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A new Spectrophotometric Method for Determination of Moxifloxacinwith 1-(2-hydroxyphenylazo)-2,7-dihydroxynaphthalene in Bulk and Pharmaceutical Formulations

Rana M. W. Kazan[1,*] Hassan Seddik[2], Mahmoud Aboudane[3]

[1]*Postgraduate student (PhD), Faculty of Science, Aleppo University, Syria*
[2]*Department of Chemistry, Faculty of Science, Aleppo University, Syria*
[3]*Department of Chemistry, Faculty of Science, Aleppo University, Syria*

* ***Corresponding Author:***
Rana M. W. Kazan, Faculty of Science, Aleppo University, Syria. E-mail: Kazan _ Rana @yahoo.com

ABSTRACT:

Moxifloxacin hydrochloride (MXF) is a fourth generation fluoroquinolonebroad spectrumantibiotic agent used in conjunctivitis. A new, simple, rapid, and sensitive spectrophotometric method was developed for the determination of a (MXF). This method is based on the formation of ion-pair complex between the basic drug (MXF), and new dye;1-(2-hydroxyphenylazo)-2,7-dihydroxy naphthalene (HPN). The formed complex was measured at 530 nm by using chloroform as solvent. The analytical parameters and their effects are investigated. Beer's law was obeyed in the rangeof0.161 – 12.043 µg/mL, with correlation coefficient R^2 *= 0.9998. The average recovery of Moxifloxacinwas between 98.14and 101.09 %. The limit of detection was 11.60ng/mL and limit of quantification was 35.16ng/mL. The proposed method has beensuccessfully appliedto the analysis of the studied drugs in pure forms and pharmaceutical formulations.*

Keywords:*Moxifloxacinhydrochloride; Spectrophotometer; pharmaceutical formulations.*

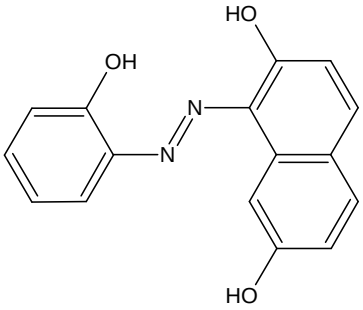
1. INTRODUCTION

Moxifloxacin,1-cyclopropyl-7-[(S,S)-2,8-diazabicyclo[4.3.0]non-8-yl]-6-fluoro-8-methoxy-1,4 dihydro-4-oxo-3 quinoline carboxylic acid is a synthetic bactericidal 4th generation fluoroquinolone (fluorinated derivative of the quinolone) discovered in 1996 and reached the UK market in 2000 [1-3].

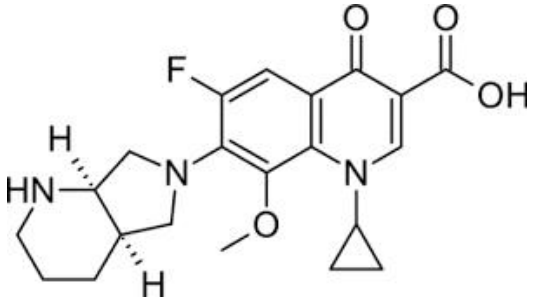
Moxifloxacin is a broadspectrum important antibacterial agent used in human medicine which is active against broad spectrum of pathogens, encompassing Gram-negative, Gram-positive bacteria including resistantstrain Streptococcus pneumonia. It is also active against other microorganisms such as *Chlamydia pneumonia* and *Mycoplasma pneumonia* [4-7].

Various analytical techniques have been applied for the determination of MFX including: High performance thin layer chromatography HPTLC[8-10],Liquid chromatography mass spectrometry (LC/MS)[11], High performance liquid chromatography [HPLC-UV][12-14],HPLC-mass spectrometry [15], Reverse phase high performance liquid chromatography [RP-HPLC][16-19], Capillaryelectrophoresis[20],potentiometry [21,22], conductometry [23],voltammetry [24],polarography analytical[25],protonation equilibrium[26],Spectrofluorimetry [27,28], and spectrophotometric methods[29-34], In the present work, we report the development of accurateand sensitive spectrophotometric methodsbased on the chloroform soluble ion-pair complexes between MXF and anew dye[35]1-(2-hydroxyphenylazo)-2,7-dihydroxynaphthaleneHPN (Fig.1). The absorbance measurements were measured at optimum wavelengths. The proposed method was

successfully applied for the determination of the studied drugs in pure and pharmaceutical formulations. No interference was observed from the additives. This method is morerapid, economic andsensitivein compared with the previously reported spectrophotometric methods, anditwas validated by the statistical data.



