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Research Article

Validation of spectrophotometric method for determination of esomeprazole and ciprofloxacin in their pure and dosage forms

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Abstract

A novel simple, accurate, sensitive and economical spectrophotometric method has been established and validated for the determination of esomeprazole and ciprofloxacin. The method is based on the oxidation of the studied drug by a known excess of potassium permanganate, followed by measuring the decrease in absorption (ΔA) of $KMnO_4$ in acidic medium at wavelength of 525nm. The detection limit is reported to be 1.01 and 1.06µg/mL showing a high degree of sensitivity. The proposed method was successfully validated according to ICH guidelines for the determination of esomeprazole and ciprofloxacin with a highly precise recovery and very low relative standard deviation. Finally, the method was compared statistically with a reference method showing equal accuracy, reproducibility and no significant difference with the reported one.

Introduction

Esomeprazole (ESM) (Figure 1) is chemically, 5-methoxy-2-{[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl] sulfinyl}-1H-benzimidazole that has S configuration at the sulfur atom. It is a proton pump inhibitor that decreases the amount of acid produced in the stomach. ESM is used to treat certain stomach and esophagus problems. It relieves symptoms such as heartburn, difficulty swallowing, and persistent cough. This medication helps heal acid damage to the stomach and esophagus, helps prevent ulcers, and may help prevent cancer of the esophagus [1]. ESM is combined with the antibiotics, clarithromycin and amoxicillin (or metronidazole in penicillin-hypersensitive patients) in the 7-14days eradication triple therapy for *Helicobacter pylori*. Infection by *H. pylori* is the causative factor in the majority of peptic and duodenal ulcers [2]. Literature survey demonstrated that few analytical techniques have been employed for the determination of ESM

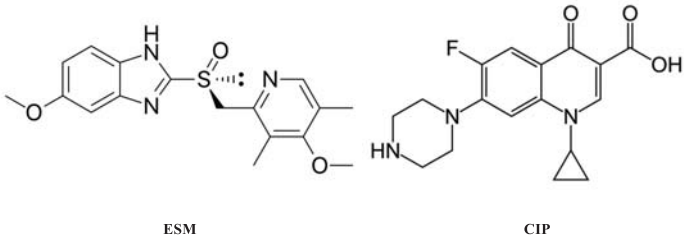

Figure 1: Chemical structures of esomeprazole (ESM) and ciprofloxacin (CIP).

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such as spectrophotometry [1-8], liquid chromatography [8,9] and spectrodensitometry method [10].

Ciprofloxacin (CIP) (Figure 1) is 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid. It is used to treat a variety of bacterial infections. CIP belongs to a class of drugs called quinolone antibiotics. It works by stopping the growth of bacteria [11]. Literature survey demonstrated that several analytical techniques have been employed for the determination of CIP such as different spectroscopic [11-14] and chromatographic [15-18] methods.

To our knowledge, no spectrophotometric method for the determination of ESM or CIP using potassium permenganate as an oxidant has yet been reported despite the versatility, simplicity and reliability of the technique in chemical analysis. As such, in this paper, the method is based on an oxidation reaction of ESM and CIP with a known excess of $KMnO_4$ followed by measuring the decrease in absorption (ΔA) of $KMnO_4$ in acidic medium at wavelength of 525nm.

Experimental

Apparatus

Labomed® Spectro UV-VIS Double Beam (UVD-2950) Spectrophotometer with matched 1cm quartz cells and connected to windows compatible computer using UV Win 5 Software v5.0.5.

