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New turbidimetric method for determination of ciprofloxacin hydrochloride in pharmaceutical drugs using continuous flow injection manifold design with CIP.HCL-sodium nitro prusside system

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A new, simple, fast and sensitive method was developed for the determination of Ciprofloxacin. HCI pure from and drugs (tablets) by continuous flow injection scatter light. The method was based on the reaction of the Ciprofloxacin. HCI with sodium nitro prussside to form a precipitate, using homemade ISNAG-FIuorimeter. Optimum parameters have been studied to increase the sensitivity for the developed method. The scatter plot range and the linear dynamic range for the instrument response versus Ciprofloxacin. HCI concentration was 0.03-15 mmoll L while the L.O.D was 65.3660 µg/sample from the step wise dilution for the minimum concentration of lowest concentration in the scatter plot range of the calibration graph. The correlation coefficient (r) was 0.9150 and 0.9972 while percentage linearity (R^2%) was 83.73% and 99.44 for the scatter plot range and the linear dynamic range, respectively. RSD % for the repeatability (n=8) was lower than 0.2% for the determination of ciprofloxacin. HCI, with concentration of 4,13 mmol/L. The developed method was applied successfully for the determination of ciprofloxacin.HCI in pharmaceutical tablets. A comparison was made between the newly-developed method with the classical method, i.e. Turbidemtric method, of analysis using the standard addition method via the use of paired t-test. It showed that there was no significant difference between the quoted values of each individual company with calculated t-value at 95% confidence interval from developed method.

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KEYWORDS

Ciprofloxacin.HCI; flow injection; scatter light; ISNAG-fluorimeter instrument.

Introduction

Ciprofloxacin hydrochloride (Figure 1), a fluoroquinolone, is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. It exhibits broad spectrum antimicrobial activity against Gram-Positive and Gram-negative bacteria such as pseudomonas aeruginosa, streptococcus faecalis, staphylococcal aureus, and Enterobacter aerogenes [1,2]. Ciprofloxacin

tablets have been marketed since 1987 for the treatment of a wide variety of infectious diseases in adults such as urinary tract, lower respiratory tract, bone and joint, and skin structure infections that are proven or strongly suspected to be caused by bacteria [3]. Ciprofloxacin hydrochloride is a pale yellow, crystalline, slightly hygroscopic powder, which is soluble in water, slightly soluble in methanol, very slightly soluble in anhydrous ethanol, practically insoluble in acetone, in ethyl acetate and in methylene chloride [4,5]. Ciprofloxacin is used to treat different types of bacterial infections, i.e., bone and joint infections, intra-abdominal infections, certain type of infectious diarrhea, respiratory tract infections, skin infections, typhoid fever, and urinary tract infections [6]. Several analytical methods have been reported in the literature for the determination of ciprofloxacin hydrochloride in its different forms and preparations, some of which are HPLC-UV detection [7], Spectrophotometric [8], Fluorescence[9], Electrochemical[10], Electrochemical-ISE [11], Electrochemical-MIP [12], and turbidity using Ayah $4S_w$-3D-T_{180^o}-$2N_{90^o}$-Solar-CFI analyzer [13], fluorescence resonance energy transducer and continuous flow injection analysis via ISNAG-fluorimeter [14]. In this research we used continuous flow injection analysis with scattering light [15-17], and measured diverged beam of light at 0-90° angle by homemade ISNAG- fluorimeter [18] via low-pressure mercury lamp as a source and using 2 sides [4 x 2.5cm] solar cells for the determination of CIP.HCL with sodium nitro prusside as a precipitating agent in the presence of ascorbic acid solutions.

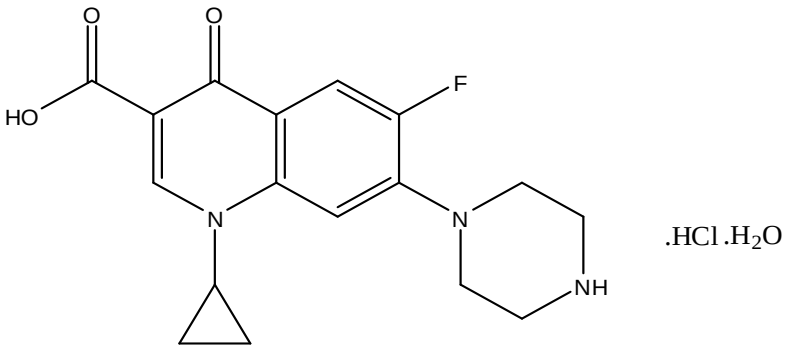


FIGURE 1 Structure of ciprofloxacin hydrochloride

Apparatus

A homemade ISANG fluorimeter was used with multichannel more than one line feed (In this part of the research work only two lines were used; four-channels peristaltic pump (Ismatec, Switzerland) and Six-port medium pressure injection valve were applied .The output of measurement, i.e., $\bar{Y}_{zi}$(mV)-t_{min}(d_{mm}) was plotted by potentiometric recorder, which was used to determine the output signals (Siemens, Germany (1-5 V)). HANNA instrument for turbidity measurement was used as a classical method.

