


Cite this: *RSC Adv.*, 2023, 13, 35733


Received 28th September 2023

Accepted 27th November 2023

DOI: 10.1039/d3ra06626f

rsc.li/rsc-advances

The first spectrofluorimetric protocol for sensitive quantitative analysis of bromocriptine in its pure and pharmaceutical forms: evaluation of the greenness of the method†

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Bromocriptine mesylate, a dopamine D₂ receptor agonist, has been quantitatively determined using a sensitive, precise, quick, and affordable spectrofluorimetric method. The proposed method relies on the estimation of bromocriptine native fluorescence after the optimization of different factors to improve its inherently weak fluorescence through the use of a sodium dodecyl sulphate micellar system (2% w/v). Following excitation at 238 nm, the enhanced fluorescence intensity of bromocriptine was determined at 418 nm. As compared to its native fluorescence, the bromocriptine fluorescence intensity has been greatly enhanced by about 15 fold by employing the micellar system. The plot of intensity of fluorescence *versus* bromocriptine concentration was linear in the range of 50–600 ng mL^{−1}. The method was found to have a high sensitivity, as indicated by the low limit of detection and limit of quantitation values (14.57 and 44.16 ng mL^{−1} respectively). Without the interference of any excipient, this method was effectively employed to quantify bromocriptine in its pharmaceutical dosage form.

1. Introduction

The ergot derivative, bromocriptine (Fig. 1), known as 2-bromo- α -ergocryptine, which acts as a dopamine D₂ receptor agonist,¹ is a treatment used in many cases of hormonal imbalance and plays an important role in hyperprolactinemia,^{2,3} infertility,⁴ acromegaly,⁵ Parkinson's disease,⁶ and diabetes.⁷ Despite its therapeutic importance, there are only a few analytical techniques available for quantitative analysis of bromocriptine mesylate, such as HPLC,^{8–13} voltammetry,¹⁴ and spectrophotometric methods.¹⁵ Previously published chromatographic methods require time-consuming sample pretreatment and consume large volumes of highly pure organic solvents which increase the analysis cost and have harmful impact on the environment. In addition, reported spectrophotometric methods suffer from low sensitivity as they can be applied for determination of bromocriptine over a linear range of 50 to 200 μ g mL^{−1}.

Spectrofluorimetric methods of analysis are one of the most widely used methods for analysis of drugs as they have several advantages, including high sensitivity, simplicity, and low cost. Nevertheless, no fluorometric techniques have been reported

for estimation of bromocriptine mesylate concentration, either in its pure form or as a pharmaceutical preparation.

The goal of this work is to evolve and validate the first spectrofluorimetric approach for determination of bromocriptine mesylate concentration with a very high sensitivity (in the range 50–600 ng mL^{−1}) in its different forms. The proposed

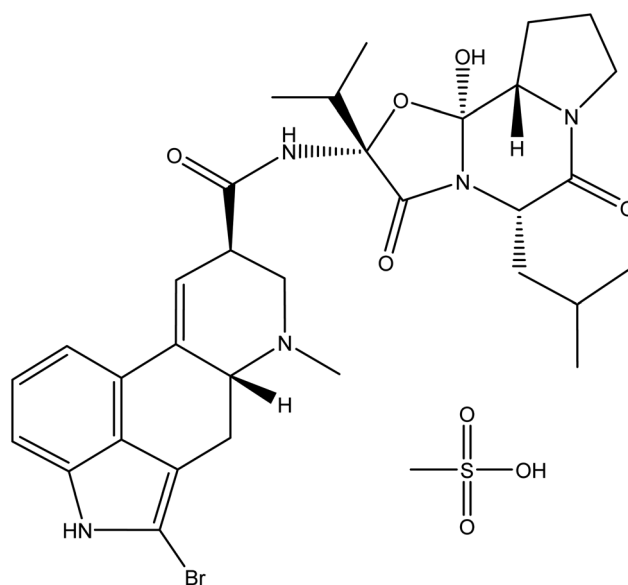


Fig. 1 Chemical structure of bromocriptine mesylate.

