

## SIMULTANEOUS DETERMINATION OF SOME MEDICAMENTS BY LINEAR SWEEP CATHODIC ADSORPTIVE STRIPPING VOLTAMMETRY

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### ABSTRACT

The simultaneous voltammetric determination of metronidazole with omeprazole as well as tinidazole with omeprazole in model solution, human urine samples and in a mixture of two pharmaceutical formulations or in a combined pharmaceutical formulation (HELI-CURE® Tablets) were applied using hanging mercury dropping electrode as a working electrode vs. Ag/AgCl sat'd KCl as reference electrode. The optimal conditions for simultaneous determinations were obtained in 0.1 M phosphate buffer (pH~7) using the standard addition method without the necessity for samples pretreatment and / or time-consuming extraction steps prior to analysis. Furthermore, the excipients present in the pharmaceutical formulations did not cause interference with tinidazole, metronidazole or omeprazole determination. The LOD of metronidazole and omeprazole in dual regime found to be  $0.7 \times 10^{-7}$  and  $0.25 \times 10^{-8}$  respectively. The LOD of tinidazole and omeprazole in dual regime found to be  $0.45 \times 10^{-7}$  and  $0.36 \times 10^{-8}$  respectively. The results showed that there was no significant difference between the calculated and real values of the analytes in biological fluids and medicaments samples. The obtained results indicate, the developed method is accurate with high recoveries and it can be recommended for routine analysis in the majority of drug quality control laboratories.

**Keyword:** 5-nitroimidazole, Omeprazole, Reduction, Medicaments

### INTRODUCTION

Metronidazole (MTZ) and Tinidazole (TNZ) are 5-nitroimidazole derivative which having a wide antibacterial and antiprotozoal spectrum<sup>1-3</sup>. Omeprazole is a benzimidazole compound that acts as proton pump inhibitor. It acts to regulate acid production in the stomach and is used to treat various acid-related gastrointestinal disorders<sup>4</sup>. Omeprazole and metronidazole or tinidazole are used in combined with antibiotics in triple and quadruple therapy for the eradication of *Helicobacter pylori* in peptic ulceration disease<sup>5-11</sup>.

The aim of this study is the simultaneous determination of metronidazole, tinidazole and omeprazole in metronidazole-omeprazole and tinidazole-omeprazole dual regimes in model solution, human urine samples and in a mixture of two pharmaceutical formulations or in a combined pharmaceutical formulation (HELI-CURE® Tablets) using linear sweep cathodic adsorptive stripping voltammetry (LSCASV).

### MATERIALS AND METHODS

#### Apparatus

Linear sweep voltammograms were obtained using an EG&G Princeton Applied Research Corporation (PAR) model 264A polarographic analyzer/stripping voltammeter, coupled with a PAR Model 303A, with a three-electrodes system consisting of a hanging mercury drop electrode (HMDE) as a working electrode, an Ag/AgCl sat'd KCl as a reference electrode and platinum wire as a counter electrode. A PAR 305 stirrer was connected to the PAR 303A SMDE. A PAR model RE 0151 X-Y recorder was used to collect the experimental data.

All the pH's were measured with Hanna microprocessor pH model 211.

#### Chemicals

A stock solution  $1 \times 10^{-3}$  M of omeprazole sodium (Sigma Chemical Co., Germany), metronidazole and tinidazole (Cipla Ltd., Mumbai, India) were prepared daily by dissolving the appropriate amounts of medicaments in double distilled water and acetone respectively.

Phosphate buffers (0.1 M, pH 6.0-/8.0) were used as supporting electrolytes.

Solutions of  $1 \times 10^{-3}$  M of metal ions i.e.  $Mg^{2+}$ ,  $Ca^{2+}$ ,  $Ba^{2+}$ ,  $Pb^{2+}$ ,  $Cd^{2+}$ ,  $Co^{2+}$ ,  $Ni^{2+}$  and  $Zn^{2+}$  ions, of the amino acids i.e. glycine, L- histidine, L-

threonine, L-methionine, L- alanine, L- valine and L-aspartic acid and of other natural organic molecules i.e. glucose, fructose, lactose, citric acid, oxalic acid, L- ascorbic acid and urea were prepared and used in the interference studies.

