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A new green fluorimetric micelle complexation approach for reduction of the consumed solvent and quantification of avapritinib in biological fluids†

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Avapritinib (AVA) is the first medication authorized by the US-FDA in 2020 for the management of gastrointestinal stromal tumours (GISTs) that can't be treated by surgery. Cancer is among the most common causes of death worldwide and is the second most common cause of death after cardiovascular disease. Therefore, a quick, easy, sensitive, and straightforward fluorimetric approach was used to analyse AVA in pharmaceutical materials and blood plasma (pharmacokinetic). The suggested technique relies on 2% sodium dodecyl sulphate (SDS, pH 4) micellar system augmentation of the fluorescence of the tested drug. The technique demonstrated high relative fluorescence intensity (RFI) at 430 nm after excitation at 340 nm. Concentrations ranging from 20.0–400.0 ng mL^{-1} with a limit of quantitation of 9.47 ng mL^{-1} were used to obtain luminescence data for the studied medicine. In addition, the quantum yield of the AVA fluorescence was increased with the gradual addition of a surfactant at a concentration above its critical micellar level. This knowledge has been exploited to enhance the effectiveness of a spectrofluorometric technique for the estimation of AVA in human plasma (98.95 ± 1.22%) and uniformity tests with greenness assessments. The conditions for enhanced fluorescence were optimized and fully validated using US-FDA and International Conference on Harmonization (ICH) rules. This innovative strategy was expanded for AVA stability research in human plasma across various circumstances. This approach is an eco-friendly solution compared to traditional testing methods that use hazardous chemicals.

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1. Introduction

The second leading cause of mortality worldwide, behind cardiovascular disorders, is cancer. This disease often results from malfunctions in the regulatory systems that control cell division and proliferation.[1,2] Every year, 1.7 million new instances of cancer are diagnosed, and 600 000 individuals pass away from cancer in the United States alone.[2,3] The cornerstones to effective cancer treatment are decreasing mortality, improving survival, enhancing patient survival, rapid diagnosis, prompt and targeted treatments. Early cancer detection is crucial since it shortens the treatment process and lowers the overall cost of care. AVA (ESI Fig. S1†) is a tyrosine kinase inhibitor that is used to treat gastrointestinal stromal tumours (GISTs). It is important to monitor the levels of avapritinib in biological fluids to ensure that patients are receiving the correct dose and to prevent drug toxicity.[4,5] Only three approaches for the AVA assay have been reported.[6–8] Moreover, earlier techniques[6,7] were not supported by bioanalytical validation studies, which are currently mandated by US-FDA recommendations, and required the use of an organic solvent, which increases environmental toxicity. Researchers' focus has recently shifted more towards green chemistry to decrease environmental pollution and enhance public health.[9–12] Green chemistry alludes to the improvement of chemical merchandise and methods that reduce or do not involve the utilization or

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generation of perilous materials. Besides, green chemistry covers all aspects of a chemical product's life cycle, such as its creation, utilization, and last transfer.[13] Many applications in the field of analysis have been made for the use of various surfactant types to increase the fluorescence of several medications. The molar absorptivity and/or fluorescence quantum yield of a given fluorophore solution frequently increases when a surfactant is added at a concentration greater than its critical micellar concentration.[14–16]

This technique has been used for the direct estimation of the anticancer drug AVA in biological fluids. This method has been applied to uniformity tests, pharmacokinetic studies, and greenness assessments. The use of this technique in drug analysis has several advantages, including high sensitivity, selectivity, and accuracy, as well as the potential to reduce the use of hazardous reagents and solvents in the analysis process. Overall, the green fluorimetric micelle complexation approach has shown great promise in drug analysis, particularly in the field of anticancer drug estimation in biological fluids.

