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New Fluorometric Method for the Determination of Ketotifen Fumarate Using Continuous Flow Injection Analysis via ISNAG-fluorimeter

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Abstract:

A newly developed analytical method was conducted for the determination of Ketotifen fumarate (KTF) in pharmaceuticals drugs via quenching of continuous fluorescence of 9(10H)-Acridone (ACD). The method was applied using flow injection system of a new homemade ISNAG fluorimeter with fluorescence measurements at ± 90◦ via 2×4 solar cell. The calibration graph was linear in the range of 1-45 mmol/L, with correlation coefficient r = 0.9762 and the limit of detection 29.785 µg/sample from the stepwise dilution for the minimum concentration in the linear dynamic ranged of the calibration graph. The method was successfully applied to the determination of Ketotifen fumarate in two different pharmaceutical drugs. A comparison was made between the newly developed method analysis and the classical method using the standard addition method via the use of individual and paired t-test and F-test. It was noticed that there was no significant difference between the two methods at 95 % confidence level.

Key words: 9(10H)-Acridone , Flow injection analysis , Fluorescence , Ketotifen fumarate .

Introduction:

Ketotifen Fumarate (KTF) is an antihistaminic drug which has the nomenclature 4-(1-Methylpiperidin-4-ylidene)-4,9-dihydro-10H-benzo[4,5] cyclohepta[1,2-b] thiophen- 10-one hydrogen (E)-butenedioate (Fig. 1) with an empirical formula of $C_{19}H_{19}NOS,C_4H_4O_4$, and it is a white or brownish-yellow, fine, crystalline powder. It is sparingly soluble in water, slightly soluble in methanol, very slightly soluble in acetonitrile (1). The main biochemical and pharmacological activities of ketotifen fumarate are H_1 receptor antagonism, phosphodiesterase inhibition and inhibition of calcium flux in smooth muscle preparations. All these actions are suited to prevent the development of asthmatic conditions (2). Many analytical methods have been reported for the determination of KTF in pure form and pharmaceutical preparations, which includes spectrophotometric methods (3-5), chemiluminescence (6, 7), electrochemical (8-10), electrochemilu-minescence (11, 12), chromatographic (13, 14), and flow injection analysis (FIA) methods (15,16,17).

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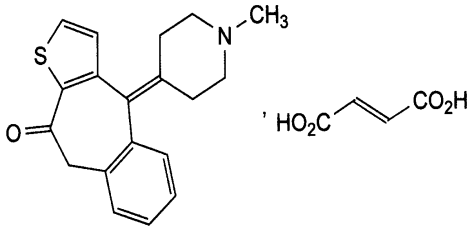
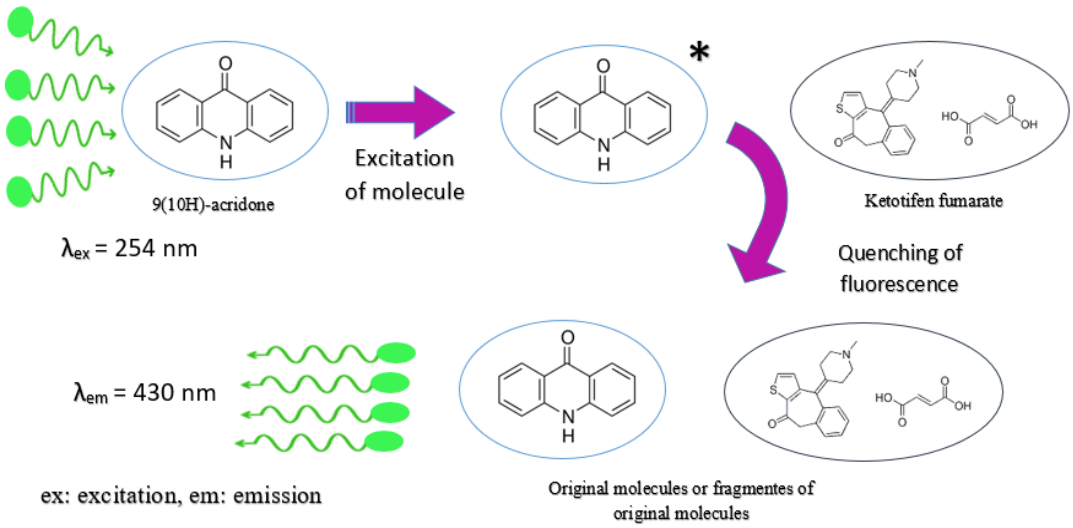


Figure1. Chemical structures of Ketotifen Fumarate.