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† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d3ra06626f>



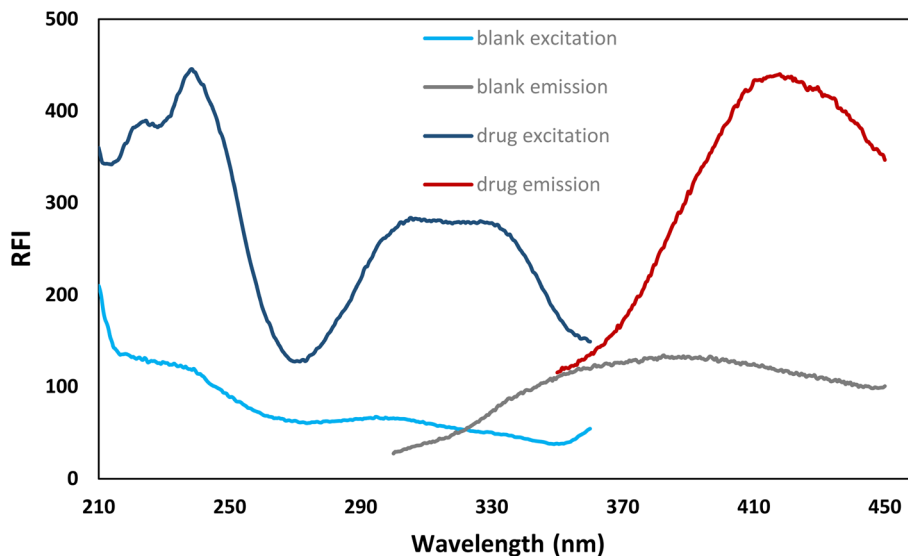


Fig. 2 The excitation and emission spectra of bromocriptine mesylate (500 ng mL^{-1}) in the presence of 2% SDS and a blank.

approach has been constructed simply to measure bromocriptine fluorescence after enhancement of the drug's very weak native fluorescence using a sodium dodecyl sulphate (SDS) micellar system in the presence of Toerell and Steinhagen buffer (pH 2.1). The developed method could be considered to be a sensitive, quick, and accurate method for determining bromocriptine mesylate concentration by utilizing all the advantages of spectrofluorimetric techniques.

2. Experimental

2.1. Apparatus

The estimation of fluorescence was performed utilizing a PerkinElmer luminescence spectrometer (LS 45; Beaconsfield, United Kingdom). A computer connected to the spectrometer running the WINLAB™ program was used for these measurements. Additionally, an AG 29 analytical balance (Glattbrug,

Switzerland) and waterproof pocket pH tester (AdwaSzeged, Hungary) were utilized.

2.2. Materials and reagents

- Bromocriptine mesylate (99.98%) was kindly given by Amoun Pharmaceuticals (El Obour city, Cairo, Egypt).
- Dopagon® tablets containing 2.87 mg of bromocriptine mesylate per tablet (Memphis Co. for Pharma. & Chemical ind., Cairo, Egypt) were bought from Egyptian pharmacies.
- SDS was purchased from Oxford lab fine chemical LLP (Navghar, Vasai East, Maharashtra 401210, India), Tween 80 from El-Nasr Chemical Co. (Cairo, Egypt), and β -cyclodextrin (β -CD) from Wacker Chemie AG (Burghausen, Germany).
- HPLC grade (100%) acetonitrile, methanol, and ethanol were purchased from Fisher Company (Loughborough, United Kingdom). Other chemicals and solvents used in this work have been purchased from Biochem Company (Industrial Zone, 6th