Materials and reagents

All solvents and reagents were of analytical grade and double distilled water was used throughout the work. Esomeprazole was kindly provided by, Copad pharma for pharmaceutical industries, Obour City, Egypt. Standard solution of 200µg/mL was prepared by dissolving (0.02g) of the pure drug in 100mL double distilled water. Ciprofloxacin was kindly provided by, Egyptian Company for Pharmaceutical & Chemical Industries (EIPICO), 10th Of Ramadan City, Egypt. Standard solution of 200µg/mL was also prepared by dissolving (0.02g) of the pure drug in 100mL double distilled water. Potassium Permanganate (Aldrich Chemical Co. Ltd., Dorset, England), Standard solution of 5.0×10^{-3}M, was prepared by dissolving (0.079g) of the $KMnO_4$ in 100mL double distilled water and stored in dark bottle. Sulfuric Acid (El-nasr chemical, Egypt) was prepared as 2M.

Pharmaceutical formulations

Esmatac® 40mg was labeled to contain 40 mg esomeprazole (Egyptian group for pharmaceutical industries). Ciprocin® 250mg was labeled to contain 250mg ciprofloxacin (Egyptian Company for Pharmaceutical & Chemical Industries (EIPICO)).

Spectrophotometric procedures

Construction of the standard calibration curves: Aliquot portions of 200µg/mL ESM and CIP ranging from (0.40-2ml) were transferred into a series of 10mL measuring flasks. To these, 1mL and 1.50mL of 2M sulfuric acid were added for both ESM and CIP respectively, then 1mL of 5×10^{-3}M $KMnO_4$ were added to both drugs then the total volume was adjusted to 10mL with double distilled water. The absorbance of a reagent blank (similarly prepared without the drug) was measured against each drug concentration at 525nm either immediately in case of ESM or after 16minutes in case of CIP.

Procedure for pharmaceutical preparations: Accurately weights of Esmatac® 40mg equal to 20mg of ESM or Ciprocin® 250mg equal to 20mg of CIP were transferred to a 100mL measuring flask and completed to volume with double distilled water to give an equivalent final concentration of 200µg/mL. The procedures were then conducted as mentioned above under the general procedures applying standard addition techniques.

Results and discussions

Optimization of the reaction conditions

The optimum conditions for the method development were established by varying each specific parameter and keeping the others constant and observing the effect produced on the absorbance of the colored species. The optimum parameters are reported in Table 1.

Absorption spectra: Absorption spectra of ESM and CIP with $KMnO_4$ was studied over a range of 400-800nm. Potassium permanganate reacts with ESM and CIP in acidic medium and the decrease in absorption can be measured at 525nm as depicted in Figure 2.

Effect of temperature

Effect of temperature was studied and results showed that there is no an evident effect of temperature on the reaction as increase in temperature is not accompanied with any increase in absorbance and so, optimum reaction was performed at room temperature.

Table 1: Analytical parameters and spectrophotometric characteristics of the proposed method for ESM and CIP determination.

parameters	ESM	CIP
λ_{max}	525nm	
Volume of the media (2 M H_2SO_4)	1ml	1.50ml
Volume of the reagents ($KMnO_4$)	1ml	
Time of reaction between drug and $KMnO_4$	immediate	16minutes
Temperature	Ambient	

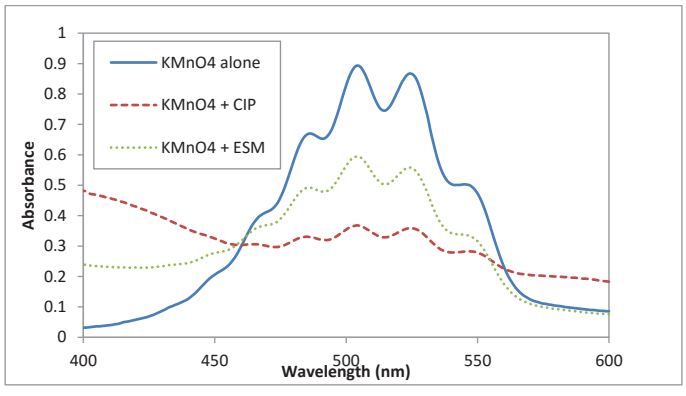

Figure 2: Absorption spectra of KMnO4 either alone (blue line), or with ESM (green dotted line) or with CIP (red dashed line) in acidic medium at 525nm.