The aim of this study was to develop a new fluorometric flow injection method for the determination of ketotifen fumarate (KTF) using the new homemade ISNAG-fluorimeter. This method is based on the quenching of 9(10H)-acridone fluorescence measured at ± 90° via the use of ISNAG-fluorimeter. 9(10H)-Acridone (ACD) is one of the acridone alkaloids which have a characteristic of fluorescence absorption due to their specific skeleton structure (18). 9(10H)-Acridone (ACD) gives a continuous fluorescence which quenches via ketotifen fumarate (KTF) with the proposed mechanism illustrated in (scheme 1). This mechanism is based on the possibility that it might be attributed to the formation of non-fluorescent derivative or decomposition of fluorescent molecule or finally might be due to excessive collision causing quenching of fluorescence (i.e.; external conversion).



Scheme 1. Proposed mechanism for quenching of ACD via the use of KTF as an injected sample.

Materials and Methods:

Apparatus and Reagents

A homemade ISNAG fluorimeter was used with 4-channels peristaltic pump (Ismatec, Switzerland) and Six-port medium pressure injection valve (I D E X corporation, USA) with sample loop (1 mm i.d. Teflon, variable length). Potentiometric recorder was used to estimate the output signals (Siemens, Germany (1- 5 V)). Spectrophotometer (UV-1800, shimadzu, Japan) was also used for classical spectrofluorometric methods.

All chemicals were used of analytical-reagent and distilled water was used to prepare all the solutions. A standard solution of 1 mmol/L and 50 mmol/L of ACD and KTF, molecular weight 195.221 and 425.497 g/mole respectively, were prepared by dissolving 0.0976 g of ACD in 500 mL of DMSO and 2.1275 g of KTF in 100 mL of distilled water. A pH range of 2.2–8.0 buffers were prepared according to McIlvaine citric acid–phosphate buffer systems (19). A series of sodium hydroxide solutions were prepared from the dilution of standardized stock solution (0.1 mol/L) with distilled water.

Sample Preparation

Twenty tablets of two different pharmaceuticals drugs (Asmafort; Julphar and Gloditen; Globalpharma) containing 1 mg of ketotifen fumarate were weighed, crushed, and grinded. A solution of 1 mmol/L was prepared by weighing 2.4474 and 3.8084 g (equivalent to 0.0213 g of active ingredient) from Asmafort, Julphar and Gloditen, Globalpharma respectively. Each one from the two kinds of sample was dissolved in distilled water. The solution was filtered to get rid of undissolved materials, the residue was washed with distilled water and completed the volume to 50 ml with the same solvent (distilled water).

Methodology

The manifold system composed of one line (Fig. 2) used for the flow injection system of ACD was used to determine the KTF using ISNAG fluorimeter with an experimental parameters of flow rate 2.75 mL/min for the ACD and 150µL of 10 mmol/L KTF as an injected sample segment. These parameters were investigated to enhance the quenching of fluorescence of ACD; effect of ACD concentration using different concentration of (0.01-0.05 mmol/L) as a carrier stream, the effect of the flow rate of ACD as a carrier stream by changing their flow rate from 0.575 to 4.3 mL/min, variation of sample loop (50-250 µL) were investigated, and the purged time were studied at (2-25 sec).

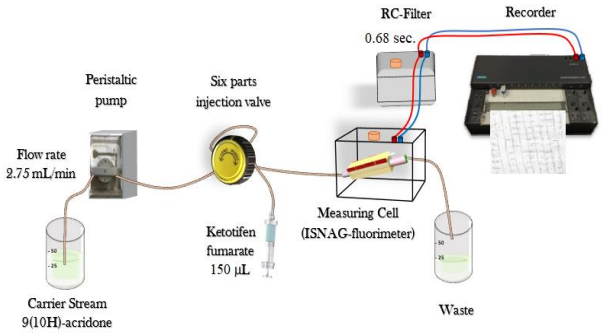


Figure 2. Single line manifold design of quenching system ACD-KTF.