Human urine samples were collected from healthy volunteers and used immediately after their collection.

All chemicals used were of analytical grade and were used without further purification.

Risek capsules (Julphar (Gulf Pharmaceutical Industries, Ras Al Khaimah, U.A.E.) and Losec® capsules (AstraZeneca AB-Sweden, Packed by AstraZeneca-Egypt, Cairo, Egypt) each capsule were labelled to contain 20 mg of omeprazole.

Amrizable tablets (Amriya Pharm. Ind., Alexandria, Egypt.) and Flagyl tablets (Sanofi-aventis egypt s.a.e., El Sawah, El Amiriya, Egypt) each tablets were labelled to contain 500 mg of metronidazole.

HELI-CURE® Tablets (Egyphar, Obour city, Egypt) each tablets were labelled to contain 20 mg of omeprazole, 500 mg of tinidazole and 250 mg of clarithromycin.

#### General procedures

A known volume of the phosphate buffer solutions (pH~7) under study was placed in the dry and clean voltammetric cell (10ml). Then deaerated by passing nitrogen for 15 min. to remove oxygen (and for 30 sec. before each measurement), the voltammogram was recorded after equilibrium for 15 s. The accumulation potential was adjusted depending upon the experimental data obtained. The scan rate was  $100 \text{ mVs}^{-1}$ . All data were obtained at  $(25 \pm 2^\circ\text{C})$ . After recording a voltammogram of blank, aliquots of each of the required standard solutions was added from the standard stock solution. Resulted voltammogram were recorded under the optimum experimental conditions. Peak currents were recorded. Calibration curve was prepared by plotting peak current versus concentration of each medicaments applied.

#### Analysis of urine samples

Human urine was obtained from healthy volunteers, known amounts of the metronidazole and omeprazole as well as tinidazole and omeprazole were added to 1 ml of medicaments free urine sample, which was further diluted with double distilled water up to 25 ml with water. A known amounts of the spiked diluted urine were

added to the voltammetric cell containing the selected supporting electrolyte. Voltammograms were recorded under the foregoing conditions. The spiked urine was analyzed using the standard addition method and the recoveries obtained after three replicate experiments were calculated.

#### Analysis of metronidazole, tinidazole and omeprazole pharmaceutical formulations

The whole content of each of the following: five capsules of omeprazole (20 mg) pharmaceutical formulation (Losec® and Risek capsules), five tablets of metronidazole (500 mg) pharmaceutical formulation (Amrizole and Flagyl tablets) and five tablets of combined dosage of tinidazole (500mg), omeprazole (20mg) and clarithromycin (250mg) formulation (HELI-CURE® Tablets) were ground. A quantity of the resulted powder equivalent to one capsule or tablet were accurately weighed and mixed with Methanol, acetone and sodium hydroxide (to remove the clarithromycin from tablet) respectively, then any undissolved excipients were removed by filtration. The filtrate and wash were collected quantitatively in a suitable measuring flask, then the analysis was done by the recommended procedure.