2. Experiments

The chemical AVA (98.70%) was obtained from Shanghai Chuangsai Technology Co. (China), and Ayvakit® (100 mg per tablet) was purchased from the Egyptian local market. El Nasr Chemical Co. provided all other chemicals, such as tween 80 (2% in distilled water), methanol, ethanol, sodium dodecyl sulphate (2% SDS), acetone, 2% polyethylene glycol 400 (PEG 400), acetonitrile, 2% cyclo-dextrin, *N*,*N*′-dimethylformamide, phosphoric acid, boric acid, carboxy methyl cellulose (CMC 2%), acetic acid, HCl, and sodium hydroxide (Cairo, Egypt). In a 10 mL calibrated flask, 20 mg of AVA was dissolved in 10 mL of methanol to create a stock AVP solution (200 μg mL^{-1}). Further dilution with ultrapure water was performed to obtain the working solutions.

Ten Ayvakit® tablets (100 mg per tablet) were weighed, mixed well, and crushed into fine powder. Then, 5 mL of methanol was added to an equivalent amount of 20 mg of the drug. The solution was ultrasonically treated for approximately 10 minutes, followed by filtering and content completion with distilled water to 100 mL. For content uniformity, each tablet was individually analysed in the pharmaceutical dosage form according to the USP procedure.[17]

The results were obtained through a grating excitation and emission monochromator with slit widths set to 2 nm, and a 1 cm quartz cell was included in the Fluorescence Spectrometer FS-2 with serial No. 1304002 with firmware version 131 024 (Sinco, Korea) apparatus. 3510 Jenwey digital pH meter (E.U.). Unicen 21 centrifuges speed (Spain).

The spiked human plasma was subjected to the following procedure: using specific amounts of the cited drug standard working solution (0.50–4.0 μg mL^{-1}), 1.0 mL of the drug-free plasma was spiked. As a protein precipitator, one millilitre of acetonitrile was included in mixture,[8] which was then diluted with distilled water to 10.0 mL and centrifuged at 4000 rpm for approximately 15 minutes. The analytical technique used one millilitre of the supernatant.

The pharmacokinetic study was performed and approved by the ethical committee of the international review board of Menoufia University, Egypt, with IRB approval no. 00437/2023. AVA pills (300.0 mg per tablet) were administered orally to ten healthy human subjects. At 1, 2, 4, 6, 8, 10, 15, 20, 25, 30, 35, 40, and 50 h, three millilitres of blood were taken intravenously into heparinized tubes.[7] To extract the plasma, blood specimens were centrifuged at 4000 rpm for 30 min. A total of 1.0 mL of the plasma was combined with 1.0 mL of acetonitrile to act as a protein precipitate agent, and the supernatant was then separated through centrifugation at 4000 rpm for 15 minutes.

2.1. Fluorimetric calibration graph

Several aliquots of AVA were placed into volumetric flasks with a volume of 10 mL to obtain the final concentration range (20.0–400.0 ng mL^{-1}). Then, 1 mL of SDS (2% solution) was added, accompanied by the addition of 1.0 mL of phosphate buffer (pH 4). Ultrapure water was added to the flasks, which were then scanned at 430 nm.

2.2. Stability study of AVA in human plasma

The stability of the pharmaceuticals under investigation in human plasma was examined using a variety of tests that used three concentrations (40.0, 100.0, and 350.0 ng mL^{-1}) of low-quality control samples (LQC), medium-quality control samples (MQC), and high-quality control sample (HQC) respectively. These studies included three freeze–thaw cycles at −24 °C, a one-month long-term stabilization test, a 12 hours short-term stability experiment, a 6 hours post-preparative test procedure, and a 12 hours post-preparative steady-state experiment.