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Effect of addition sequence: Addition sequences were studied and results revealed that the most appropriate sequence was the drug then the added acid then the added $KMnO_4$.

Effect of acidity : To study the effect of sulfuric acid volume, the reaction was performed in a series of 10mL volumetric flasks containing different volumes (0.5-4ml) of 2M sulfuric acid. It was found that the maximum absorbance was obtained when using 1mL of 2M sulfuric acid with ESM and 1.50mL with CIP as seen in Figure 3.

Effect of permenganate concentration: By studying the effect of $KMnO_4$ concentration referring to decrease of its color intensity, it was observed that the absorbance reached its maximum when 1mL of 5×10^{-3}M $KMnO_4$ was used in case of both ESM and CIP (Figure 4).

Effect of time: The effect of time on the oxidation reaction was studied to obtain the highest and most stable absorbance. As depicted in Figure 5, This absorbance can be achieved immediately after the reaction between the drug and $KMnO_4$ in case of ESM while it takes 16 minutes in case of CIP to complete the reaction.

Method validation

The method validation was performed according to International Conference of Harmonization (ICH) guidelines [19].

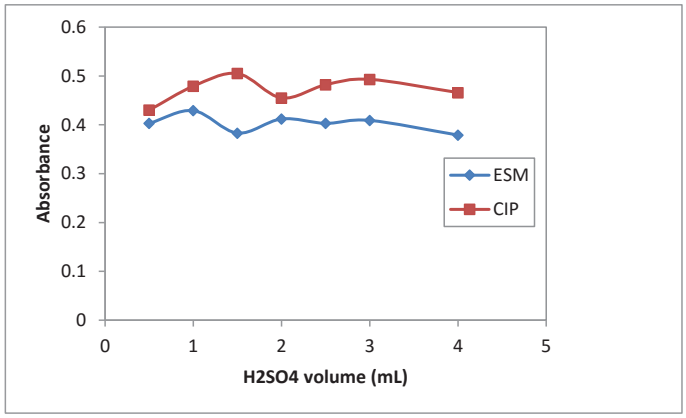

Figure 3: Effect of acidity on the reaction of $KMnO_4$ with ESM (blue) or with CIP (red) at 525nm.

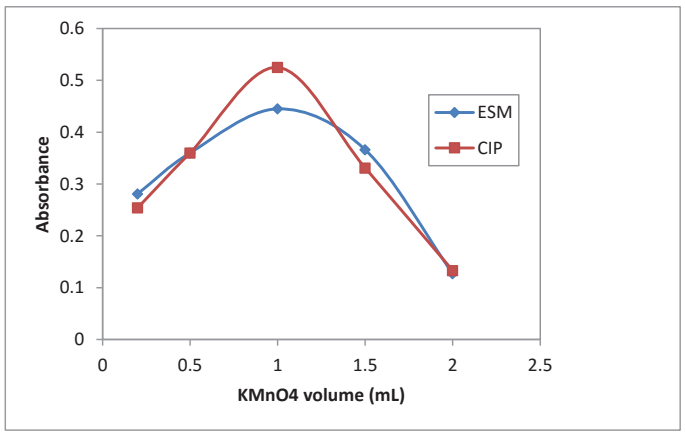

Figure 4: Effect of volume of $KMnO_4$ with ESM (blue) or with CIP (red) in acidic medium at 525nm.

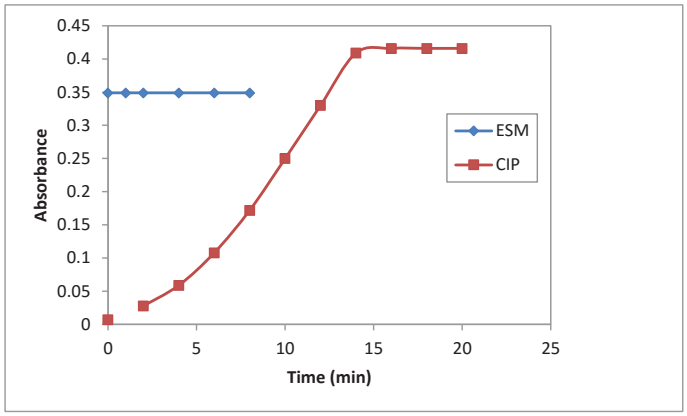

Figure 5: Effect of time on the reaction of $KMnO_4$ with ESM (blue) or with CIP (red) in acidic medium at 525nm.