Materials and methods/reagent and chemical

All chemicals used were of analytical-reagent and distilled water to prepare all the solutions. A standard solution of ciprofloxacin (CIP.HCl) ($C_{17}H_{18}FN_3O_3$.HCl.H_2O, molecular weight 385.8, SID, 0.1 mol.L^{-1}) was prepared by dissolving 3.858 g in 100 mL distilled water. A stock solution sodium nitro prussidNa_2 [Fe(CN)$_5$NO].$2H_2O$,molecular weight 297.95 g/mol. 14.8975 g/250 mL, Na_2CO_3 5.299 g/100 mL, CH_3COONH_4 3.884 g/100 mL, KCl 7.350 g/100 mL,NaCl 7.313 g/250 mL, NH_4Cl 2.675 g/100 mL, CH_3COOH 57.47 mL/L, HCl 88.28 mL/L and H_2SO_4 55.52 mL/L.

Sample preparation

Twenty tablets of three different pharmaceutical drugs companies (Microflox–micro-India, citroflox-Citropharmainc-Cande and Ciproneer-pioneer -IRAQ) containing 500 mg of Ciprofloxacin.HCI were weighed then crushed and ground. A solution of 20 mmol.L^{-1} was prepared from different pharmaceutical drugs by weighing 0.5800 g, 0.4743 g and 0.5510 g equivalent to 0.36780 g of active ingredient from Microflox–micro-India, Citroflox-Citropharmainc-Cande and Ciproneer-Pioneer-Iraq, respectively. Each one form of the three kinds of sample was dissolved in distilled water. The solution was filtered to remove any undissolved materials that affected the response; the residues were washed to complete the volume to 25 mL with distilled water.

Methodology

A study was conducted using CIP.HCl (4 mmol/L), 140 µL as a sample volume, 4 mmol/L of sodium nitro prusside and 1.8 mL/min flow rate for each line. A manifold design system consists of two lines was used for determination of CIP.HCl as shown in Figure 2. The first line is the carrier stream of ascorbic acid solutions (70 mmol/L) as a carrier stream that will carry the sample segment (140 µL) into the reaction system at 1.8 mL/min flow rate then combine with the second line (SNP) at 1.8 mL/min at Y-junction point that will initiate the formation of white ion pair precipitate. So, when the reagent (precipitating agent) combines with the drug through the first line in flow injection analysis manifold, it causes the formation of small crystalline precipitate particulate, which is followed by the measurements of divergent light caused by the scattered precipitate particulate at very high repeatability that gives a complete confidence with measurements conducted using ISNAG-Fluorimeter instrument. The tube contains a product designed at an angle in order to prevent the formation of bubbles. The proposed probable reaction pattern of ion pair is expressed in Scheme 1 [19,20].

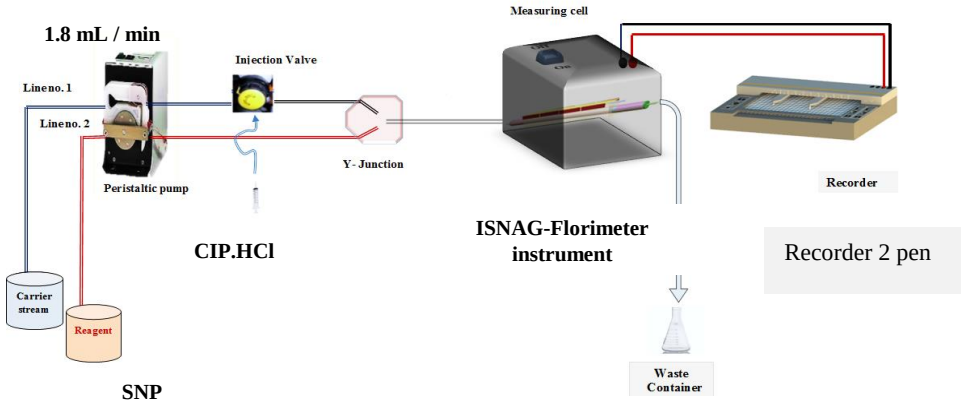
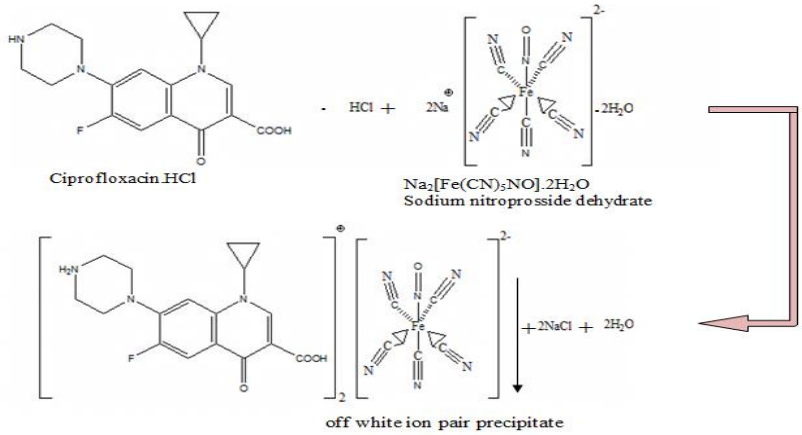