3. Results and discussion

To create a new approach for the examination of AVA, this work attempted to determine the amount of the referenced drug in tablets and conduct a pharmacokinetic analysis using an enhanced emission band. Many approaches in the analysis field have been developed for the use of various surfactant types to increase the fluorescence of several medications. The molar absorptivity and/or fluorescence quantum yield of a given fluorophore solution is frequently increased when a surfactant is added at a concentration over its critical micellar concentration.[14,15,18] This technique has been employed to enhance the effectiveness of spectroscopic techniques for several different compounds. Various types of media (beta-cyclodextrin, PEG 400, tween 80, and SDS) were used to investigate the luminescence characteristics of the drugs under investigation. When 2% SDS surfactant was added, the fluorescence intensity increased 6.8-fold more than that in aqueous solution Fig. 1.

As shown in Fig. 1, the micelle complexation of AVA with 2% SDS provided an emission wavelength of 430 nm (excitation of 340 nm) with a calibration range of 20.0–400.0 ng mL^{-1}. The purpose of this research was to develop a straightforward, sensitive, trustworthy, selective, and affordable spectrofluorimetric technique for the evaluation of the purest forms of

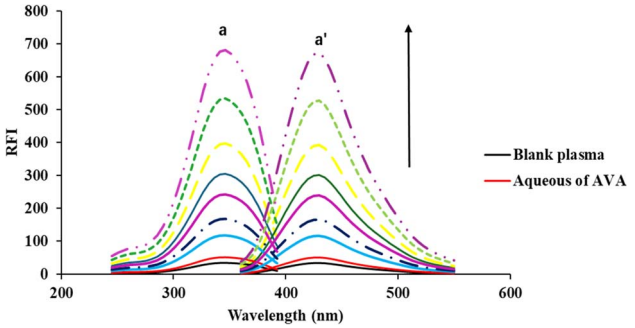


Fig. 1 Fluorescence spectra (a,a′ excitation and emission) of AVA in the presence of 2% SDS at different concentrations (20.0, 50.0, 100.0, 150.0, 200.0, 300.0, 400.0 ng mL^{-1}).

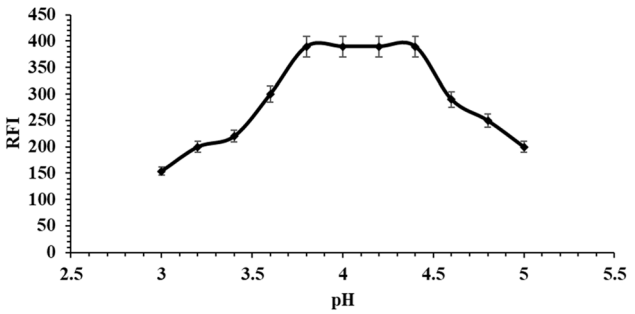


Fig. 2 Effect of pH on RFI for analysis of AVA (200 ng mL^{-1}) using 2% SDS.

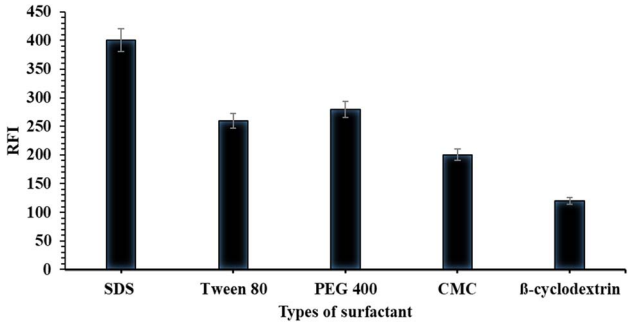


Fig. 3 Effect of various type of surfactants with AVA (200 ng mL^{-1}) using the proposed method.