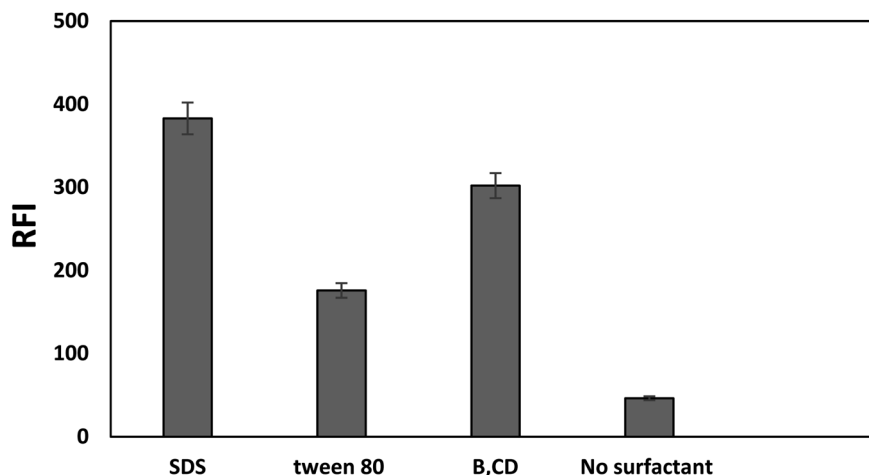


Fig. 3 Effect of different surfactants (bromocriptine mesylate conc 500 ng mL^{-1}) on the RFI value.



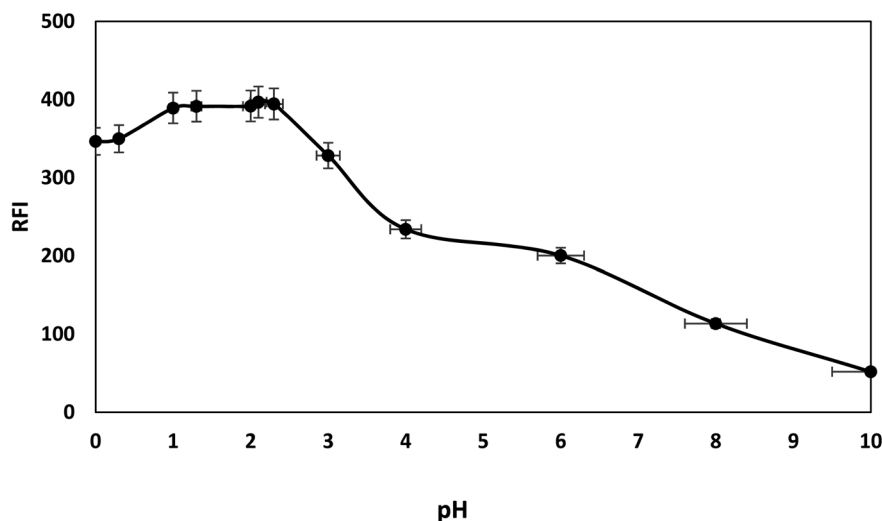


Fig. 4 Effect of different pH levels, using Toerell and Steinhagen buffer (pH 2.0–10) and HCL (pH less than 2), on fluorescence intensity of 500 ng mL⁻¹ bromocriptine with SDS.

October, Giza), including sodium hydroxide, hydrochloric acid, phosphoric acid, citric acid, and sulfuric acid.

- In order to prepare the buffer solution, 1 M solutions of sodium hydroxide, phosphoric acid, and citric acid were combined. The pH of the mixture was then adjusted using 0.1 M hydrochloric acid to achieve the required range.

2.3. Standard solutions preparation

In a volumetric flask (100 mL), accurately weighed ten mg of bromocriptine mesylate was dissolved in 50 mL of methanol and diluted to the mark with methanol to prepare 100 µg mL⁻¹ standard stock solutions which is freshly prepared. Working solutions of bromocriptine mesylate have been prepared in serial concentration from 0.5 µg mL⁻¹ up to 6 µg mL⁻¹.

2.4. General analytical procedure

In a 10 mL volumetric flask, 1.5 mL of 2.0% SDS solution and Toerell and Steinhagen buffer solution (pH 2.1) were added, followed by addition of 1.0 mL of bromocriptine mesylate working solution (0.5–6 µg mL⁻¹) and diluted to the mark with double distilled water, giving solutions with final

concentrations over the range 50–600 ng mL⁻¹. Following excitation at 238 nm, the fluorescence intensity was measured at 418 nm. Blank solutions were treated using the same procedure but without the drug.