FIGURE 2 Flow diagram of used manifold throughout this part of research work



SCHEME 1 Proposed reaction between CIP.HCI with SNP to form ion pair

Optimization of reaction pattern parameters

Chemical variables

Effect of sodium nitro prusside concentration

Using two-line system with expected parameters of 140 µL, which is injected on a carrier stream line, 1.8 mL/min flow rate for each line and CIP.HCl (4 mmol/L)-SNP system, was chosen for a set of variable sodium nitro prusside ranging 1-6 mmol/L. Figure 3 shows a kind of responses emission versus time profile. It was noticed from Figure 3 that the increase in solar cell output expressed as peak height reached the value of 4 mmol/L; this increase could be attributed to the excessive availability of the precipitating agent that itself is the responsible part in an increasing the small nuclei density, which in turn starts growing up to the formation of granules, reflecting light surface toward the detector in a more intense and in a shorter frequency that falls within solar cell limit of sensing the released or divergent light photon. Dealing with high concentration causes low sensitive responses due to the possible formation of vacancies or pockets to accommodate unwanted particulate i.e., impurities relative to the nature of precipitate causing spreading or dispersed particulate to be a way from crystalline that is quite necessary to diverge light tower the sensor. Therefore, 4 mmol/L was chosen as the best concentration for next studies. When applying slope-intercept, it was noticed that the chosen segment (i.e., segment 3) included best value of a-intercept (i.e. segment a_3-a_5). Any other concentration can be chosen within this segment.

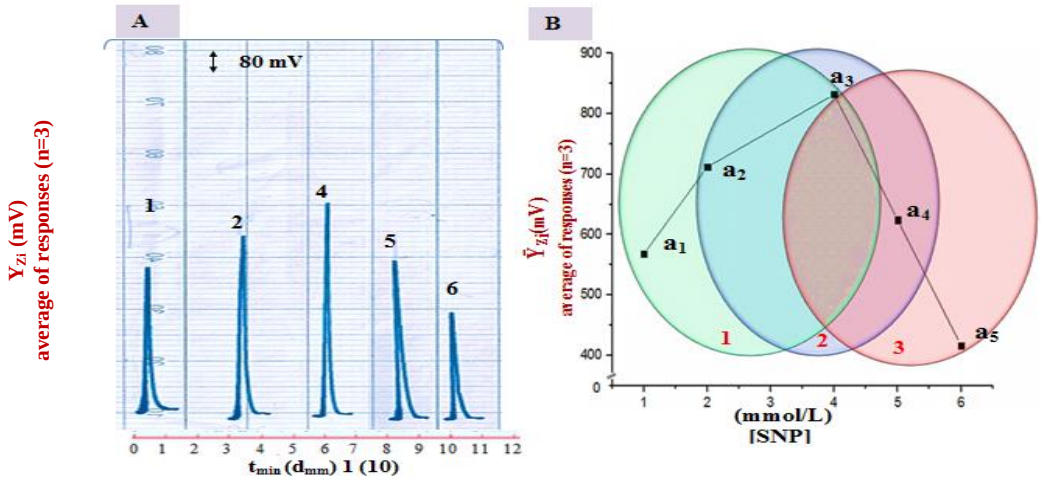


FIGURE 3 Variation of SNP concentration on A: Profile of CIP. HCl–SNP system. B: Height of $\bar{Y}_{Zi}$(mV) energy transducer response in mV with three data points as one segment of their interaction and choice

Type of media effect (salt and acid)

The effect of the concentration of salts and acids as a carrier stream medium and the selection of the optimal one was studied and it was found that the optimal medium for the carrier stream was ascorbic ascid. CIP.HCl is being fixed. The impact of salt solution (CH_3COONH_4, $NaNO_3$, NH_4Cl, NaCl, Na_2SO_4, KCl, and KBr) was considered as a carrier stream to increase light scattering in the HCl (4 mmol/L)-SNP(4 mmol/L) system. The reactions from the salt solution were discovered. Sodium sulphate was giving the most pronounced responses compared with D.W. This might be due to the ions that Na_2SO_4 possess: Strong acid and strong base which might help a dense precipitate and decrease inter molecular spaces reaching the state of granulation forming compact crystals that will act as a reflecting surfaces (like broken mirrors) which in turn increases the intensity of the scattered light. In addition to the study of the effect of acids, i.e. ascorbic acid, HNO_3, H_2SO_4, HCl, CH_3COOH and Tartaric acid, it was found that the most effect belonged to ascorbic acid, due to being weak, its nature as a reducing agent, and most probably, its tendency to dispersing the particulate and recrystallization and a new formation that avoid ions or the occluded within it. In addition to forming large deposits, a compacted mattress acts as a reflective surface at 0-900 and increases light scattering