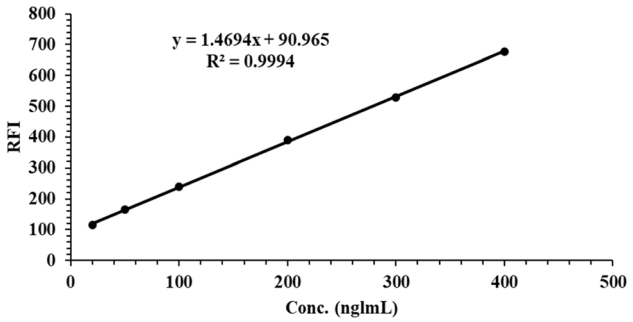


Fig. 4 Calibration graph for quantification of AVA using the proposed method.

examined drugs, pharmaceutical preparations, biological fluids, and content uniformity. The green fluorimetric micelle complexation approach is fast and sensitive and has a low limit of detection. Its accuracy is comparable to that of traditional methods, making it an excellent alternative for the evaluation of avapritinib in biological fluids. Its application in the pharmaceutical industry has provided a solution to the need for a safer, more efficient, and more environmentally responsible approach to drug testing.

3.1. Optimization of the calibration graph conditions

The factors that impact the reaction's advancement, sensitivity, and stability, as well as the properties of the fluorescence results, were thoroughly analysed and improved. Only these factors changed, while others remained constant. The examined parameters included pH, buffer type and quantity, surfactant quantity, and solvent dilution type. The selection of an appropriate pH for the reaction between the surfactant and the studied drug (AVA) was conducted using various buffers at different pH levels, as shown in Fig. S2.† The results showed that AVA fluorescence was enhanced with phosphate buffer at a pH of 4 ± 0.2; these findings are presented in Fig. 2. Additionally, the volume of phosphate buffer at pH 4 generated the highest fluorescence with 1.0 ± 0.25 mL Fig. S3.†

The fluorescence of the examined medications was increased using a variety of surfactants, including 2% β-cyclodextrin, PEG 400, Tween 80, SDS, and CMC. It was observed SDS was the most sensitive surfactant with high fluorescence intensity using 1.0 ± 0.25 mL Fig. 3.

Compared with other solvents such as water, methanol, ethanol, acetonitrile, acetone, and DMF, distilled water was shown to be the best solvent for studying the influence of micelle production Fig. S4.†

3.2. Analysis validation of the fluorimetric approach

The proposed fluorometric technique was fully verified by the International Conference on Harmonization (ICH) and FDA recommendations.[19,20]

3.2.1. Linearity and range. Six concentration points for AVA were used to test the linearity of the proposed

Table 1 Quantification analytical parameters for analysis of AVA using fluorimetric approach[a]

Parameter	Results
λ_{ex} (nm)	340
λ_{em} (nm)	430
Concentration range (ng mL^{-1})	20.0–400.0
Determination coefficient (r^2)	0.9994
Slope	1.47
Intercept	90.96
SD the intercept (Sa)	1.40
LOD (ng mL^{-1})	3.14
LOQ (ng mL^{-1})	9.47

[a] LOD: lower limit of detection; LOQ: lower limit of quantitation.

Table 2 Accuracy and precision of the proposed method with AVA using green approach

Sample number	Taken conc. (ng mL^{-1})	Found conc. (ng mL^{-1})	% Recovery[a] ± RSD
1	40.0	40.21	100.52 ± 0.33
2	80.0	82.33	102.90 ± 0.65
3	100.0	102.40	102.40 ± 0.87
4	200.0	203.00	101.50 ± 0.78
5	350.0	350.83	100.32 ± 0.60
Intra-day precision	50.0	50.24	100.48 ± 0.93
	200.0	201.50	100.75 ± 0.72
	300.0	303.37	101.12 ± 0.98
Inter-day precision	50.0	49.97	99.94 ± 1.07
	200.0	200.20	100.10 ± 1.29
	300.0	298.80	99.60 ± 0.80

[a] Average of three determinations. RSD: Relative standard deviation.