Linearity: Six different concentrations of ESM and CIP were prepared for linearity studies. The linearity ranges of absorbance as a function of drug concentration (Table 2) provided acceptable indication about sensitivity of reagents used. Linear regression equations of ESM and CIP were found to be y=0.0334x+0.0379 and y=0.0444x+0.2459, respectively and the regression coefficient values (R^2) were found to be 0.9994 and 0.9991, respectively indicating a high degree of linearity for both drugs (Figure 6).

Accuracy: The accuracy of the method was determined by investigating the recovery of ESM and CIP concentration levels covering the specified range using the standard addition technique. It was performed by adding a fixed standard drug concentration at different levels of the pharmaceutical products (Esmatac® and Ciprocin®) and the proposed method was followed. From the amount of the drug estimated, the percentage recovery was calculated and the results are shown in Table 3.

Specificity: The specificity studies revealed that the presence of the excipents in Esmatac® 40mg and Ciprocin® 250mg formulations didn't show any kind of impurity interference, since the recoveries lied in the range of 96.90-104.85% as reported in Table 3.

Limits of detection and limits of quantification: The calculation of limits of detection and quantitation was based on the following equations: LOD=3.3S/K and LOQ=10S/K, respectively, where S is the standard deviation of the seven replicate values under the same conditions as for the sample analysis in the absence of analyte and K is the sensitivity, namely, the slope of calibration graph. Limits of detection were calculated to be 1.01 and 1.06µg/mL while limits of quantification were 3.35 and 3.55µg/mL, for ESM and CIP respectively (Table 2).

Robustness: The robustness of the method was evaluated by making small changes (±0.05ml) in the volume of H_2SO_4 and $KMnO_4$ keeping the other conditions constant where the effect of the changes was studied on the percent recovery and standard deviation of 20µg/mL ESM and CIP. The changes had negligible influence on the results where SD values were in the acceptable range as reported in Table 4.

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Ruggedness: The ruggedness of the method was tested by measuring three concentrations of the standard working solution using a different double beam spectrophotometer (model Jenway 6500, UK). The absorbances in case of the three procedures for both instruments were exactly similar indicating that the method is fairly rugged. According to ICH guidelines, the obtained values indicated high sensitivity of the proposed method.

Statistical analysis of the pharmaceutical formulation

Esmatac® 40mg and Ciprocin® 250mg have been successfully analyzed by the proposed method. Results obtained were compared to those obtained by applying reference methods [4,11] where Student's t-test and F-test were performed for comparison. Results are shown in table 5 where the calculated t and F values were less than tabulated values at p=0.05, which in turn indicate that there is no significant difference between proposed method and reference one relative to precision and accuracy.

Conclusion

Unlike GC and HPLC techniques, spectrophotometry is simple and inexpensive. The proposed oxidation- reduction method requires reagents which are very cheap and readily available, no pH adjustment is required and the procedure does not involve any critical reaction conditions or tedious sample preparation. According to ICH guidlines, the method is simple, fast, accurate, sensitive, rugged and free from interference by excipients which makes it ideal for routine quality control analysis. The amounts obtained by the proposed method for pharmaceutical products lied in the acceptable range of 96.90-104.85% and were statistically superior to the reference methods with respect to both sensitivity and selectivity.