Effect of ascorbic acid concentration

A series of ascorbic acid solutions (10-100 mmol/L) as a carrier stream were prepared. 4 mmol/L of CIP.HCl was used, 140 µL sample segment at 1.8 mL/min flow rate. While working with acids, it was noticed (Figure 4, Table 1) the concentration of ascorbic acid caused the light scattering to increase and its deviation toward the detector up to 70 mmol/L. Then, it caused a decrease in peak height of responses. This could be attributed to the penetration of ascorbic acid to the precipitate depth during its crystal growth forming a soft particulate, which was unable to deviate the incident light toward the sensor (detector). This was noticed using slope-intercept method; which shows that the selected segment with the highest value is a_3-a_5 in which 70 mmol/L falls within its boundaries. Also any chosen concentration of ascorbic acid within this segment can be used as an alternative to the newly developed methodology of optimization.

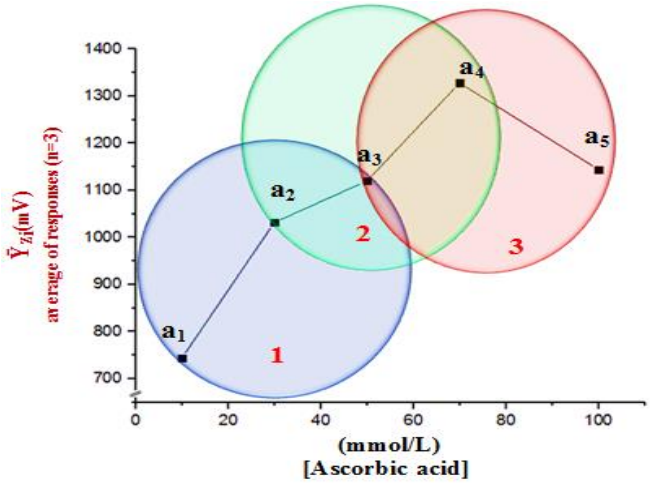


FIGURE 4 Effect of variable concentration of Ascorbic acid solution on output of (S/N) energy transducer response in mV with chosen segment

TABLE 1 Data set point obtained for the variation of Ascorbic acid concentration in the determination of CIP. HCl using CIP.HCl (4 mmol/L)–SNP(4 mmol/L)-Ascorbic acid system

[Ascorbic acid] mmol/L	$\bar{Y}_{zi}$(mV) average of response (n=3)	RSD%	Confidence interval at 95 % $\bar{Y}_{zi}$(mV) ± $t_{0.05/2,n-1}\,\sigma_{n-1}/\sqrt{n}$
10	744	0.31	744±5.738
30	1032	0.17	1032±4.372
50	1120	0.14	1120±3.925
70	1328	0.10	1328±3.527
100	1144	0.17	1144±4.918

$t_{0.05/2,2}$=4.303, $\bar{Y}_{Zi}$ (mV): (S/N) energy transducer response

Physical variables

Variation effect of flow rate

A variable flow rate from 0.7–2.8 mL/min for each line was studied using optimum chemical parameters for CIP.HCl (4 mmol/L)- SNP (4mmol/L)-Ascorbic acid (70 mmol/L) system and experimental physical parameters achieved in previous section. It was noticed that at slow flow rate (0.7 mL/min), a large particulate with large volume was obtained and it is considered heavy that will not deal with the passage of the carrier stream through the flow tube, producing a delay and elongation in the measuring cell, resulting in a distorted profile of the measured response with a broad Δt_B (Figure 5). When increasing flow rate reaching to 1.8 mL/min, high responses were obtained, that might be attributed to the increase of diverged light to the detector. More than 1.8 mL/min caused a decrease of peak height response, most probably due to unavailability of sufficient time for crystal to grow to higher size particulate that works as a reflecting mirror for the incident light. Therefore, the sensitivity of measurements will be small at high speed of flow rate. Accordingly, 1.8 mL/min is the most suitable flow rate which also falls within the slope- intercept method with segment no.4 as the most reliable confident flow rate, which can be used to obtain a regular response, and narrower Δt_B and minimize the consumption of reactants solution.