2.5. Preparation of pharmaceutical dosage solution

Ten tablets were ground into a powder and mixed. The amount of the mixed powder equivalent to 10 mg of the drug was accurately weighed, dissolved in a volumetric flask (100 mL) with 50 mL of methanol, and sonicated for 10 minutes. The solution was then filtered and filled to the mark with methanol. After that, the solution was further diluted with methanol to obtain working bromocriptine mesylate solutions in the range 0.5–6.0 µg mL⁻¹. The previous general procedures were then followed.

3. Results and discussion

Bromocriptine mesylate possesses a very weak native fluorescence in methanol with two excitation maxima at 238 and 308 nm and an emission at 418 nm. Measurement of the native

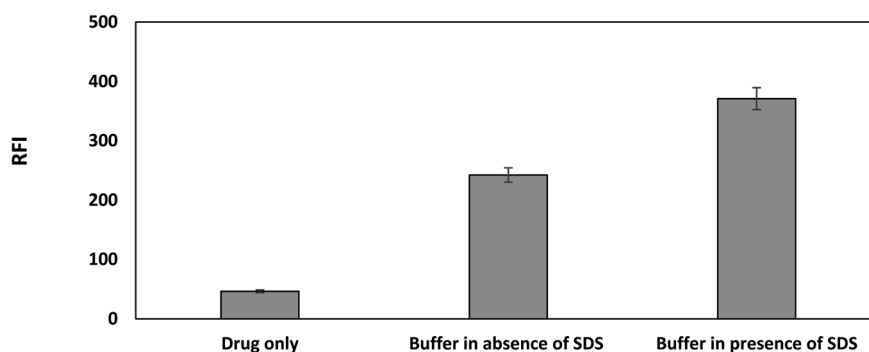


Fig. 5 Effect of pH in the presence and absence of SDS (bromocriptine mesylate conc 500 ng mL⁻¹).

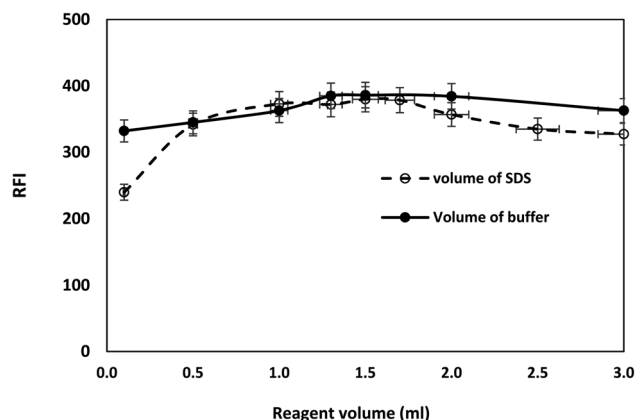


Fig. 6 Effect of SDS and buffer solution volumes on the RFI of bromocriptine mesylate (500 ng mL^{-1}).

fluorescence of investigated drug in methanol has been carried out at an excitation wavelength of 308 nm to avoid the high blank value introduced by methanol itself.

It is widely recognized that adding a surfactant with a concentration higher than its critical micellar concentration could increase both the quantum yield and molar absorptivity of fluorophore fluorescence.¹⁶ This approach has been utilized to enhance the effectiveness of spectrofluorimetric techniques for a variety of analytes.^{17–19}

Thus, the present work aims to enhance the native weak fluorescence of bromocriptine by utilizing SDS as an anionic surfactant in aqueous media to establish a simple and highly sensitive green protocol for bromocriptine mesylate quantitation. The intensity of the enhanced fluorescence was monitored at 418 nm after excitation at 238 nm. The measurements were carried out at an excitation wavelength of 238 nm with a low blank value as water was used as the diluting solvent instead of methanol. The type of surfactant and the amount used, as well as any other factors that could influence the bromocriptine mesylate fluorescence have been thoroughly examined and optimized.

