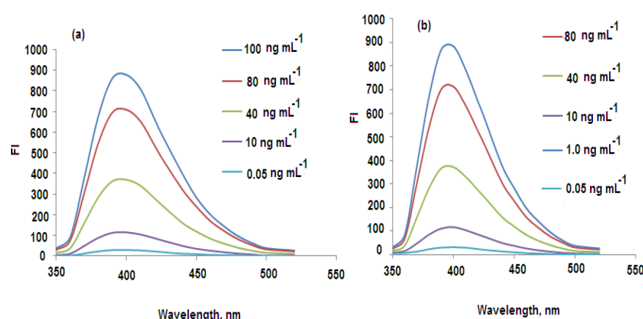

Figure 8: (a) Fluorescence emission spectra of spiked (a) plasma and (b) urine using 80, 40, 10, 1 and 0.05 ng mL^{-1} of GFX-Al^{3+}-SDS complex.

Analysis of dosage forms

The suggested Al^{3+}- GFX complex system was exploited in the presence of SDS to determine the investigated GFX drug in tablets (Factive® 320 mg/tablet), and the outcomes were matched with those of previously reported spectrophotometric method which is based on first-order derivative spectroscopy GFX at absorption wavelength 360 nm.[13] The outcome data are summarized in Table 2. It can be noticed that excellent acceptance between the labeled content and that resulted by the proposed technique.

Analysis of bio-samples

The suggested method was potentially applied for estimating GFX in bio-samples. The previously published method,[40] described that GFX is quickly absorbed after oral dosing and the maximum drug concentration in the plasma C_{max} is gradually increased linearly with increasing the dose taken. After 1hr of administering a single dose (320 mg GFX), plasma C_{max} was 1.48±0.39 µg mL^{-1}. The ultrasensitivity of the suggested study facilitated the quantification of GFX in biological fluids such as spiked human serum and urine (Figures 8a and 8b) revealed the increase of the

Table 1: A comparative study between the present study of the determination of GFX and the previously reported analytical methods.

Method	Linear range	Detection limit	Reference
Spectrofluorimetry	0.05-100 ng mL^{-1}	0.049 ng mL^{-1}	Present study
HPLC	25-5000 ng mL^{-1}	10 ng mL^{-1}	[20]
HPLC-MS/MS	10-5000 ng mL^{-1}	10 ng mL^{-1}	[24]
CE	5-50 µg mL^{-1}	2.93 µg mL^{-1}	[26]
Voltammetry	2.47-15.5 µg mL^{-1}	0.90 ng mL^{-1}	[28]
Fluorescence	0.05-1.3 µmL^{-1}	7.65×10^{-3} µg mL^{-1}	[17]
UV-visible	1.0-30 µg mL^{-1}	0.23 µg mL^{-1}	[14]
CL	1.0×10^{-9}-3.0×10^{-7} ng mL^{-1}	7.3×10^{-10} ng mL^{-1}	[18]
ISEs	1.0×10^{-7}- 1.0×10^{-3} mol L^{-1}	4.68×10^{-8} mol L^{-1}	[32]

Table 2: The outcomes of estimating the pure form and pharmaceuticals in comparison with those obtained from previously published method.[13]

	Bulk powder				Tablets (Factive® 320 mg)			
	Taken ng mL^{-1}	Found ng mL^{-1}	% Recovery	Reference method [13]	Taken ng mL^{-1}	Found ng mL^{-1}	% Recovery	Reference method[13]
	100	99.00	99.00	98.00	100	99.5	99.33	99.5
	40	41.00	100.25	99.94	40	40.5	99.71	101.25
	8	7.98	99.75	99.75	8	7.97	98.75	99.63
	2	1.99	99.50	99.91	2	1.99	99.11	99
	0.8	0.799	99.88	99.6	0.8	0.796	99.6	99.5
	0.05	0.497	99.40	99.82	0.05	0.0501	99.82	100.2
Mean ± SD	99.63±0.43			99.50±0.75	99.85±0.79			99.38±0.39
t-test	0.37 (2.228) *				1.31(2.228) *			
F-test	2.59 (5.05)*				4.13(5.05)*			

*Tabulated values of t-test (2.228) and F-test (5.05) at 95% confidence level.

Table 3: The validity data of the current method for quantification of GFX in authentic samples.