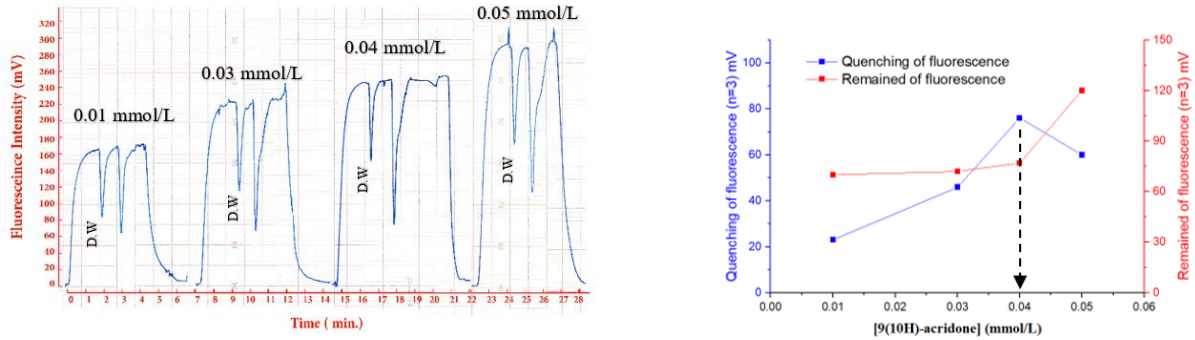
Results and Discussion:

Study of the Optimum Parameters

Effect of Variable Concentration of 9(10H)-acridone

A series of ACD (0.01-0.05 mmol/L) which is used as a continuous fluorescent molecule for the quenching system ACD–KTF at a flow rate of 2.75

mL/min, 150µL sample volume of 10 mmol/L KTF were injected. Increasing ACD concentration up to 0.04 mmol/L gives a better quenching response (Fig. 3A) 0.04 mmol/L has been chosen as the best concentration due to its better quenching by KTF and its less effect by blank (D.W) as shown in Fig. 3B. These quenching of ACD fluorescence by KTF might be due to several possibility non-radiative processes that lead to routes back to the ground electronic state. One process is the energy transfer between molecules through molecular collisions (i.e: external conversion, internal conversion and vibrational relaxation).



A **B**

Figure 3. Variation of ACD concentration effect on A: Response profile-time, B: Quenching of fluorescence by KTF and remained of fluorescence.

Physical Parameters Optimization

Effect of Flow Rate

Using 150 µL of KTF (10mmol/L) as an injected sample segment in an open valve mode and 0.04 mmol/L of ACD as a carrier stream with flow rate range (0.575-4.3 mL/min). It was noticed that there was a decreased in response height as well as in peak base width (Δ_{tb}) with increasing the flow rate. A regular and sharp responses with narrow (Δ_{tb}) were obtained at higher flow rate i.e. >1.7 mL/min (Fig. 4). So, 2.2 mL/min was chosen as the optimum flow rate to decrease the effect of dilution and dispersion which due to diffusion and convection. All the results tabulated in Table 1.

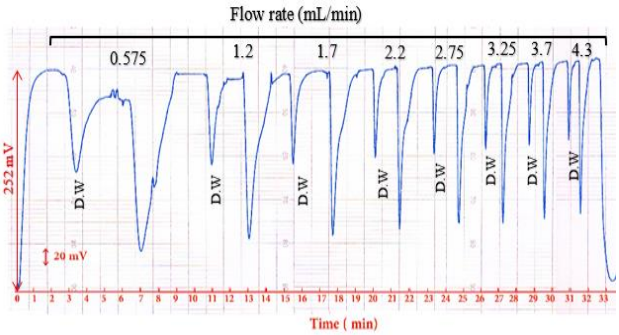


Figure 4. Variation of flow rate on response profile-time.

Table 1. Effect of variable flow rate of ACD-KTF quenched fluorescence system using 150µL of 10 mmol/L of KTF as an injected sample.