Fig. 2 displays the fluorescence spectrum of bromocriptine mesylate in the SDS system. By comparison to the relative fluorescence intensity of a methanolic solution of SDS-free

bromocriptine mesylate, it was found that the fluorescence intensity in the presence of SDS was increased by about 15 fold.

3.1. Optimization of the experimental conditions

The fluorescence intensity of bromocriptine mesylate has been investigated by changing one experimental parameter whilst the other parameters were kept constant.

3.1.1 Effect of different organized media. Using various organized media, the fluorescence characteristics of the studied drug were investigated. Various surface-active agents, such as a non-ionic surface-active substance (2% v/v Tween 80), an anionic surface-active substance (2% w/v SDS), and one macromolecule (0.1% w/v β -CD), have been examined. All surfactants were investigated using various volumes, buffer systems (whether used or not), and incubation times. As shown in Fig. 3, the relative fluorescence intensity (RFI) values of the studied drug increased in the presence of Tween 80 and β -CD. However, there was a greater increase in RFI value when SDS was used, resulting in an excellent 15 fold fluorescence enhancement. This might be explained by the electrostatic attraction of the drug's positively charged amino group to the negative sulfonate group of SDS, allowing bromocriptine to establish an ion-pair complex with SDS. The reduction of free rotation and collisions with the solvent molecules caused by micellar binding increased the intensity of bromocriptine fluorescence. However, when using the nonionic surfactant Tween 80 and the macromolecule β -CD, the ability to form a complex is lower and thus the free rotational movements are less restricted, thus giving lower RFI values than SDS.

3.1.2 Effect of pH. Toerell and Steinhagen buffer solutions with pH values in the range 2–10 have been investigated for their effects on bromocriptine native fluorescence and micelle-enhanced fluorescence. It was noted that the highest fluorescence intensity of the bromocriptine-SDS micellar system was obtained with an acidic pH within the range 2.0–2.3.

Furthermore, the effects of using different acids (hydrochloric acid, sulfuric acid, and acetic acid) were checked and compared with Toerell and Steinhagen buffer (pH 2.1). Compared to acetic acid, stronger acids such as hydrochloric

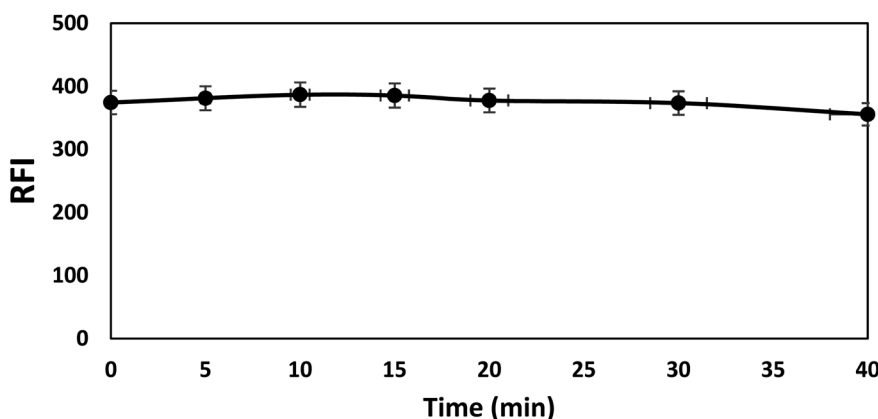


Fig. 7 Effect of time on the RFI of bromocriptine mesylate (conc 500 ng mL^{-1}).