1-(2-hydroxyphenylazo)-2,7-dihydroxynaphthalene (HPN)



Moxifloxacin (MXF)

Fig. 1: The chemical structure of the studied compounds.

2. MATERIALS AND METHODS

2.1 Apparatus

UV/VIS double beam spectrophotometer V-630 (JASCO, Japan) equipped with 1 cm quartz cells;ultrasonic bath (Daihan, Korea); analytical balance TE64 (Sartorius, Germany) with accuracy ±0.1 mg;digital pipettes (Accumax);drying oven (WTB binder-78532 TUTTLINGEN, Germany).

2.2 Reagents and Materials

All reagents and chemicals used were of analytical reagent or pharmaceutical grade.

Methanol and chloroform(≥99.0%,Sigma-Aldrich).

HPN(Mw=280.00 $g.mol^{-1}$) [35].

Moxifloxacin hydrochloride (MXF) (≥99.2%, Mw=437.89 $g.mol^{-1}$,ROCHE PHARMA AG, Germany).

Syrian commercial dosage forms of MXF:

- Moxicin tablet (Ibn Al haytham) 400 mg of MXF.
- Moxiflox tablet (Razi) 400 mg of MXF.
- Moxaquin tablet (Obari) 400 mg of MXF.
- Megamox eye drope (Rama pharma), 5 mg of MXF/mL.

2.3 Preparation of solutions.

2.3.1 . Preparation of Standard Stock Solution MXF (2.10^{-3} M)

Standard Stock solution of Moxifloxacin was prepared by dissolving an accurately weighted88.3 mg of MXF.HCL (including the purity, 99.2 %) in 100mL of Methanol to get a suitable concentration.This solution was prepared fresh daily.

2.3.2 Preparation of Standard Stock Solution (HPN) (2.10^{-3} M)

Standard Stock solutions of (HPN) was prepared by dissolving an accurately weighed 56.0mg in 100mL of Methanol to get a suitable concentration. This solution are stable for at least one week if kept in the refrigerator.

2.3.3 . Preparation of calibration curve

To prepare calibration standards,compatible volumes ofstock standard solutionswere dilutedwith chloroform into volumetric flasks (10 mL) to obtain final drug concentration of (0.161, 0.241, 0.321, 0.401, 0.482, 0.562, 0.642, 0.723, 0.803, 2.007, 4.014, 6.021, 8.029, 10.036, 10.839, 12.043) µg/mL and linearity was

studied. Linearity relationship was observed in the range 0.161 to 12.043 µg / mL (Fig. 2) against a reagent blank as reference at 530 nm (Table 1).

3. Estimation of Moxifloxacin in commercial formulations.

3.1 Estimation of Moxifloxacin in tablets.

For analysis of commercial formulations, ten tablets were weighed, powdered and thenmixed well. Tablet powder equivalent to 400 mg of Formulation were transferredinto 100 ml volumetric flask and dissolved in methanol. Then the solution was sonicated using ultrasonic for 30 minutes and filtered. 1 ml of the filtrate was taken and further diluted with methanol to 100 ml (to form 40 µg/mL). Then 1.25 ml ofthe last solution was diluted with chloroform to 10 ml (to form 5 µg/mL).

The absorbance of the prepared solutions were measured at 530 nm for Moxifloxacin solutions against blank and the drug content was estimated. The results are shownin table(3).

3.2 . Estimation of Moxifloxacin in eye drops.

0.1 mlwas taken from eye dropof the mixed contents of fiveeye drops and diluted with methanol to 10 ml (to form 50 µg/mL). Then 1 ml of the last solution was diluted with chloroform to 10 ml (to form 5 µg/mL).Table (3).

4. Results and Discussions

4.1 Spectrophotometric analysis of Moxifloxacin with HPN.

The method is based on the formation of anorange ion-pair complex in chloroform, between the fluorquinolone MXF and the reagent HPN.Theabsorptionspectra oftheion-paircomplex,MXF-HPN, was measuredintherangeof480– 600nmagainsttheblanksolution. The complex has a maximum absorbanceat 530 nm as shown in (Fig. 2).