#### RESULTS AND DISCUSSION

The simultaneous determination of metronidazole with omeprazole as well as tinidazole with omeprazole in human urine samples and pharmaceutical formulations were done using linear sweep voltammetry (LSV) technique. LSV were used owing to its good sensitivity and resolving power. The peak current of metronidazole with omeprazole as well as tinidazole with omeprazole depends on pH of the medium, concentration and chemical composition of the buffer solution, and instrumental parameters. We have studied optimization of the proposed procedure and examined conditions which could affect the results. During optimization of the conditions, the linear sweep voltammetric response of metronidazole with omeprazole as well as tinidazole with omeprazole in different buffer solutions have been studied i.e. Acetate, Phosphate and Britton-Robinson Buffer. phosphate buffer solutions at different pH values (6-8) were used as supporting electrolytes. As the pH was shifted from acidic to basic there is change in peak potential was observed. Furthermore, the effect of the supporting electrolyte concentrations were studied. Finally 0.1 M phosphate Buffer solution of pH ~7 was chosen as the suitable conditions, due to good separation of both analytes, more uniform peak shape, less broadening of peak and suitable current response of both analytes. Under the optimum conditions the LSCA<sub>2</sub>SV curves presented a single well-defined reduction peak of MTZ and TNZ at -0.58 and -0.49V respectively corresponding to the reduction of the nitro group<sup>12-18</sup> and -0.98V for OMZ due to the direct reduction of the sulfoxide group<sup>19-22</sup>. These good peaks potential separation of about 0.4 and 0.49V for MTZ-OMZ and TNZ-OMZ dual regimes respectively clearly allows the simultaneous determination of these medicaments at pH~7. Representative voltammograms for the determination of analysed medicaments in phosphate buffer solution at pH ~7 are presented in (Fig's. 1 and 2).

#### Validation of method

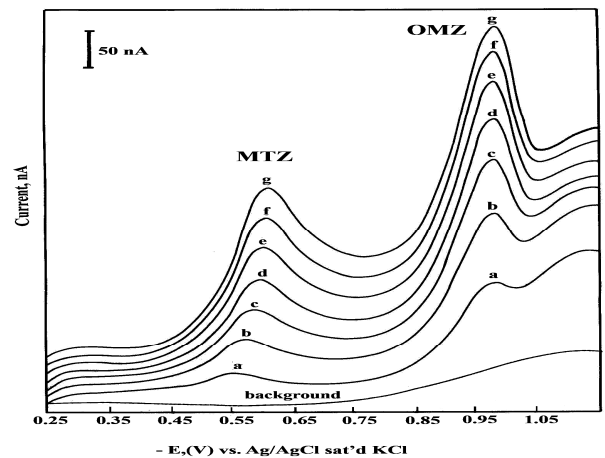
Validation of analytical procedure determination of analysed medicaments was performed. All these determinations were performed in triplicate. Medicaments identification was performed according to peaks potential by comparison with standard solutions, and by the standard addition method.

#### Calibration curves and linearity

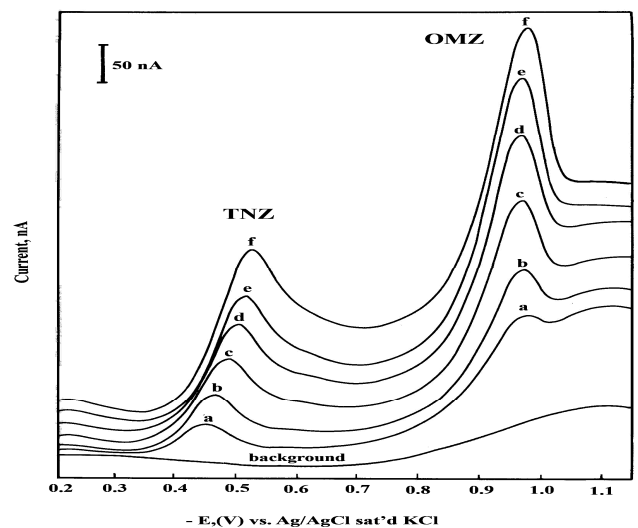
The calibration curves were measured in

triplicate and evaluated by the least squares linear regression method. Calibration curves of determinations for analysed medicaments in model solutions were constructed by the plots of the peak current ( $i_p$ ) of the medicaments versus the concentrations (C) presented in  $i_p = aC + b$  equation, where "a" is the slope, "b" is the intercept. The calibrations were linear for MTZ and OMZ in MTZ-OMZ dual regime in the concentration ranges of  $5-50 \times 10^{-7}$  and  $2-44 \times 10^{-8}$  M respectively and for TNZ and OMZ in TNZ-OMZ dual

regime in the concentration ranges of  $5-80 \times 10^{-7}$ , and  $2-35 \times 10^{-8}$  M respectively. The results associated with the calibrations are reported in Table 1.