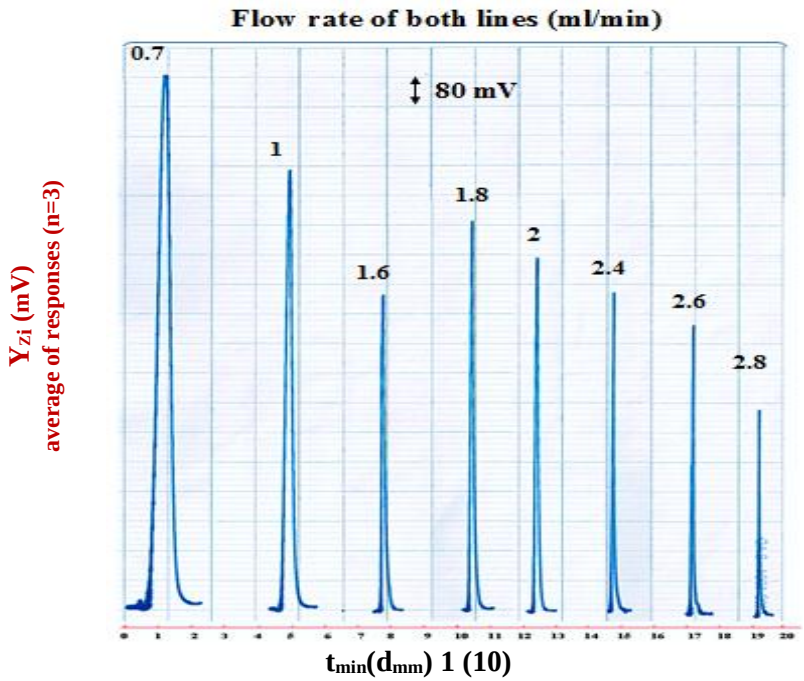


FIGURE 5 Effect of flow rate on A-Response profile $\bar{Y}_{Zi}$(mV)-t_{min} (d_{mm})

Variation effect of sample volume

The injected volume of segment varied from 40 µL to 175 µL by changing the length of the sample loop within the injection value, while the other chemical and physical parameters remained fixed. It can be noticed that an increase in the injection volume led to a significant increase in sensitivity than low volumes, the optimum sample segment of 140 µL giving a regular profile of the diverged incident of light, while at larger than 140µL, it gave a decrease of peak height with a wider Δt_B of response. This corresponds with slope–intercept method, which shows that the selected segment is given a highest value of intercept by a_4-a_6 (i.e., segment no.4), in which any sample segment within it can be used to obtain acceptable results and high sensitivity.

Effect of delay reaction coil on S/N response profile

Variable volume of coil ranging 78.5 µL to 236 µL connected after Y- junction point directly in manifold design system was studied, while keeping all other variables constant, i.e. CIP. HCl (4 mmol/L)–SNP (4 mmol/L)–Ascorbic acid (70 mmol/L) system, 140 µL sample segment and 1.8 mL/min flow rate. The increase of coil volume to 78.5 µL led to increase of peak height. While more than 78.5 µL led to decrease of diverged light with increase of base width and departure time of sample segment from injection value reaching the measuring cell. This might be attributed to an increase of diffusion and dispersion of precipitate particulate segment causing loss of some of the reflecting surface. So, it can clearly be seen that the use of 78.5 µL delay reaction coil is necessary for the completion of the reaction between CIP.HCl with SNP in the presence of ascorbic acid. And this result was proven through slope- intercept method (Figure 6), in which the segment No.2 is the most suitable, which can be used to obtain sufficient acceptable results compromised with the other variables that were chosen.

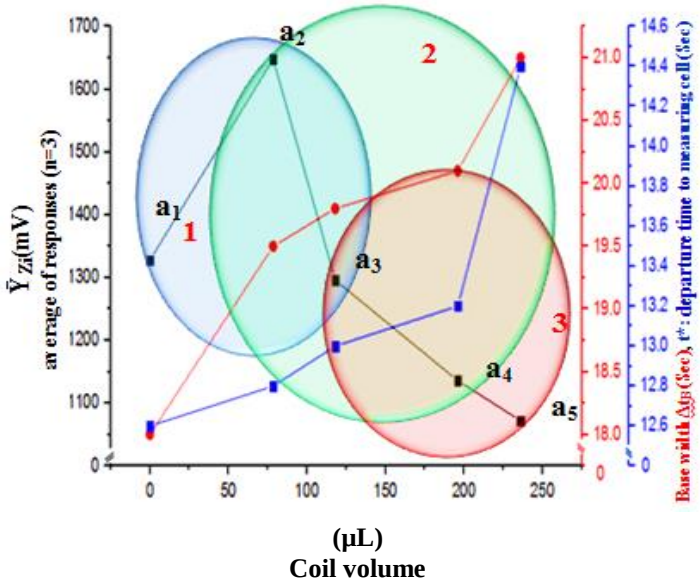


FIGURE 6 Variation effect of Coil volume on height of $\bar{Y}_{Zi}$ (mV): (S/N) energy transducer response in mV, three segments (Three-point data) and chosen segments

Studying the variation of energy transducer output of diverged light versus CIP.HCl concentration