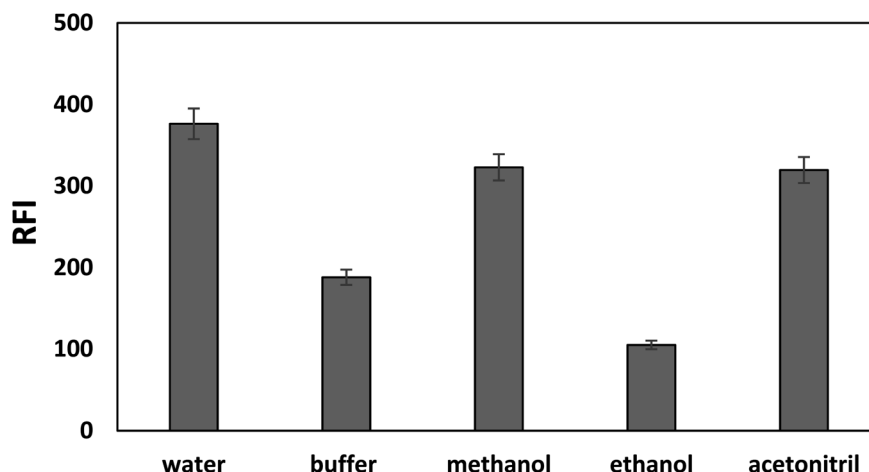


Fig. 8 Effect of different diluting solvents on the RFI of bromocriptine mesylate (500 ng mL⁻¹).

Table 1 Analytical parameters for the analysis of bromocriptine mesylate using the proposed spectrofluorimetric method

Parameter	Native	Micellar Enhanced
λ_{ex}	308	238
λ_{em}	418	418
Linear range (ng mL ⁻¹)	100–3000	50–600
Correlation coefficient (r)	0.9992	0.9996
Determination coefficient (r^2)	0.9984	0.9993
Intercept \pm SD	23.03 \pm 1.85	14.76 \pm 3.16
Slope \pm SD	0.047 \pm 0.001097	0.72 \pm 0.0087
LOD (ng mL ⁻¹)	128.85	14.57
LOQ (ng mL ⁻¹)	390.47	44.16

and sulfuric acid have higher protonation ability and thus resulted in a higher enhancement in the relative fluorescence intensity of the drug examined with SDS. However, the fluorescence intensities when using these acids were still lower than that achieved by using Toerell and Steinhagen buffer. In addition, different concentrations of hydrochloric acid (0.01–1.0 M) were also studied to investigate the effect of pH values lower than 2 (Fig. 4). It was observed that the relative fluorescence intensity value obtained using Toerell and Steinhagen buffer (pH 2.1) was also higher than that obtained with hydrochloric acid at all the studied concentrations. The slight decrease in the fluorescence intensity at low pH values (<2.0) may be due to the protonation of the indole nitrogen. This protonation can disrupt the electronic structure and conjugation within the indole aromatic system, resulting in decreased fluorescence efficiency. Protonation of the indole nitrogen can also lead to increased internal conversion or non-radiative decay processes, reducing the number of excited states and thus reducing the fluorescence intensity.

As a result, the optimum intensity of native bromocriptine fluorescence and micelle-enhanced fluorescence was attained using pH 2.1 Toerell and Steinhagen buffer (Fig. 4).

In addition, the effect of Toerell and Steinhagen buffer (pH 2.1) was investigated both with and without SDS. Fig. 5

illustrates how the use of the buffer with SDS significantly enhances the drug's relatively weak native fluorescence over the use of buffer alone. Bromocriptine has an indole ring, which is the fluorophore, and it also contains a tertiary amine on the piperidine moiety. At alkaline pH, the nitrogen atom of the tertiary amine is not ionized and carries a lone pair of electrons which could be transferred to the indole ring resulting in quenching of its fluorescence through a photoinduced electron transfer (PET) process. Upon protonation of the tertiary amine group using an acidic medium, the tertiary amine nitrogen will carry a positive charge. Thereafter, intramolecular electron transfer processes in the excited state of the drug would cease upon protonation of the tertiary amine nitrogen atom. Thus, the electron lone pair will no longer be available and consequently the PET process will be blocked, resulting in restoration of the fluorescence (ESI S1†). Moreover, the presence of a positive charge on the nitrogen atom also facilitates the electrostatic attraction between the positively charged drug molecules and the negatively charged sulfonyl group of the SDS. As a result of binding the drug to the SDS micellar system, restriction of intramolecular free rotation and increased rigidity of the drug molecules will occur, potentially increasing the drug fluorescence quantum yield.^{18–20}