**Fig. 1:** It Shows Concentration dependence of LSCA<sub>2</sub>SV peak of a dual regime of MTZ (from a to g:  $5, 10, 15, 20, 25, 30$  and  $35 \times 10^{-7}$  M) and OMZ (from a to g:  $2, 4, 6, 8, 10, 12$  and  $14 \times 10^{-8}$  M) in 0.1 M phosphate buffer solution (pH~7), accumulation time 120 second and scan rate =  $100 \text{ mVs}^{-1}$ .



**Fig. 2:** It shows Concentration dependence of LSCA<sub>2</sub>SV peak of a dual regime of TNZ (from a to f:  $5, 10, 15, 20, 25$  and  $30 \times 10^{-7}$  M) and OMZ (from a to f:  $2, 4, 6, 8, 10$  and  $12 \times 10^{-8}$  M), other conditions are as in Fig. 1.

#### Limits of detection and quantification

The limits of detection (LOD) and limits of quantification (LOQ) for determination of analysed medicaments in model solutions were calculated on the peak current using following equations<sup>23</sup>:  $\text{LOD} = 3\text{S.D.}/a$  and  $\text{LOQ} = 10\text{S.D.}/a$ , where "S.D." is the standard deviation of the intercept and "a" is the slope of the related calibration equation. The LOD and LOQ values are reported in Table 1.

#### Accuracy/recovery studies

The recovery was used to evaluate the accuracy of the method. The recovery study was performed by adding a known amounts of the medicaments studied to healthy human urine or to a known concentration of the commercial pharmaceutical formulations. Obtained recovery results of spiked human urine sample and commercial pharmaceutical formulation were given in Table 2 and 3.

Table 1. Analytical parameters of metronidazole (MTZ), tinidazole (TNZ) and omeprazole (OMZ) in a dual regimes in model solution (n=3)

Dual regime	Medicaments	Linear range (M)	Slope	Intercept	Corr. Coeff.	LOD (M)	LOQ (M)
MTZ-OMZ	MTZ	$5-50 \times 10^{-7}$	8.55	-17.14	0.9993	$0.7 \times 10^{-7}$	$2.3 \times 10^{-7}$
	OMZ	$2-44 \times 10^{-8}$	36.52	15	0.9991	$0.25 \times 10^{-8}$	$0.82 \times 10^{-8}$
TNZ-OMZ	TNZ	$5-80 \times 10^{-7}$	9.97	28	0.9991	$0.45 \times 10^{-7}$	$1.5 \times 10^{-7}$
	OMZ	$2-35 \times 10^{-8}$	47.42	-12.7	0.9992	$0.36 \times 10^{-8}$	$1.2 \times 10^{-8}$

### Precision

The precision measured from repeatability of the determination in terms of peak current for MTZ, TNZ and OMZ (n = 3) in healthy human urine and Pharmaceutical formulations indicated relative standard deviations (RSD) were given in Table 2 and 3.

### Specificity

The specificity of the method was investigated by observing any interference encountered from:

a. foreign species such as metal ions ( $Mg^{2+}$ ,  $Ca^{2+}$ ,  $Ba^{2+}$ ,  $Pb^{2+}$ ,  $Cd^{2+}$ ,  $Co^{2+}$ ,  $Ni^{2+}$  and  $Zn^{2+}$ ), amino acids (glycine, L-histidine, L-threonine, L-methionine, L-alanine, L-valine and L-aspartic acid) and some

natural organic molecules (glucose, fructose, lactose, citric acid, oxalic acid, urea and L-ascorbic acid).

b. common excipients of the pharmaceutical formulation such as hydroxypropyl cellulose, magnesium stearate, starch, sodium lauryl sulfate and titanium dioxide.

It was found that these foregoing species and excipients did not interfere with the determination of MTZ, TNZ and OMZ in dual regimes.