Table 3 Robustness of the proposed approach for analysis of AVA (100 ng mL^{-1})

Variations	% Recovery[a] ± RSD
Optimum condition	101.99 ± 0.55
1-Effect of pH	
3.8	100.22 ± 0.19
4.2	100.11 ± 0.27
2-Volume of buffer (mL)	
0.75	99.90 ± 0.64
1.25	99.99 ± 0.26
3-Volume of 2% SDS	
0.75	99.87 ± 0.55
1.25	99.95 ± 0.30

[a] Mean of three determinations.

spectrofluorometric technique (three measurements) as shown in Fig. 4. The calibration graph was obtained by plotting the relative fluorescence intensity (RFI) against AVA concentration with linearity from 20.0–400.0 ng mL^{-1}. The analytical parameters were established through statistical processing of the data *via* regression analysis Table 1.

$$A_{AVA} = 1.47C + 90.96,\ r^2 = 0.9994$$

where A represents the RFI of AVA, C represents the drug concentration in ng mL^{-1}, and r^2 represents the determination coefficient. Lower limit of quantitation (LOQ) was calculated as (10σ/slope) and the lower limit of detection (LOD) as (3.3σ/slope).[20,21] The lower limit of detection (LOD) and the lower limit of quantitation (LOQ) for the AVA reaction were observed to be 3.14 and 9.47 ng mL^{-1}, respectively.

3.2.2. Accuracy and precision. The accuracy of the suggested fluorimetric technique was evaluated at five concentrations (40.0, 80.0, 100.0, 200.0, and 350.0 ng mL^{-1}) (triplicate measurements of each concentration) within the analytical range of the studied drug. Table 2 shows the standard deviation and the recovery percentage of the measurements, the results refer to the high accuracy of the reaction. On the other hand, both the intraday and inter-day precision of the analytical process were calculated to evaluate its accuracy. For intraday accuracy, three concentrations of AVA (50.0, 200.0, and 300.0 ng mL^{-1}) were used, and each concentration was tested three times on the same day (repeatability) within the analytical range of AVA. The same three concentrations were used to measure the inter-day precision of AVA; each concentration was measured three times over three days (with intermediate precision). The results (Table 2) demonstrate that both the intraday and inter-day levels of the suggested analytical technique have good precision.

3.2.3. Method robustness. The robustness of the innovative method was tested *via* slight changes in pH, volume of buffer, and volume of 2% SDS in the presented methodology. The results in Table 3 show that each change in the analytical parameters causes minor changes in the relative fluorescence intensity (RFI). No significant change in the results was observed after minor modifications of the analytical parameters Table 3.

3.2.4. Stability and selectivity of AVA in human plasma. The stability of the reaction of AVA with SDS was investigated in human plasma using a variety of tests that used three concentrations (40.0, 100.0, and 350.0 ng mL^{-1}) of LQC, MQC, and HQC, respectively ($n = 5$), for quality assurance. Table 4 shows the high stability of AVA under different conditions in human plasma. The percentage of records was in the range of 96.28 to 98.97%.

In addition, the selectivity of the proposed method was checked in human plasma using three concentrations, 50.0, 150.0, and 350.0 ng mL^{-1}. As shown in Table 5, the results indicated the high selectivity of the proposed method in human plasma.

Table 4 AVA stability in human plasma using green fluorimetric approach[a]

	LQC 40.0 ng mL^{-1}	MQC 100.0 ng mL^{-1}	HQC 350.0 ng mL^{-1}
Three freeze–thaw cycle stability (−24 °C)	97.51 ± 1.60	98.00 ± 1.33	97.72 ± 2.07
Long-term stability (1 month at −24 °C)	97.63 ± 1.74	98.12 ± 1.12	97.21 ± 2.19
Short-term stability (12 h at −24 °C)	98.97 ± 1.29	97.19 ± 1.55	98.10 ± 1.38
Post-preparative stability (6 h at room temperature 25 °C)	98.41 ± 1.30	97.66 ± 1.72	96.28 ± 1.47
Post-preparative stability (12 h at room temperature 25 °C)	96.88 ± 1.80	97.10 ± 1.22	97.18 ± 1.68

[a] Data presented as recovery (%) ± SD ($n = 5$).