3.1.3 Effect of SDS and buffer volumes. Different SDS volumes ranging from 0.1 mL up to 3.0 mL were used to demonstrate the influence of SDS volume on the fluorescence

Table 2 Standard addition method for evaluation of the accuracy of the proposed spectrofluorimetric method

Amount analyzed (ng mL ⁻¹)	Amount added (ng mL ⁻¹)	% Recovery ^a \pm % RSD ^b
100	0	98.74 \pm 0.99
100	50	100.47 \pm 1.81
100	100	98.06 \pm 0.79
100	200	98.49 \pm 0.67

^a Average of three determinations. ^b % RSD, % relative standard deviation.



Table 3 Evaluation of intraday and interday precision of the proposed spectrofluorimetric method

Sample		Intraday precision		Interday precision	
Number	Conc (ng mL ⁻¹)	% Recovery ^a	% RSD ^b	% Recovery	% RSD
1	50	101.36	0.97	100.27	1.17
2	300	98.09	0.38	98.24	0.47
3	600	101.85	0.83	100.93	0.82

^a Average of three determinations. ^b % RSD, % relative standard deviation.

intensity of bromocriptine (Fig. 6). The RFI increases when the volume of SDS is increased to 1.7 mL. After that, the RFI slightly decreases up to a volume of 3 mL. The maximum fluorescence intensity was obtained at volumes within the range 1.3–1.7 mL. As a result, 1.5 mL of SDS was selected as the ideal volume. Furthermore, the influence of the buffer volume (Toerell and Steinhagen buffer; pH 2.1) was carefully investigated to determine the volume of buffer that gives the greatest fluorescence intensity. Maximum values were attained in a range of 1.0 mL to 2.0 mL (Fig. 6). Therefore, 1.5 mL was used in subsequent investigations.

3.1.4 Time effect. The reaction time was studied up to 40.0 min (as shown in Fig. 7). It was found that an immediate enhancement in fluorescence intensity occurred. Furthermore, as the reaction time is increased, the RFI values of the bromocriptine-SDS micellar system are not affected greatly.

3.1.5 Diluting solvents effects. Ethanol, distilled water, acetonitrile, methanol, and different buffer solutions were used to investigate the effect that different diluting solvents have on the enhanced RFI of the studied drug. As shown in Fig. 8, distilled water was used as the diluting agent since it produced the highest fluorescence intensity. The RFI was reduced in other solvents. The size of the micelles has been reported to be reduced in methanol and ethanol (short chain alcohols), and the surfactant aggregate gradually breaks down.²¹

3.2. Validation of the proposed method

The developed approach has been certified in concert with the parameters specified in the International Conference on Harmonization (ICH) guidelines. Linearity, accuracy, precision, limits for quantitation and detection, and robustness are the validation parameters that have been studied.²²

3.2.1 Range and linearity. For constructing bromocriptine calibration curves, the RFI was plotted *versus* the serial concentration of bromocriptine (ng mL⁻¹). The linearity range of the developed method was between 50 and 600 ng mL⁻¹. Table 1 lists the calculated values for slopes and intercept with their standard error, in addition to determination and correlation coefficients. The good linearity of the proposed method was shown by the correlation coefficients (*r*) value of 0.9996.

3.2.2 Accuracy and precision. Through using the method of standard addition, the accuracy of the proposed method was validated. To a Dopagon® tablet solution that had already been analyzed, standard bromocriptine solutions of varying concentrations were added, and then the standard procedure was carried out. The results in Table 2 show that the recoveries were nearly 100%, indicating the brilliant accuracy of the proposed

approach. To evaluate both the interday and intraday precisions, three different bromocriptine concentrations (50, 300, and 600 ng mL⁻¹) were tested three times each on the same day and on three consecutive days. As presented in Table 3, relative standard deviation percentages were all under 2%, indicating the good precision of the developed approach.