### Application of the method to urine samples

The proposed procedure was applied to the simultaneous assay of investigated medications (MTZ with OMZ and TNZ with OMZ) spiked in human urine samples in phosphate buffer solution pH~7. Figure 3 shows the linear sweep adsorptive stripping voltammograms of MTZ and OMZ at -0.59 V and -0.98 V respectively when two medicaments co-exist in urine sample in phosphate buffer solution pH~7. Variations of the peak current vs. the MTZ, TNZ and OMZ concentrations were represented by straight lines equation. The results obtained for the assay of the investigated medicaments spiked in urine sample were summarized in Table 2. The observed better recoveries (93.2 and 102.5) and relative standard deviation of spiked MTZ, TNZ and OMZ in urine indicate that this method could be efficiently used for the simultaneous determination of MTZ, TNZ and OMZ in real samples.

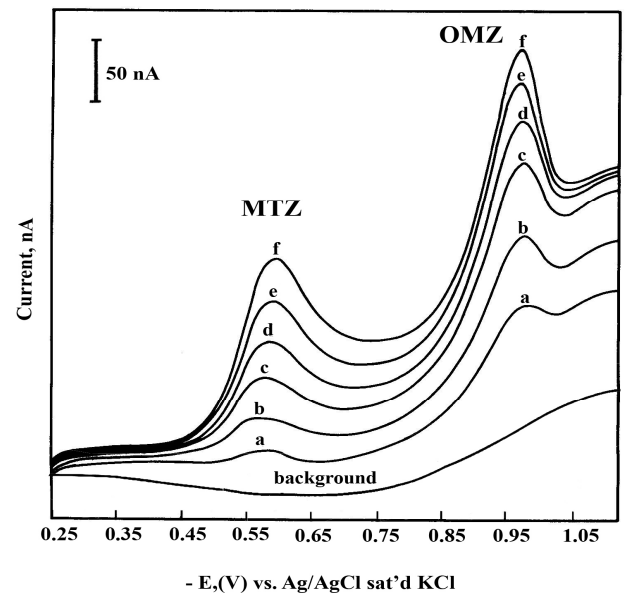


Fig. 3: It Shows Concentration dependence of LSCaSV peak of a dual regime of MTZ (from b to f: 5,10,15,20 and  $25 \times 10^{-7}$  M) and OMZ (from b to f: 2,4,6,8 and  $10 \times 10^{-8}$  M) in human urine sample spiked with  $5 \times 10^{-7}$  M of MTZ and  $2 \times 10^{-8}$  M of OMZ (a), other conditions are as in Fig. 1.

### Application of the method to pharmaceutical formulations

The proposed method was used for simultaneous determination of metronidazole with omeprazole as well as tinidazole with omeprazole in mixture of two pharmaceutical formulations solutions (Amrizole-Losec®, Flagyl-Losec®, Amrizole-Risek and Flagyl-Risek) and in combine dose formulation ((HELI-CURE®) solution respectively in phosphate buffer solution, pH~7. Figure 4 shows the voltammograms for mixture of MTZ and OMZ in combined solutions of Flagyl-Risek pharmaceutical formulations in phosphate buffer solution pH~7. The reduction peak currents of MTZ and OMZ in previous Four dual dose were linearly proportional to MTZ and OMZ concentrations with very good correlation coefficients as shown in Table 3.

LSCaS voltammograms for mixture of TNZ and OMZ in combined dosage formulation (HELI-CURE® Tablets) solution in phosphate buffer solution pH~7 are shown in Figure 5.

Table 2. Results of recoveries and relative standard deviation examination for simultaneous determination of metronidazole (MTZ)-omeprazole (OMZ) and timidazole (TNZ) -omeprazole (OMZ) dual regimes from human urine samples (n=3)

Dual regime	Medicaments	Concentration (M)	added Concentration (M)	found	Corr. Coeff.	Recovery (%)	RSD (%)
MTZ-OMZ	MTZ	$5 \times 10^{-7}$	$4.9 \times 10^{-7}$	0.9991	98	0.51	
	OMZ	$2 \times 10^{-8}$	$1.99 \times 10^{-8}$	0.9992	99.5	0.32	
TNZ-OMZ	TNZ	$5 \times 10^{-7}$	$4.66 \times 10^{-7}$	0.9996	93.2	0.63	
	OMZ	$2 \times 10^{-8}$	$2.05 \times 10^{-8}$	0.9993	102.5	0.39	