Speed of peristaltic Pump (indication approximate)	Flow rate (mL/min)	Total quenching of ACD fluorescence $\bar{y}_{iTQAF}$ (mV) Expressed as an average peak heights (n=3)	Quenching of ACD fluorescence $\bar{y}_{iQAF}$ (mV)	RSD%	Confidence interval of the average response (at 95% confidence level) $\bar{y}_{iQ} \pm t_{0.05/2,\, n-1}\, \sigma_{n-1}/\sqrt{n}$	Remained of ACD fluorescence $\bar{y}_{iR}$ (mV)	Δt_b Peak base width (min)	V_{final} (mL)	C_{final} (mmol/L)	$Df = \frac{C_0}{C_{final}}$
5	0.575	204	86	0.97	86 ± 2.062	48	2.4	1.530	0.9804	10.1999
10	1.200	188	84	0.67	84 ± 1.3912	64	1.5	1.950	0.7692	13.0005
15	1.700	186	82	0.82	82 ± 1.6645	66	1.1	2.020	0.7426	13.4662
20	2.200	185	83	1.12	83 ± 2.3104	67	0.9	2.130	0.7042	14.2005
25	2.750	180	76	0.78	76 ± 1.4658	72	0.7	2.075	0.7229	13.8332
30	3.250	182	76	0.91	76 ± 1.7142	70	0.7	2.425	0.6186	16.1655
35	3.700	174	75	1.28	75 ± 2.3850	78	0.6	2.370	0.6329	15.8003
40	4.300	170	78	0.83	78 ± 1.6148	82	0.5	2.300	0.6522	15.3327

Response of continuous fluorescence: 252 mV. Δ_{tb} (min): Time lapse for the quenching of 9(10H)-acridone fluorescence by ketotifen fumarate within the measuring cell. Quenching of 9(10H)-acridone fluorescence by ketotifen fumarate $\bar{y}_{iQAF}$ (mV) = Total quenching of 9(10H)-acridone fluorescence by ketotifen fumarate $\bar{y}_{iTQAF}$ (mV) – Quenching of 9(10H)-acridone fluorescence by D.W $\bar{y}_{iQ\ D.W.}$ (mV).

Effect of Sample Volume

Flow rate 2.2 mL/min for 0.04 mmol/L of ACD was used as a carrier stream with continuous fluorescence intensity of 252 mV, the injected volumes varied from 50-250 µL in an open valve mode to study the effect of sample segment. It was noticed that an increase in the sample volume leads to an increase in the height of responses with a minor decrease or being approximately constant base peak width. Also, it was observed that when dealing with larger sample segment i.e > 100 µL (Fig. 5) leads to increasing a significant difference between quenching of continuous fluorescence of ACD by KTF compared with distilled water (blank). Therefore, 100 µL was chosen as the optimum sample volume that gave the maximum quenching of ACD fluorescence by KTF with minimum effect of blank.

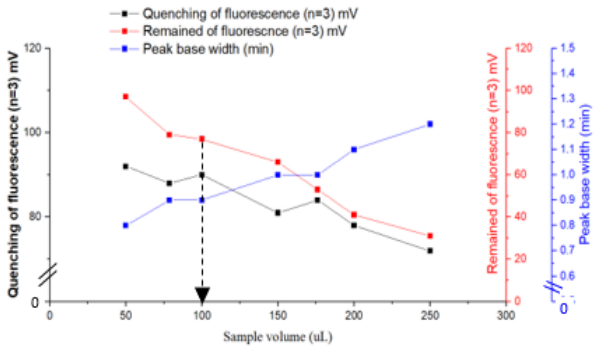


Figure 5. Effect of quenching of ACD fluorescence, remained of ACD fluorescence and peak base width.

Purge Time Effect

Using the optimum parameters achieved in previous study, different purge time (2-20 sec) an addition to open valve mode (25 sec) were studied. It is noticed that there is an increase in the response with increasing the allowed permissible time for the sample injection as shown in Fig. 6. Therefore, open valve mode was chosen as the best with maximum quenching of ACD fluorescence by KTF and minimum RSD% (0.71%).