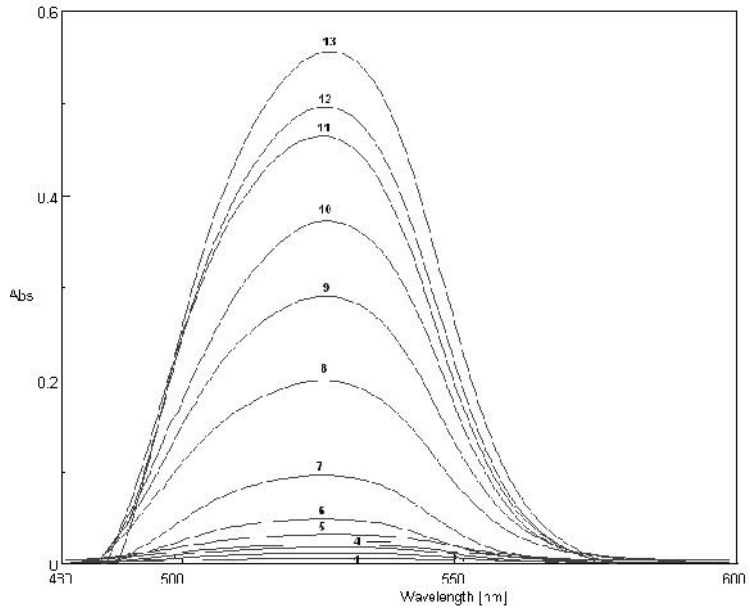


Fig.2: Spectra of complex MXF- HPN for various concentrations of MXF (µg/mL) 1) 0.161, 2) 0.241, 3) 0.321, 4) 0.401, 5) 0.723, 6) 0.803, 7) 2.007, 8) 4.014,9) 6.021, 10) 8.029,11) 10.036, 12) 10.839, 13) 12.043

4.2 Optimization of the reaction conditions.

The optimization conditions of the method were carefully studied to achievecompletereactionformation,highestsensitivity,and maximum absorbance.

4.2.1 Effect of solvents.

The effect of several solvents, namely, chloroform, acetone,acetonitrile,benzene,diethyl ether, dichloromethane, dichloroethane, andtetrachloromethane,was studiedin order to choose the effective solvent for complex which it had a maximum absorbance.

Chloroform was found to be the most suitable solvent for colored ion-pair complex. Experimental resultsindicatedthat the complex withtotalvolume10mL chloroform, yielding maximum absorbance intensity, stable absorbance for the studied drugs and considerably lower extraction ability for the reagent blank. The optimization of the method was carefully studied to achieve complete reaction formation, high estsensitivity, and maximum absorbance.

4.2.2 Effect of Reagent Concentration.

The effect of the reagent was studied by measuring the absorbance of solutions containing a fixed concentration of MXF, varied amounts of HPN reagent. Maximum color intensity of the complex was achieved with 1.0mL of 2.0×10^{-3} M of HPN solution, (Fig. 3).

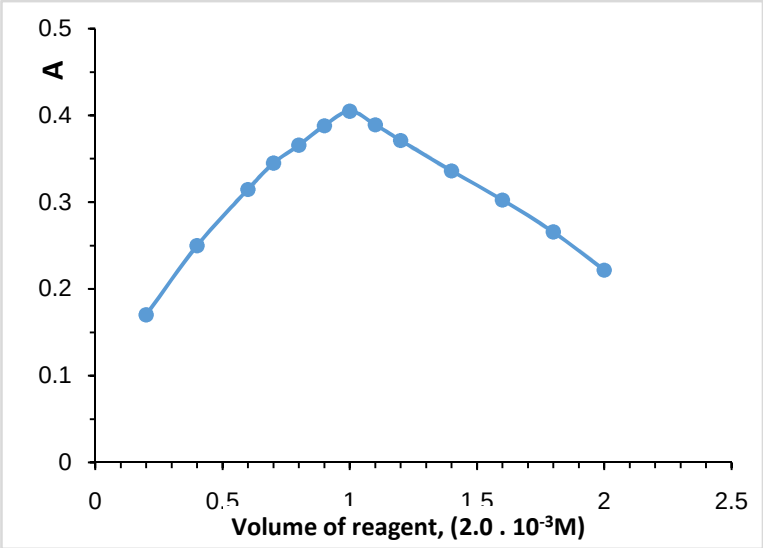


Fig.3: Effect of volume of (2.0 x 10^{-3} M) reagent on the ion-pair complex MXF- HPN

4.2.3 Effect of Time and Temperature.

The optimum reaction time was investigated from 0.5 to 5.0 min by following the colored development at ambient temperature (25 ± 2°C). Complete color intensity was attained after 2.0 min of mixing of the complex. The effect of temperature on colored complexes was investigated by measuring the absorbance values at different temperatures. It was found that the colored complexes were stable up to 35°C. At higher temperatures, the drug concentration was found to increase due to the volatile nature of the chloroform. The absorbance remains stable for at least 10 h at room temperature.