Table 2: Results of the analysis for determination of ESM and CIP in pure samples using the proposed method.

parameters	ESM			CIP		
	Taken µg/ml	Found µg/ml	Recovery %	Taken µg/ml	Found µg/ml	Recovery %
	5	5.032	100.658	4	3.898	97.466
	8	8.146	101.833	8	8.132	101.661
	10	10.002	100.029	12	11.894	99.117
	14	13.775	98.396	14	14.033	100.241
	16	16.05	100.318	16	16.195	101.224
	20	20.122	100.613	18	17.795	98.861
Mean			100.308			99.762
±SD			1.12			1.579
±RSD			1.117			1.583
±SE			0.457			0.644
Variance			1.255			2.494
Slope			0.033			0.044
LOD			1.01			1.06
LOQ			3.35			3.55

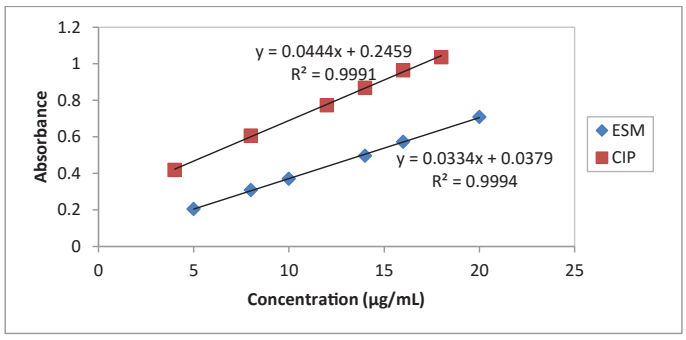

Figure 6: Calibration curves of ESM and CIP using the proposed method.

Table 3: Application of standard addition technique for the determination of Esmatac® 40 mg and Ciprocin® 250 mg using the proposed method.

parameters	ESM				CIP			
	Added pure ESM µg/ml	Taken µg/ml	Found µg/ml	Recovery %	Added pure Cip µg/ml	Taken µg/ml	Found µg/ml	Recovery %
	2	3	5.242	104.85	2	2	3.876	96.903
	2	6	7.937	99.214	2	6	7.997	99.971
	2	8	10.212	102.125	2	10	11.781	98.179
	2	12	14.404	102.887	2	12	14.304	102.171
	2	14	16.35	102.189	2	14	16.578	103.617
	2	18	20.332	101.661	2	16	18.065	100.362
Mean				102.154				100.201
±SD				1.827				2.473
±RSD				1.788				2.468
±SE				0.745				1.009
Variance				3.339				6.119

Table 4: Results of the robustness for 16µg/mL CIP and ESM samples using the proposed method.

	ESM			CIP		
Procedure/ Parameter changes	Mean recovery±SD	CV (%)	% Accuracy	Mean recovery±SD	CV (%)	% Accuracy
+ 0.05mL H_2SO_4	101.24±3.15	1.24	1.24	102.15±6.91	2.15	2.153
- 0.05mL H_2SO_4	100.87±2.28	0.87	0.87	101.8±6.01	1.78	1.779
+ 0.05mL $KMnO_4$	102.2±5.54	2.24	2.2	98.3±2.92	-1.69	-1.7
- 0.05mL $KMnO_4$	100.6±1.72	0.62	0.6	102.76±8.38	2.76	2.75

Table 5: Statistical analysis of results obtained by the proposed method applied on Esmatac® 40mg and Ciprocin® 250mg dosage forms compared with reference methods.

Parameters	Proposed method (ESM)	Reported method [4]	Proposed method (CIP)	Reported method [11]
N	6	5	3	5
Mean Recovery	102.154	100.10	99.50	99.64
SE	0.745	0.87	0.67	0.22
Variance	3.339	3.82	1.35	0.25
Student-t**	1.80(1.83)a	0.61(1.89)a	0.23(1.94)a	
F-test**	1.14(5.19)b	1.46(6.59)b	5.35(6.94)b	

[a] and [b] are the theoretical Student t-values and F-ratio at p= 0.05.

Ethical approval

This manuscript does not include any studies on human or animals.

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