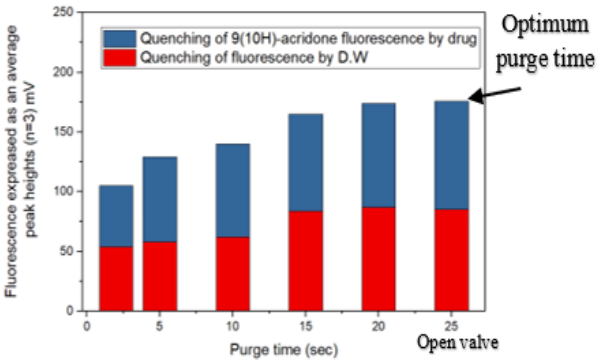


Figure 6. Quenching of ACD continuous fluorescence by KTF and quenching of ACD continuous fluorescence by blank vs. purge time.

Calibration Graph for the Variation of KTF Concentration Versus Quenching of Fluorescence of ACD

A series of KTF ranging from 1-50 mmol/L were prepared and injected on 0.04 mmol/L of ACD as a carrier stream using all achieved parameters in previous sections. A responses profile of total quenching of ACD fluorescence, quenching of ACD fluorescence by KTF and remained of ACD fluorescence (all in mV) and the calibration graph obtained were plotted against the concentration of KTF. It was noticed from the linear calibration graph for the variation of KTF concentration gave a correlation coefficient r: 0.9762, r^2: 0.9529, R^2%: 95.29% and the calculated t-value at 95% confidence level of 14.229 (Table 2). With range from 1-45 mmol/L, above 45 mmol/L leading to deviation of correlation coefficient and deviate from linearity most probably due to the high intensity of the fluorescent molecule in front of detector which in turn to excessive collision of excited molecule causing as non-radiative emission process and quenching of fluorescence such as vibrational relaxation and internal conversion.

The method achieved in this work was compared with classical method (Spectrophotometric methods) via the measurement of absorbance spectrum at λ_{max} = 302 nm (Fig. 7), calibration graph was obtained for classical spectrophotometric method and table 2 sum up all the results obtained using linear regression analysis for both methods. The limit of detection was calculated for the developed method and the reality and repeatability was studied for eight repeated injections for (10 and 30 mmol/L) of Ketotifen fumarate (Fig. 8).

Table 2. Summary of calibration graph results for quenching of ACD fluorescence by KTF at 95% confidence level.

Type of method	Measured conc. (mmol/L)	Range of calibration graph (mmol/L)	Equation of calibration graph $\hat{y}_i = a \pm S_a t + b \pm S_b t$ $[Ketotifen\ fumarate] mmol/L$ at confidence level 95%, n-2	r r^2 R^2%	$t_{tab} = t_{0.025}$, n-2	$t_{cal} = \frac{\lvert r\rvert\sqrt{n-2}}{\sqrt{1-r^2}}$
Total quenching of fluorescence	1-50	1-45 (n=12)	$\hat{y}_i(\text{mV}) = 134.98 \pm 11.34 + 2.96 \pm 0.47$ [Ketotifen fumarate]$mmol/L$	0.9762 0.9529 95.29	2.228<<14.229	
Quenching of fluorescence			$\hat{y}_i(\text{mV}) = 50.98 \pm 11.34 + 2.96 \pm 0.47$ [Ketotifen fumarate]$mmol/L$	0.9762 0.9529 95.29	2.228<<14.229	
Remained of fluorescence			$\hat{y}_i(\text{mV}) = 123.02 \pm 11.34 - 2.96 \pm 0.47$ [Ketotifen fumarate]$mmol/L$	0.9762 0.9529 95.29	2.228<<14.229	
λ_{max} = 302 nm	0.001-0.04	0.001-0.03 (n=9)	$\hat{y}_i = -0.01 \pm 0.02 + 59.63 \pm 1.28$ [Ketotifen fumarate]$mmol/L$	0.9997 0.9994 99.94	2.365<<109.825	

Limit of detection (Sample volume = 100 µL)

Practical based on the gradual dilution for the minimum concentration (0.7 mmol/L)	Theoretical based on the value of slope $X=3S_B/slope$	Theoretical (linear equation) based on the value of $\hat{Y} = Y_b + 3S_b$
0.298 g/L 29.785 µg/sample	0.259 g/L 25.875 µg/sample	4.520 g/L 451.950 µg/sample