4.3 Stoichiometric Relationship.

The stoichiometric ratio between drug and dye in the complex MXF-HPN was determined by Job's method of the continuous variation method, and Molar ratio method as following:

4.3.1 Job's method of the continuous variation.

Job's method of continuous variation of equimolar solutions was employed: 2.0×10^{-4} M standard solution of MXF and $2..0\times10^{-4}$ M solution of HPN was used. A series of solutions wasprepared in which the total volume of MXF and HPN was kept at 2.0 mL and diluted with chloroform to 10 ml.

A_{max}= f([MXF]/[MXF]+[HPN]), The absorbance was measured at the optimum wavelength. The results showed two molar ratios 1:1 and 2:1 (HPN: MXF),(Fig. 4).

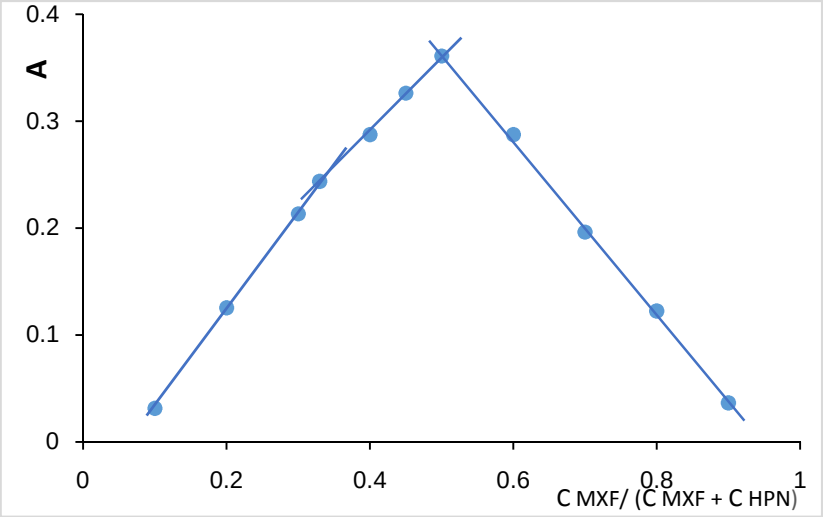


Fig.4. Job's method of the continuous variation of MXF-HPN complex

4.3.2 Molar ratio method.

The stoichiometry of MXF-HPN complex by molar ratio method was studied according tothe following equation: A_{max}= f([HPN]/[MXF]), the results confirm the Stoichiometry of complex MXF-HPNthat are 1:1 and 2:1 (HPN: MXF); Where the concentration of MXF is constant (2×10^{-5} M), and the concentrations of HPN are changed from (0.4 to 5.2) $\times10^{-5}$ M(Fig. 5).