Using the fixed optimum chemical and physical parameters (Ciprofloxacin.HCl –SNP(4 mmol/L)-Ascorbica cid (70 mmol/L) system, sample volume 140 µL, 78.5 delay coil reaction and 1.8 mL/min flow rate of each lines, a series of ciprofloxacin.HCl ranging 0.03-30 mmol/L solution were prepared,

which were directly proportional up to 30 mmol/L between the variation of precipitate particulate formation and concentration. It might be attributed to an increase of many factors such as refraction, absorbance, reflection and diverged light from the precipitated particles when the beam of light diffused inside of particles. The measurement was only at 0-90° , represented by scatter plot at range 0.03-30 mmol/L, a correlation of Y_{Zi} (mV) versus t_{min} (d_{mm})1(10) of 0.9150 with coefficient of determination of 0.8373, and linear dynamic range 0.03-15 mmol/L., A narrower range that should be utilized to better evaluate mathematical formulation and the best fit. The correlation of ciprofloxacin is represented by a linear equation. HCl concentration (independent variable) versus diverging light as a dependent variable with r=0.9972 and 99.44 percent capital R-squared (Table 2) on the form are as follows:

$\hat{Y}_{Zi}$ =80.286±122.749+366.949±16.992 [CIP.HCl] mmol/L explained much of obtained results from n= 21 as the outcome of scatter plot. The assessment evaluation of the new developed methodology for the determination of ciprofloxacin.HCl was compared with available reference method, namely turbidometry method, which was based on the reaction between SNP as a precipitating agent with optimum concentration 5 mmol/L in aqueous medium and the drug of ciprofloxacin.HCl for a variable range of concentration 0.01-8 mmol/L. The results are dispalayed in Table 2 at confidence level 95% using first degree equation of the form of:

$$\hat{Y}_i(NTU) = a + b\,[CIP.HCl]\ mmol/L$$

Intercept Slope

The best linear range extends from 0.01-5 mmol/L of n=9 with correlation coefficient of 0.9940 and % capital R-squared=98.80 % (Table 2).

The limit of detection of ciprofloxacin.HCl using SNP(4 mmol/L), 140 µL sample volume, was calculated by three different approach depending on the practical research need as tabulated in Table 2.

The repeatability was studied for the determination of ciprofloxacin.HCl *via* the measurements of the diverged of incident light using ISNAG-fluorometer, formed by the reaction of ciprofloxacin.HCl with SNP in the prescence of ascorbic acid. The relative standard deviation as a percentage (RSD %<0.2%) is equal to the repeatability of the measurement. A repeated measurement for eight successive injection was carried out at fixed concentration of CIP.HCl for two concentrations of 4 and 13 mmol/L, respectively, in optimum parameters.

TABLE 2 Summary of different range using linear regression for the variation of S/N energy transducer response and turbidity with Ciprofloxacin.HCI concentration using first degree equation of linear $\hat{Y}$=a+bx at optimum condition for both methods

Type of mode	Range of [CIP.HCI] mmol.L^{-1}(n)	$\hat{Y}_i$=a±s_at+b±s_bt[CIP.HCI]mmol.L^{-1} at confidence interval 95 %, n-2	r, r^2, R^2 %	t_{tab} at 95% ,n-2	Calculated t-value $\frac{\lvert r\rvert}{\sqrt{1-r^2}}\sqrt{n-2}$
Developed method using ISNAG-fluorimeter					
Turbidometry method (FTU) Using Hanna Instrument					
Scatter plot	0.03-30 (21)	754.239±623.687+233.622±49.501 [CIP.HCl] mmol/L	0.9150,0.8373, 83.73	2.093<9.887	
	0.01-8(12)	57.684±70.560+97.103±17.102[CIP.HCl] mmol/L	0.9702, 0.9412, 94.12	2.228<12.650	
Linear range	0.03-15(17)	80.286±122.749+366.949±16.992[CIP.HCl]mmol/L	0.9972, 0.9944,	2.131<51.7020	

or Liner dynamic range	0.01-5(9)	19.464±31.022+127.001±12.519[CIP.HCI]mmol/L	99.44 0.9940,0.9880, 98.80	2.365<23.992

Limit of detection(LOD) for CIP.HCIusing 140 µL as an injection sample and optimum parameters				
Practically based on the gradual dilution for the minimum concentration in calibration curve Newly developed method (0.005) mmol.L^{-1}	Classical method (0.005) mmol.L^{-1}	Theoretical (slope method) based on the value of slope X=3S_B/slope	Theoretically (linear equation) based on the value of $\hat{Y}= Y_b +3S_b$	Limit of quantitative L. O. Q $\hat{Y}=Y_b+10S_b$
257.4614 ng/sample	18.3901 µg/sample	0.2442 µg/sample	65.3660 µg/sample	217.924 $\mu g/sample$

Repeatability			
[CIP.HCI] mmol.L^{-1}	$\bar{Y}_{Zi}$ (mV) average (n=8)	RSD % =σ_{n-1}/ $\bar{Y}_{Zi}$ (mV)×100	Confidence interval at 95% $\bar{Y}_{zi}$ (mV)± $t_{0.05/2,n-1}\sigma_{n-1}/\sqrt{n}$
4	1648	0.129	1648± 1.7775
13	4720	0.068	4720± 2.6837