Repeatability

[Ketotifen fumarate] mmol/L	Quenching of 9(10H)-acridone fluorescence by ketotifen fumarate expressed as an average peak heights (n=8) $\bar{y}i$ (mV)	RSD%	Confidence interval of the average response (at 95% confidence level) $\bar{y}_i \pm t_{0.05/2,\ n-1}\ \sigma_{n-1}/\sqrt{n}$
10	89.7	1.37	89.7 ± 1.0285
30	147.4	0.88	147.4 ± 1.0870

n: No. of measurements in calibration graph, $\hat{y}_i$: Estimated value in mV for developed method and absorbance for UV-spectrophotometric method, r: correlation coefficient, r^2: coefficient of determination, R^2%(Percentage capital R-squared): explained variation as a percentage total variation. X: value of L.O.D based on slope, S_B: Standard deviation of blank repeated for 13 times, Y_b: average response for blank = intercept, S_b: standard deviation equal to $S_{y/x}$ (residual), $t_{0.025,10}$=2.228, $t_{0.025,7}$=2.365.

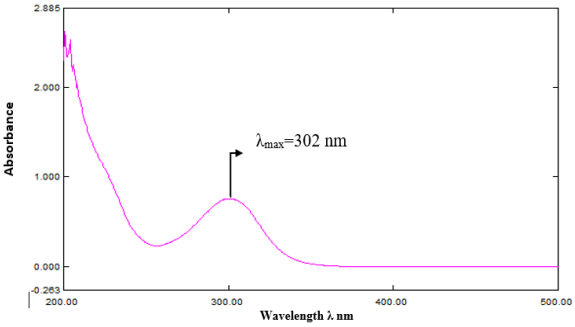


Figure 7. Absorbance spectrum of 0.01 mmol/L KTF with maximum wavelength of 302 nm.

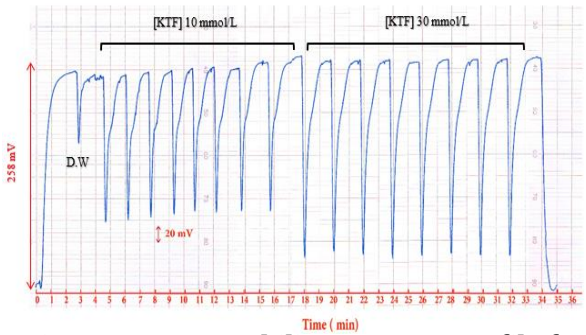


Figure 8. Repeatability response profile for quenching of ACD fluorescence by KTF.

Assessment of the Use of ACD-KTF System Using ISNAG-fluorimeter

Two methods were used for the determination of KTF in two different pharmaceutical drugs. The first method was the new developed methodology using ISNAG-fluorimeter and the second was the classical spectrophotometric method using maximum wavelength absorbance at 302 nm (1). A series of solutions were prepared of each pharmaceutical drug (1 mmol/L) by transferring 5 mL to each five volumetric flasks (10 ml), followed by the addition of gradual volumes of standard KTF (20 mmol/L) for developed method, while for classical method solutions of (0.01 mmol/L) were prepared from the previous samples and 5 mL were transferred to each five volumetric flasks (10 ml), followed by the addition of (0.04 mmol/L) standard ketotifen fumarate. Figure9 shows the calibration plot of these methods and the results were mathematically treated (20, 21)and tabulated in Table 3 at confidence level of 95%.