Conc. (μg mL^{-1})	Recovery %	% RSD	% Error
Intra-day precision			
8.0×10^{-2}	100.00	1.25	0.72
1.0×10^{-2}	99.00	1.00	0.58
8.0×10^{-4}	100.42	1.44	0.83
Inter-day precision			
8.0×10^{-2}	99.17	0.73	0.42
1.0×10^{-2}	98.67	0.59	0.33
8.0×10^{-4}	98.75	1.27	0.72

Table 4: Outcomes of GFX analysis in spiked serum and urine samples using the proposed Spectrofluorimetric method.

	Spiked serum samples			Spiked urine samples		
	Taken ng mL^{-1}	**Found ng mL^{-1}**	**Recovery %**	**Taken ng mL^{-1}**	**Found ng mL^{-1}**	**Recovery %**
	0.05	5.03×10^{-2}	100.6	0.05	4.93×10^{-2}	98.6
	0.8	0.79	98.8	0.8	7.9×10^{-1}	98.9
	2	1.97	98.5	2	1.98	99.0
	8	7.95	99.4	8	7.95	99.4
	40	39.80	99.5	40	39.90	99.8
	100	99.70	99.7	100	101.00	101.0
Mean ± SD	99.42±0.74			99.45±0.87		
RSD %	0.74			0.87		

FI with increasing the drug concentration. The obtained recoveries % was 99.40 and 99.44 % for serum and urine samples, respectively (Table 4).

CONCLUSION

This study focused on the prospective of a ternary complex GFX-$AlCl_3$ in the presence of SDS to enhance the FI and propose an accurate and fast probe for the quantification of GFX in both pharmaceutical and biological samples. The simplicity and rapidity of the suggested method over other chromatographic methods which need more pre-treated samples, consuming large quantities of solvents, reagents and required higher technical skills gave this probe the opportunity to be a promising precise analytical method. Also, confirm the suitability of this probe for the quantification of the drug in bio-fluids and commercial tablets.

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CONFLICT OF INTEREST

The authors declare that no any conflict of interest associated with this research work.

ABBREVIATIONS

GFX: Gemifloxacin mesylate; **SDS:** Sodium dodecyl sulfate; **CTAB:** Cetyltrimethyl ammonium bromide; **g/mol:** Gram per mole; **g mL^{-1}:** nanogram per milliliter; **CPC:** cetylpyridinium chloride; **$AlCl_3$:** Aluminum chloride; **UK:** United Kingdom; **NaOH;** Sodium hydroxide; **USA:** United States of America; **FI:** Fluorescence intensity; **c.m.c:** Critical micelle concentration; **nm:** nanometer; **g:** Gram; **FL:** Fluorescence; **$C_{max:}$** Maximum drug concentration; **GFX-$AlCl_3$:** Gemifloxacin-Aluminum chloride; **µg mL^{-1}:** Microgram per milliliter; **RSD %:** Relative standard deviation percentage; **pH:** Hydrogen ion concentration; **LOD:** Lower limit of detection; **LOQ:** Lower limit of quantification; **C:** Concentration.

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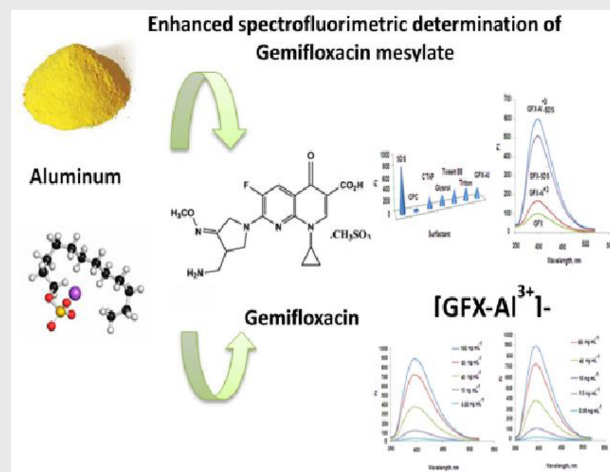
PICTORIAL ABSTRACT



SUMMARY

The use of a ternary complex GFX-$AlCl_3$ in the presence of SDS was suggested to enhance the FI and develop a precise and fast probe for the determination of GFX in both pharmaceutical and biological samples. The simplicity and rapidity of the suggested method over other separation methods which need more pre-condition samples, consuming large quantities of reagents and solvents required higher technical skills gave this probe the opportunity to be a promising precise analytical method. Also, confirm the suitability of this probe for the quantification of the drug in bio-fluids and commercial tablets.

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