$\hat{Y}i$: Estimated response(n=3) in mV for newly developed method and without unit for Turbidometer method (classical method) for n=3 expressed as an average peaks heights of linear equation $\hat{Y}$=a+bx of the form or turidometer value, r: Correlation coefficient, r2:Coefficient of determination, R2:% capital R-square, R2= explain variation/total variation, [CIP.HCI] concentration Ciprofloxacin- HCI of developed method using ISNAG-fluorimeter, n:no.of measurements, ttab.=0.05/2, n-2., $\hat{Y}$: estimated response (mV), X :value of LOD based on the slope (depending on analytical range), SB: standard deviation of blank(n=13), Yb: average response for blank= intercept (a), Sb: standard deviation equal to Sy/x (residual), (LOD depend on linear equation of linear range due to low Sy/x) and sample volume of turbidity method = 10 mL(1000 µL); $\bar{Y}_{Zi}$ (mV): Energy transducer response expressed, $t_{0.05/2,7}$=2.365, n= number of injection.

Determination of Ciprofloxacin.HCl in drugs using a homemade ISNAG-fluoremiter analyzer

Three different drugs of the companies (microflox 500 mg-micro-India, Citroflox-500 mg-citropharmaic-cande, and Ciproneer-500 mg-pioneer-Iraq) were injected on 70 mmol/L of Ascorbic acid as a carrier stream through a two line manifold design system via using a homemade ISNAG-fluormiter, in which mercury tube lamp was as a source and four solar cells at each two side (0-90°) were as a detector; this was compared with the turbidometry–classical method via turbidity-meter-HANNA-Taiuan. Each method depended on the preparation of each drug: 20 mmol/L equivalent to 0.3678 g of active ingredient in 50 mL by transferring 2.5 mL to each of five volumetric flaks (25 mL), followed by addition of gradual volumes of standard solution (4 mmol/L) of ciprofloxacin.HCl (0, 2.5, 3, 3.5 and 4 mL) to the obtained (0, 2, 2.4, 2.8 and 3.2 mmol/L) concentration. Table 3A shows the results and mathematically treated ones [21,22] using two different methods of developed method and turbidometry method, with a practical content of active ingredient at 95% confidence level and efficiency of determination; in addition to t-test which means a comparison of two different tests.

First test

Individual t-test comparison of practicality of active ingredient (using Newly developed methodology) with claimed value (i.e., µ=500 mg) [23,24] was used, as shown in Table 3B. (Column 5).

Null hypothesis

There is no significant different between the means ($\underline{w}_i$ (Micro, 495.2120 mg, India), (Citroflox, 492.7720 mg, Cande), (Ciproneer, 506.3230 mg, Iraq) (average weight)) obtained from three sources of three different

companies and claim value (μ=500 mg), i.e;H_0 : $\underline{w}_i$ = μ (500 mg) [23,24] for Microflox(Micro, 500 mg, India), Citroflox(citropharma, 500 mg, Canada), Cipronеer (pioneer, 500 mg, Iraq).

Alternative hypothesis

There is a significant difference between the means and claim value [18,19], i.e., H_1: $\underline{w}_i \neq$ μ (500 mg) for each different company. For all values obtained, $t_{cal} > t_{tab}$ (4.303) at α = 0.05 (at confidence level 95%). The null hypothesis was rejected and the alternative hypothesis was accepted, meaning that there is a significant difference between the claim value (active ingredient value) and the measured value due to the interference effect.

Second test

Paired t-test at α= 0.05 of three drugs from different manufacturers was applied. The comparison was made between developed method using ISNAG-fluorimeter analyzer (depending on scattered light ± 90°) and turbidimetry *via* turbidity-meter, HANA, (Taiuan). The results of comparison are summed up in Table 3B (Column 6). The null hypothesis is as follows [21-24]:

H_0: $\mu_{ISNAG\text{-}fluorimeter} = \mu_{turbidimetry}$

There is no significant different between the mean of turbidity method and ISNAG-fluorimeter analyzer

Alternative hypothesis

H_1: $\mu_{ISNAG\text{-}fluorimeter} \neq \mu_{turbidimetry}$

The obtained results indicated that there was no significant difference between developed method and turbidimetric method (classical method) at α= 0.05 (95% confidence level) of the determination of ciprofloxacin.HCl in pharmaceutical drugs as shown in Table 3B (column 6) due to t_{cal}(0.481) << t_{tab}(4.303).