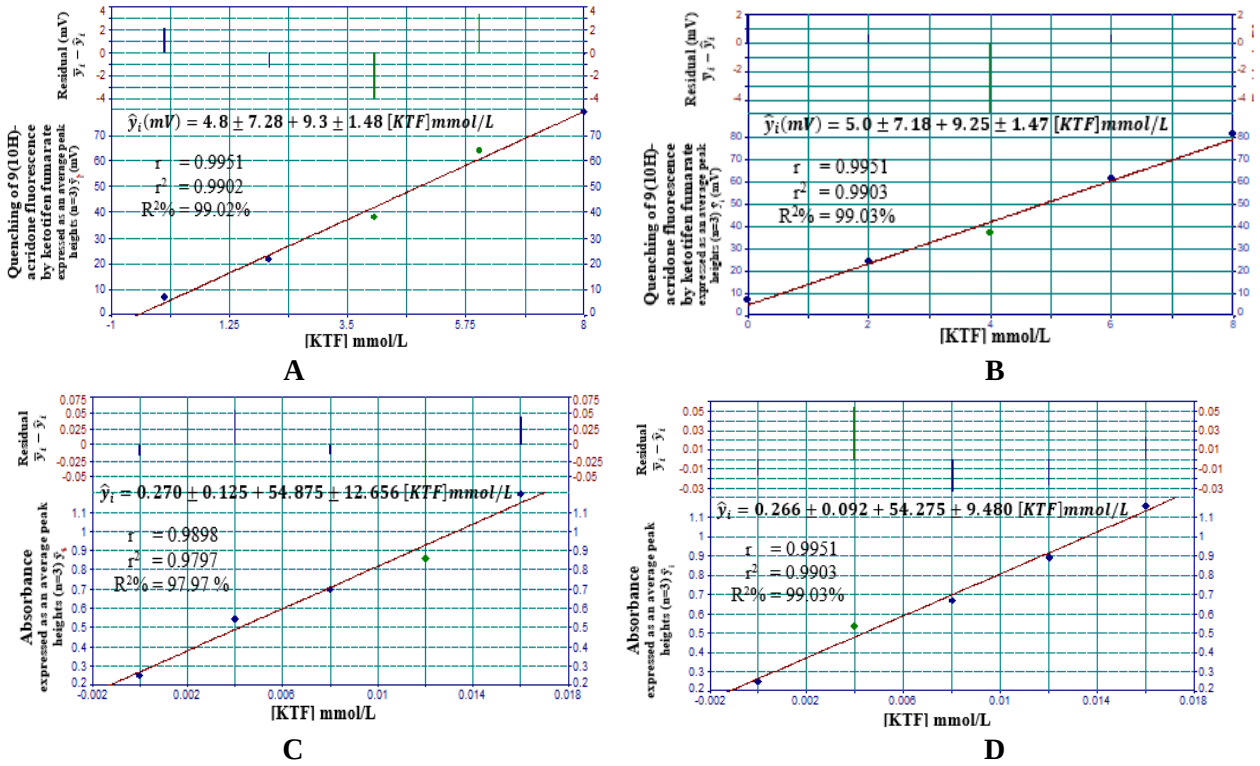


Figure 9: Standard addition graph for A- Developed method for Asmafort, B- Developed method for Gloditen, C-Classical method for Asmafort, D- Classical method for Gloditen.

$Residual = \bar{y}_i(practical\ value) - \hat{y}_i(estimated\ value)$.

Table 3: Standard addition results for the determination of KTF in two different pharmaceuticals drugs using two methods.

Commercial name, Company, Content, Country	Newly developed methodology using ISNAG-fluorimeter (mV)					
	UV- spectrophotometric classical method absorbance measurement at λ_{max} = 302 nm					
	Confidence interval for the average Weight of tablet $\bar{W}_i \pm 1.96\,\sigma_{n-1}/\sqrt{n}$ at 95% (g) (n=30)	Weight of sample equivalent to 0.0213 g (1 mmol/L) of active ingredient	Theoretical content for the active ingredient $W_i \pm 1.96\,\sigma_{n-1}/\sqrt{n}$ at 95% (mg)	Equation of standard addition at 95% for n-2 $\hat{y}_i = a \pm S_a t + b \pm S_b t$ $[KTF]mmol/L$		r | r^2 | R^2%
Asmafort, Julphar, 1mg, UAE	0.1149 ± 0.0006	2.4474	1 ± 0.0052	$\hat{y}_i(mV) = 4.8 \pm 7.28 + 9.3 \pm 1.48$ $[KTF]\ mmol/L$		0.9951|0.9902|99.02%
				$\hat{y}_i = 0.270 \pm 0.125 + 54.875 \pm 12.656\ [KTF]mmol/L$		0.9898|0.9797|97.97%
Gloditen, Global-pharma, 1mg,UAE	0.1788 ± 0.0008	3.8084	1 ± 0.0045	$\hat{y}_i(mV) = 5.0 \pm 7.18 + 9.25 \pm 1.47\ [KTF]mmol/L$		0.9951|0.9903|99.03%
				$\hat{y}_i = 0.266 \pm 0.092 + 54.275 \pm 9.480\ [KTF]mmol/L$		0.9941|0.9883|98.83%
Commercial name, Company, Content, Country	Practical concentration (mmol/L) in 10 mL *	Weight of ketotifen fumarate in tablet $\bar{W}_{i(mg)} \pm 4.303\,\sigma_{n-1}/\sqrt{n}$	Efficiency of determination Recovery %	t-test		F-test
				Individual t-test for compared between claim & practical value $(\bar{W}_i - \mu)\sqrt{n}/\sigma_{n-1}$	Paired t –test compared between two methods	compared between two methods $F = {s_1}^2/{s_2}^2$ $F > 1$
Asmafort, Julphar, 1mg, UAE	0.516	1.032 ± 0.0848	103.2 %	1.625 << 4.303	$t_{cal} = \frac{\bar{X}d\sqrt{n}}{\sigma_{n-1}}$ t_{tab} at 95% confidence level (n-1)	$S_1^2 = 1.25 \times 10^{-3}$
	** 0.00492 in 10mL 0.00984 in 50mL (diluted sample)	0.984 ± 0.1093	98.4 %			$S_2^2 = 8 \times 10^{-6}$
						156.25 << 648
Gloditen, Global-pharma, 1mg,UAE	0.541	1.082 ± 0.1928	108.2 %	1.830 << 4.303	$\bar{X}d$: 0.075 σ_{n-1}: 0.03818 2.778 ≪ 12.706	
	** 0.00490 in 10mL 0.00980 in 50mL (diluted sample)	0.980 ± 0.1838	98.0 %			