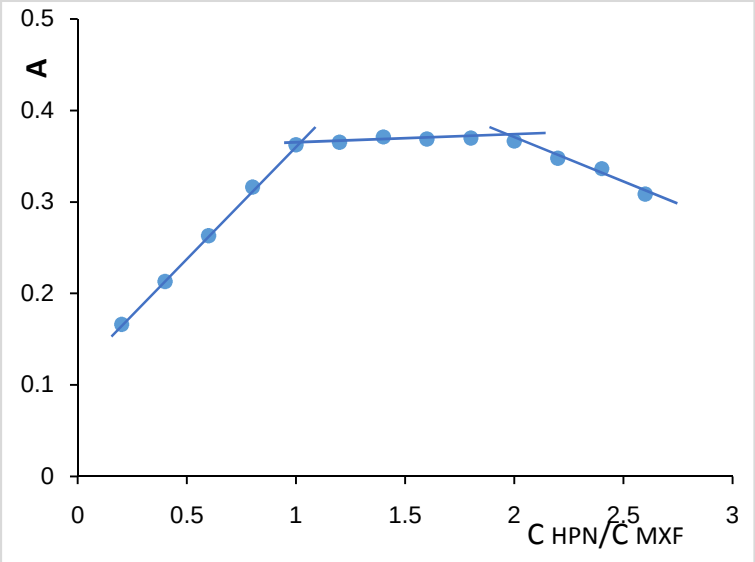


Fig.5. Molar ratio method of MXF-HPN complex

5. METHOD VALIDATION

5.1 The linearity.

At described experimental conditions for MXF determination, standard calibration curves with reagent were constructed by plotting absorbance versus concentration. The absorbance obtained for the five analyses averaged at each concentration. The statistical parameters were given in the regression equation calculated from the calibration graphs. The linearity of calibration graphs was proved by the high values of the correlation coefficient (R^2= 0.9998) and the small values of the *y*-intercepts of the regression equations (fig.6). The apparent molar absorptivities of the resulting colored ion-pair complexes and relative standard deviation of response factors for each proposed spectrophotometric method were also calculated and recorded in Table1.

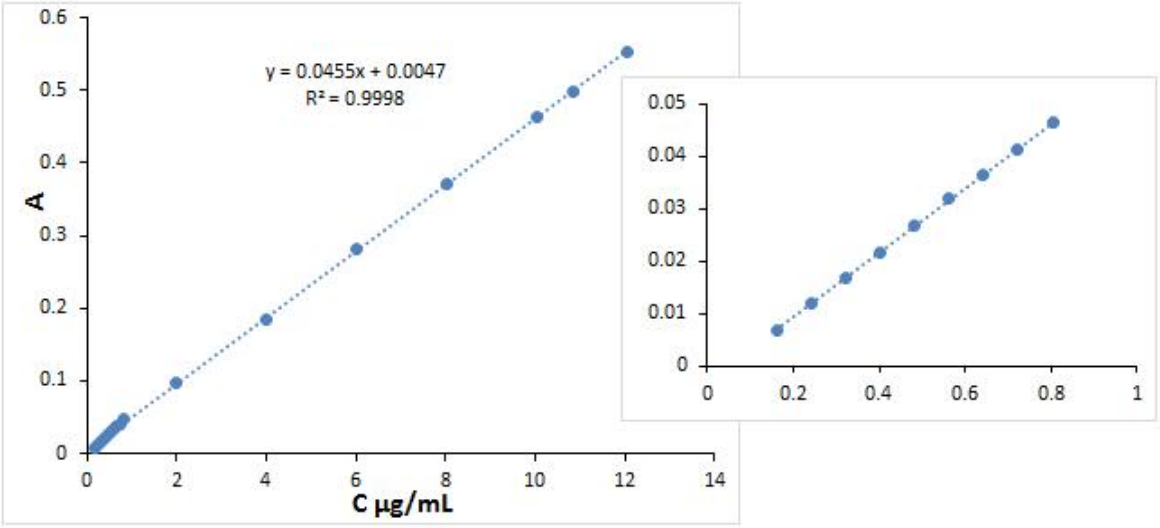


Fig. 6. Calibration curve fordetermination of MXF –HPN complex

Table 1: Spectrophotometric determination of MXF from MXF–HPNcomplex in chloroform

(µg/mL)		SD (µg/mL)	RSD%	Analytical standard error ASE $\bar{X}\frac{SD}{\sqrt{n}}$ (µg/mL)	Confidence Limits $\bar{x} \pm \frac{t \mid SD}{\sqrt{n}}$ (µg/mL)	Recovery %
X taken	X^* found					
0.161	0.158	0.004	2.48	0.0018	0.158 ± 0.0050	98.14
0.241	0.239	0.005	2.07	0.0022	0.239 ± 0.0061	99.17
0.321	0.321	0.007	2.18	0.0031	0.321 ± 0.0086	99.95
0.401	0.400	0.008	1.99	0.0036	0.400 ± 0.0100	99.75
0.482	0.483	0.009	1.87	0.0040	0.483 ± 0.0111	100.00
0.562	0.567	0.011	1.96	0.0049	0.567 ± 0.0136	100.89