Table 5 Matrix effect and selectivity of the fluorimetric method for analysis AVA in human plasma

	Intra-day assay ($n = 6$)		Inter-day assay ($n = 18$)	
Conc. (ng mL^{-1})	Accuracy (%)	Precision (CV %)	Accuracy (%)	Precision (CV %)
50.0	96.80	1.43	95.80	1.00
150.0	98.11	1.75	97.50	1.83
350.0	97.77	1.39	97.00	1.65

Table 6 Application of the proposed method for analysis of AVA in plasma samples

Added conc. (ng mL^{-1})	Found conc. (ng mL^{-1})	% Recovery[a] ± RSD
20	19.34	96.70 ± 1.10
50	49.00	98.95 ± 1.22
100	97.80	97.80 ± 1.31
150	145.86	97.24 ± 1.72
200	190.66	95.33 ± 1.93
350	335.30	95.80 ± 1.62
400	385.11	96.27 ± 1.50

[a] Average of three determinations.

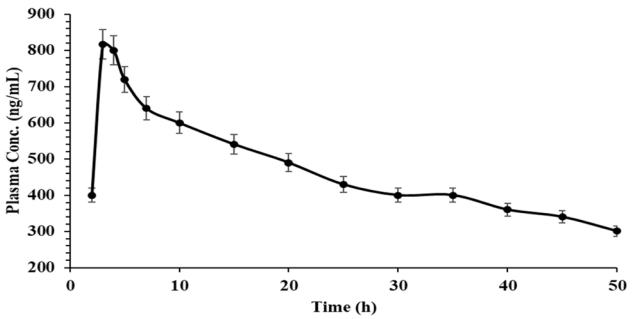


Fig. 5 Pharmacokinetic study of AVA using the proposed green method.

3.3. Applications of the inventive approach

AVA was evaluated in real and spiked human plasma utilizing the proposed method, which is a highly fluorogenic method with high affectability and selectivity. The recovery rate for the proposed strategy ranged from 95.33 ± 1.93 to 98.95 ± 1.22, utilizing six concentration levels inside the calibration run Table 6.

The high affectability of the appropriate approach has been effectively applied to pharmacokinetic measurements, as shown in Fig. 5. The pharmacokinetics of AVA were evaluated in solid human volunteers, and the maximal plasma concentration (C_{max}) was 817.13 ± 3.40 ng mL^{-1}, t_{max} of 3.50 ± 0.50 hours, the half-life was 35.20 ± 4.11 hours, and the area under curve (AUC) was determined to be 15 430.0 ± 104.90 ng h mL^{-1}, as shown in Table 7. The impacts are reliable with already detailed approaches.[8,22,23]

Table 7 Pharmacokinetic analysis for the estimation of AVA using creative approach

Time (h)	Found conc. (ng mL^{-1})	Parameters	Results
2	402.52 ± 1.50	C_{max} (ng mL^{-1})	817.13 ± 3.40
3	817.73 ± 3.40	t_{max} (h)	3.5 ± 0.50
4	801.25 ± 1.67	$t_{\frac{1}{2}}$ (h)	35.20 ± 4.11
5	703.20 ± 2.21	AUC (ng h mL^{-1})	15 430.0 ± 104.90
7	655.94 ± 1.11		
10	612.10 ± 3.76		
15	544.87 ± 2.60		
20	492.70 ± 2.30		
25	432.55 ± 0.75		
30	399.40 ± 1.90		
35	395.93 ± 2.16		
40	393.21 ± 1.40		
45	384.82 ± 1.22		
50	297.50 ± 1.00		

The endorsed strategy was effectively utilized to evaluate AVA within the pharmaceutical dose range of Ayvakit® (100 mg per tablet). The rate of recovery ± SD was 102.57 ± 0.45, with t-value and F-value equal to 1.21 and 2.43, respectively, compared with the detailed strategy.[8]