$\hat{y}_i$: in mV for developed method and absorbance for classical method, r: correlation coefficient, r^2: coefficient of determination, R^2%(Percentage capital R-squared): explained variation as a percentage total variation, $t_{0.025,\infty} = 1.96\ at\ 95\%$,t_{tab}: $t_{0..025,3} = 3.182$ for n=5 & $t_{0..025,2} = 4.303$ for n=3 & $t_{0..025,1} = 12.706$ for n=2, $\bar{W}_i$:Mean of weight for n=30. μ: claim value (g). * Practical concentration (mmol/L) in 10 mL for newly developed methodology, ** In classical method the concentration diluted to 0.01 mmol/L by draw 0.5 mL from 1 mmol/L, $F_{tab} = F_{\frac{0.05}{2},\nu1,\nu2} = F_{\frac{0.05}{2},1,1} = 648\ at\ 95\%\ confidence\ level\ (two\ tailed)$.

Conclusion:

The newly developed method was simple, sensitivities and rapid. The comparison between this work with classical spectrophotometric method via the t-test and F-test (the comparison tools) was shown that with no doubt that newly developed method (ISNAG procedure) is as good as the classical method. An alternative analytical method is found through this research work which is based on simple parameter conditions.

Conflicts of Interest: None.

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طريقة فلورة جديدة لتقدير كيتوتيفين فيوماريت باستخدام تقنية الحقن الجرياني المستمر بوساطة مقياس الفلورة ISNAG

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الخلاصة:

طريقة تحليلية مطورة جديدة لتقدير الكيتوتيفين فيوماريت في الادوية باستخدام تقنية اخماد الفلورة المستمرة لجزيئة الاكريدون. تم تطبيق هذة الطريقة باستخدام تقنية الحقن الجرياني لمقياس الفلورة محلي الصنع ISNAG مع قياس للفلورة ±90°بإستخدام اربعة خلايا شمسية؛ وتم الحصول على مدى منحني المعايرة 1-45 ملي مول/لتر، ومعامل ارتباط 0.9726، مع حد للكشف 29.785 مايكروغرام/نموذج باستخدام طريقة التخفيف التدريجي لاقل تركيز في منحني المعايرة. تم تطبيق هذه التقنية بنجاح لقدير الكيتوتيفين فيوماريت في نوعين مختلفين من الادوية. تمت المقارنة بين الطريقة المطورة الجديدة مع الطريقة التقليدية باستخدام طريقة الاضافات القياسية وباستخدام اختبار t المنفرد والمزدوج وكذلك اختبار F. تم ملاحظة عدم وجود اختلاف جوهري بين الطريقتين وبحدود ثقة 95%.

الكلمات المفتاحية: أكريدون، تقنية الحقن الجرياني، فلورة، كيتوتيفين فيوماريت.