0.642	0.649	0.012	1.87	0.0045	0.649 ± 0.0150	101.09
0.723	0.727	0.013	1.80	0.0058	0.727 ± 0.0161	99.45
0.803	0.801	0.014	1.77	0.0063	0.801 ± 0.0175	99.75
2.007	2.013	0.024	1.19	0.011	2.013 ± 0.030	100.30
4.014	3.962	0.046	1.16	0.021	3.962 ± 0.058	98.70
6.021	6.070	0.062	1.02	0.028	6.070 ± 0.078	100.81
8.029	8.031	0.077	0.96	0.034	8.031 ± 0.094	100.02
10.036	10.055	0.086	0.85	0.038	10.055 ± 0.105	100.19
10.839	10.826	0.077	0.71	0.034	10.826 ± 0.094	99.88
12.043	12.022	0.082	0.68	0.037	12.022 ± 0.103	99.82

n = 5, t = 2.776

5.2 Sensitivity.

The limits of detection (LOD) and quantitation (LOQ) for the proposed method were found to be 11.60, 35.16ng/mL respectively, (Table 2).

Table-2 The optimal spectrophotometric parameters for the determination of Moxifloxacin

Parameter	Value
λ_{max} (nm)	530
Beer`s law limits (µg/mL)	0.161 – 12.043
Molar absorptivity, ε (L/mol.cm)	20230.36
Regression equation	Y = 0.0455X +0.0047
Slope (b)	0.0455
Intercept (C)	+ 0.0047
R^2	0.9998
LOD (ng/mL)	11.60
LOQ (ng/mL)	35.16
Sandell sensitivity SS (µg/cm^2)	0.0397

Note: Y = bX+ c, where X is the concentration of drug in µg/mL.

5.3 Accuracy and Precision.

Percentage relative standard deviation (RSD%) and Analytical standard error (ASE%)of the suggested method were calculated and shown in Tables(1) These results of accuracy and precision show that the proposed method have good repeatability and reproducibility.

5.4 Analysis of Pharmaceutical Formulations.

The proposed method has been successfully applied to the determination of MXF in pharmaceutical dosage forms in four trade mark Syrian products: Moxicin (Ibn Al haytham), Moxiflox (Razi), Moxaquin (Obari), and Megamox (Rama pharma). Table 3.

Table-3The obtained results for pharmaceuticals samples

Trade mark	Dose	$\bar{x}^*$ (mg/dose)	RSD%	Recovery %
Moxicin	400 mg/Tab	404.57	1.04	101.14
Moxiflox	400 mg/Tab	399.92	0.98	99.98
Moxaquin	400 mg/Tab	399.85	1.10	99.96
Megamox	5 mg/ml	5.04	1.53	100.76

Moreover,tocheckthe validity of the proposed method, pharmaceutical dosage forms were tested for possible interference with standard addition method (Tables 4,5,6and 7). There was no significant difference between slopes of calibration curves and standard addition methods.Therefore,itisconcludedthattheexcipientsinpharmaceutical dosage forms of MXF did not cause any interference in the analysis of MXF.

Table-4The recovery of Moxifloxacin in Moxicin

	*Sample µg/mL	*Added µg/mL	*Found µg/mL	RSD%	Recovery %
Moxicin	5	2	6.983	0.77	99.15
	5	4	8.991	0.74	99.77
	5	6	11.073	0.69	100.62

* n = 5

Table-5The recovery of Moxifloxacin in Moxiflox

	*Sample µg/mL	*Added µg/mL	*Found µg/mL	RSD%	Recovery %
Moxiflox	5	2	7.021	0.80	101.05
	5	4	9.011	0.73	100.27
	5	6	11.052	0.65	100.87

* n = 5

Table-6 The recovery of Moxifloxacin in Moxaquin

Moxaquin	*Sample µg/mL	*Added µg/mL	*Found µg/mL	RSD%	Recovery %

	5	2	7.013	0.87	100.65
	5	4	8.986	0.82	99.65
	5	6	10.987	0.61	99.78

* n = 5

Table-7The recovery of Moxifloxacin in Megamox

	*Sample µg/mL	*Added µg/mL	*Found µg/mL	RSD%	Recovery %
Megamox	5	2	7.033	0.77	100.40
	5	4	9.017	0.71	100.52
	5	6	11.047	0.65	100.23

* n = 5

6. CONCLUSION

The newmethod is simple, rapid, economical, accurate and precise, and it is free from tedious experimental steps such as heating unlike the previously reported spectrophotometric methods cited earlier. The most attractive feature of this method is their relative freedom from interference by the usual diluents and excipients in amounts far in excess of their normal occurrence in pharmaceutical formulations. So it can be used for routine estimation of MXF from its pharmaceutical formulations.

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