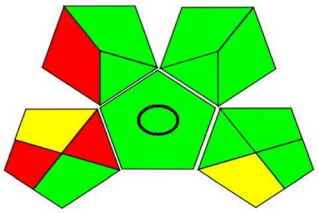
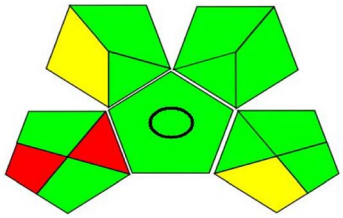
To ensure uniformity in dosage units, each prescription pill in a batch must have an active ingredient within the predetermined range of values listed on the label. The AVA method is perfect for checking content consistency because it requires less time and has a greater effect on greenness than traditional analysis techniques. Indeed, the proposed technique is very sensitive and allows fast and accurate measurement of the fluorescence intensity of a single-pellet extract. The testing procedure was performed according to USP rules Table S1.† [17]

3.4. Evaluation of the greenness of the creative method

From the creation of energy, food, and clean drinking water to pharmaceuticals, household cleaners, personal care items, and a wide range of other products, chemistry has a role in almost every area of modern life. In this sense, the chemical sector makes a substantial contribution to increasing living standards by offering fertilizers and agrochemicals to increase the availability of food as well as improving nutrition, sanitation, and a wide range of treatments to improve quality of life and life expectancy.[13,24] Green chemistry is a basic component of feasible chemistry and centres on making chemical responses and forms more ecologically invasive, considering variables such as molecular productivity, vitality proficiency, safe reactants, renewable assets, and contamination avoidance. Two analytical techniques were applied for measurements of the greenness effect of the proposed method (GAPI and agree methods).[25–29]

The proposed method provides eco-friendly and high-greenness measurements that can be used for environmental applications Table 8.

Table 8 The greenness assessment of the proposed method for determination of AVA under different applications

Technique*	Spectrofluorimetry	
Application	Plasma samples	Tablets
Organic solvents	ACN as protein precipitating agent	Totally free
Conditions	Enhancement of native fluorescence of AVA in the presence of 2% SDS using phosphate buffer pH 4	
Range	20.0–400.0 ng mL^{-1}	
GAPI assessment		
AGREE assessment		

4. Conclusion

This technique has been used for the direct estimation of the anticancer drug avapritinib in biological fluids (pharmacokinetic study) with (C_{max}) equal to 817.13 ± 3.40 ng mL^{-1}. The use of this technique in drug analysis has several advantages, including high sensitivity (LOQ equal to 9.47 ng mL^{-1}), selectivity, and accuracy, as well as the potential to reduce the use of hazardous reagents and solvents in the analysis process.

Ethical statement

All the experiments were conducted and approved according to the ethical committee of the international review board of Menoufia University, Egypt with IRB approval no. 00437/2023. The authors confirmed informed consent was obtained from all subjects participating in the experiments.

Author contributions

Conceptualization, B. I. Salman, and R. E. Saraya; methodology, B. I. Salman, H. A. Batakoushy, E. A. M. El-Shoura, and R. E. Saraya.; software, A. I. Hassan., M. A. A. Abdel-Aal, Y. F. Hassan. and B. I. Salman; validation, B. I. Salman, A. E. Ibrahim, and E. A. M. El-Shoura; formal analysis, B. I. Salman and A. E. Ibrahim.; investigation, Y. F. Hassan, H. A. Batakoushy and B. I. Salman; resources, A. I. Hassan and B. I. Salman; data curation, A. E. Ibrahim and E. A. M. El-Shoura.; writing – original draft preparation, B. I. Salman; writing – review and editing, B. I. Salman, Y. F. Hassan, and A. E. Ibrahim; visualization, B. I. Salman; supervision, B. I. Salman; project administration B. I. Salman and E. A. M. El-Shoura; all authors have read and agreed to the published manuscript.

Conflicts of interest

There are no conflicts of interest to declare.

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