TABLE 3A Standard addition results for the determination of CIP.HCl in three samples of drug using ISNAG-fluorimeter analyzer for developed method and turbidometry method

	Commercial Name, Company Content	Type of method Developed method using ISNAG Fluorimeter (mV) Turbidometry method (Classical method) NTU										
No. of sample	Country	Confidence interval For the average Weight of Tablet $\bar{w}i \pm 1.96\sigma n-1/\sqrt{n}$ at 95% (g)	Weight of Sample equivalent to 0.367802 gm (20 mmol/L) of the active ingredient W_i (g)	Theoretical content for the active ingredient at 95% (mg) $Wi \pm 1.96\ \sigma_{n-1}/\sqrt{n}$	0	2.5 mL	3 mL	3.5 mL	4mL	Equation of standard addition at 95% for n-2 $\hat{Y}_i(mV)=a\pm s_a t+b\pm s_b t$ [CIP.HCl]mmol/L $\hat{Y}_i=a\pm s_a t+b\pm s_b t$ [CIP.HCl]mmol/L	r r^2 R^2%
1	Microflox micro CIP.HCl=500 mg India	0.778067±0.000616	0.57235	500±3.95853	740 265	1436 560	1600 580	1770 650	1920 700	728.371±64.972+367.706±27.534 [CIP.HCl]mmol/L 269.020±43.559+135.567±18.459 [CIP.HCl]mmol/L	0.9991 0.9983 99.83 0.9972 0.9945 99.45
2	Citroflox Citropharma inc CIP.HCl=50 mg Cande	0.665615±0.000323	0.48963	500±2.42632	595 295	1140 510	1235 560	1390 610	1560 650	576.082±122.766+292.268±52.027 [CIP.HCl]mmol/L 293.144±13.853+111.469±5.871 [CIP.HCl]mmol/L	0.9953 0.9906 99.06 0.9995 0.9991 99.91
3	Cipronеer Pioneer CIP.HCl=500 mg Iraq	0.755565±0.000788	0.55579	500±5.21464	575 270	1110 540	1200 580	1310 635	1500 700	561.907±114.656+277.448±48.590[CIP.HCl]mmol/L 269.587±21.949+132.409±9.301 [CIP.HCl]mmol/L	0.9954 0.9909 99.09 0.9992 0.9985 99.85

$\bar{Y}i$: Energy transducer in mV for developed method and *Turbidimetric method (NTU)) for (n=3), r: correlation coefficient, r^2 coefficient of determination, R^2%: Percentage capital R- squared: R^2= explains variation as a percentage/ total variation, $t_{0.05/2,\infty}$ =1.96 at 95 %, $t_{0.05/2,3}$ = 3.182 for n=5

TABLE 3B Summary of results for practical content, (Rec %) efficiency for determination of CIP.HCl in three samples of drugs and t-test for comparison between two methods

No. of sample	Type of method: Developed method using ISNAG Fluorimeter (mV) / Turbidometry method (Classical method) NTU: Practical concentration (mmol.L^{-1}) in 25 mL / Practical concentration (mmol.L^{-1}) in 50 mL / Practical weight of ClP.HCl in (g)	Weight of CIP.HClin each sample (g) $\underline{W}_{i(g)}$ ±4.303 $\sigma_{n-1}/\sqrt{n}$ / Weight of CIP.HCl in tablet $\underline{W}_{i(mg)}$ ±4.303$\sigma_{n-1}/\sqrt{n}$	Efficiency of determination Rec.%	Individual t-test For compared between claim value & practical value ($\underline{W}_{i(mg)}$-μ) $\sqrt{n}$ /σ_{n-1}	Paired t –test Compared between two methods: t_{cal}= $\underline{w}$d $\sqrt{n}$ /σ^*_{n-1}	t_{tab} at 95% confidence level (n-1)
1	1.9809 19.8085 0.3643	0.3643±0.0023 495.2120±3.253	99.04	/ - 6.333 / > 4.303		
	1.9844 19.844 0.3649	0.3649±0.0035 496.1080± 4.825	99.22			
2	1.9711 19.710 0.3624	0.36248± 0.0017 492.7720 ± 2.325	98.55	/ - 13.378 / > 4.303	$\underline{W}$d= 1.6906 σ^*_{n-1}=6.092 0.481< 4.303	
	1.9364 19.3648 0.3561	0.3561 ± 0.0026 484.124±3.5820	96.83			
3	2.0253 20.2527 0.3724	0.3724±0.0024 506.3230±3.2840	101.26	8.290 > 4.303		
	2.0360 20.360 0.3744	0.3744±0.0028 509.009±3.8250	101.80			

μ: claim value =500mg, $\underline{W}$i: practical weight (n=3), $\underline{W}$d: average of different between two methods (developed method &*Turbidimetric (NTU) using Hanna Instrument (classical method), for n(No. of samples) =3 , σ_{n-1}: standard deviation, σ^*_{n-1}:standard deviation of difference (paired t-test), $t_{0.025,2}$= 4.303.

Conclusion

A new turbidimetric, simple, sensitive, accurate and fast method was suggested for determination of ciprofloxacin.HCI in pharmaceutical drugs (Tablets) using a newly developed homemade ISNAG-fluorimeter - CFIA. The comparison between this work with classical turbidometry method *via* the t-test (as the comparison tools) showed that the newly developed method (ISNAG-fluorimeter procedure) is as good as the classical one.

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