3.2.3 Limits of quantitation and detection. The data in Table 1 show that the computed limits for quantitation and detection are 44.16 and 14.57 ng mL⁻¹, respectively. This indicates the high sensitivity of the proposed approach. The intercept standard deviation and slope of the calibration curve were used to calculate these values.

3.2.4 Robustness. The robustness of the proposed approach was evaluated by studying how minor variations through experimental factors (SDS volume, buffer volume, and pH) could affect the results of the method. The results presented in Table 4 indicate the reliability and robustness of the developed approach. With small changes in the experimental factors, almost no significant changes in the RFI were detected with high percentage recovery and low standard deviation values (lower than 2%) observed.

3.3. Application to the detection of bromocriptine mesylate in its pharmaceutical dosage form

The proposed approach can be effectively applied for the estimation of the quantity of bromocriptine mesylate in its

Table 4 Results showing robustness of the proposed method (bromocriptine mesylate conc 500 ng mL⁻¹)

Method parameters	Concentration found ^a	% Recovery ± % RSD ^b
1 Buffer pH		
2.0	490.00	98.00 ± 0.16
2.1	498.95	99.79 ± 0.44
2.2	503.07	100.61 ± 0.26
2 Buffer volume		
1.3 mL	503.49	100.69 ± 0.53
1.5 mL	493.03	98.6 ± 1.32
1.7 mL	499.71	99.94 ± 1.21
3 Volume of SDS		
1.3 mL	500.48	100.09 ± 0.32
1.5 mL	499.30	99.86 ± 0.14
1.7 mL	495.59	99.12 ± 0.59

^a Average of three determinations. ^b % RSD, % relative standard deviation.



Table 5 Results for the determination of bromocriptine in its pharmaceutical dosage form using proposed and reported methods

Dosage form	% Recovery ^a ± % RSD		<i>t</i> -value ^b	<i>F</i> -value ^b
	Proposed method	Reported method		
Dopagon® tablets	98.48 ± 0.65	97.8 ± 0.49	1.782	1.801

^a Average of five determinations. ^b Tabulated values at 95 percent confidence level: *t* = 2.776, *F* = 6.39.

Table 6 Assessment of the greenness of the proposed method using the analytical eco-scale

Eco-scale		
Parameters		Penalty points
Reagents	Citric acid	1
	Phosphoric acid	2
	NaOH	2
	SDS	8
	Water	0
Instrument		0
Occupational hazard		0
Waste		8
Total penalty points		21
Analytical eco-scale score		79

pharmaceutical dosage form (Dopagon® tablets). Statistical comparisons between the obtained results and those of another reported method¹⁵ were carried out. There were no detectable variations between the calculated and theoretical values when the results were compared at the 95% confidence level using *t*- and *F*-tests (Table 5). These results indicate that the proposed method for analyzing the quantity of bromocriptine mesylate in its pharmaceutical dosage form has good accuracy and precision.

3.4. Evaluation of the greenness of the proposed method using the analytical eco-scale

The analytical method is considered green because it does not involve the use of hazardous substances, high energy consumption, or waste products. In the current study, the eco-scale score was used to assess how environmentally friendly the proposed approach is.^{23–25} This can be determined by giving points to each component in the method. The outcome of the analytical eco-scale evaluation is represented with a number which is calculated by subtracting penalty points from 100. As presented in Table 6, the eco-scale score of the proposed approach was higher than 75 which proves the greenness of the method.

4. Conclusions

The first spectrofluorimetric method for estimation of bromocriptine quantities in its pure and pharmaceutical dosage forms was proposed. This method relies simply on measurement of the native bromocriptine fluorescence and its fluorescence enhanced using a sodium dodecyl sulphate micellar system.

The micellar enhanced spectrofluorimetric method is simple, cheap, rapid, accurate, and precise and does not require harmful and expensive solvents or derivatization steps. Thus, this method could be successfully applied in quality control laboratories.

Conflicts of interest

There are no conflicts to declare.

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