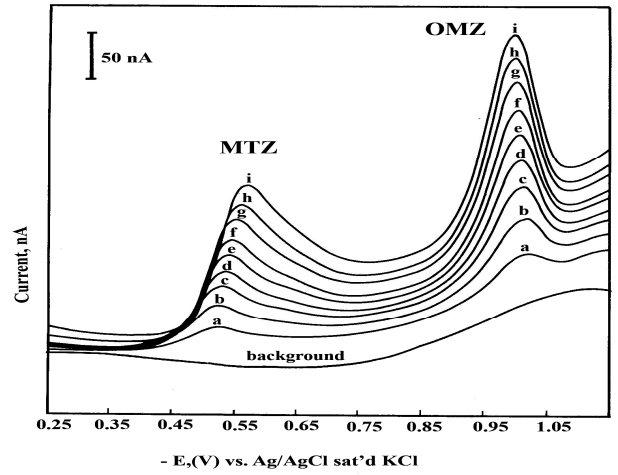


Fig. 4: It Shows LSCAS voltammograms for determination of MTZ and OMZ (in a dual regime) in a mixture of Flagyl and Risek pharmaceutical formulation solution, 0.005 ml of Flagyl solution + 0.04 ml of Risek solution (a), MTZ (from b to f:  $5, 10, 15, 20, 25, 30, 35$  and  $40 \times 10^{-7} M$ ), OMZ (from b to f:  $2, 4, 6, 8, 10, 12, 14$  and  $16 \times 10^{-8} M$ ), other conditions are as in Fig. 1.

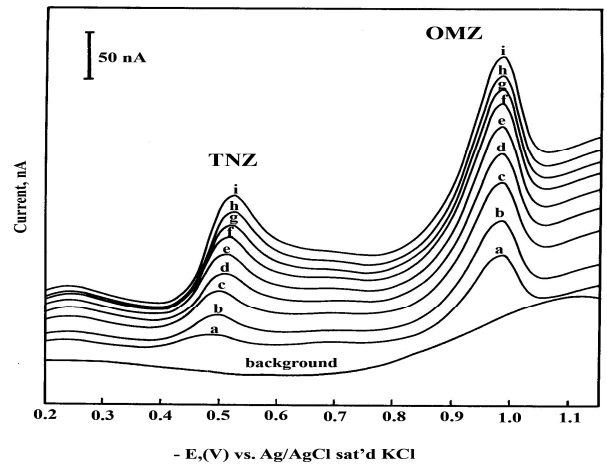


Fig. 5: It Shows LSCAS voltammograms for determination of TNZ and OMZ (in a dual regime) in a combined dosage formulation (HELI-CURE® Tablets) solution (0.005 ml (a), MTZ (from b to f:  $5, 10, 15, 20, 25, 30, 35$  and  $40 \times 10^{-7} M$ ), OMZ (from b to f:  $2, 4, 6, 8, 10, 12, 14$  and  $16 \times 10^{-8} M$ ), other conditions are as in Fig. 1.

**Table 3. Results of recoveries and relative standard deviation examination for simultaneous determination of metronidazole (MTZ)-omeprazole (OMZ) and tinidazole (TNZ) - omeprazole (OMZ) dual regimes in pharmaceutical formulations (n=3).**

Dual dose	Dual regime	Medicaments	Amount labeled (mg/ phar. Form.)	Amount Found (mg/ pham.form.)	Cort. Coeff.	Recovery (%)	RSD (%)
Amrizable - Losec®		MTZ	500	495	0.9998	99.0	2.3
		OMZ	20	18.8	0.9992	94.0	1.5
Flagyl - Losec®		MTZ	500	498	0.9996	99.6	2.8
		OMZ	20	19.2	0.9991	96.0	0.9
Amrizable - Risek	MTZ-OMZ	MTZ	500	499	0.9994	99.8	3.5
		OMZ	20	19.5	0.9996	97.5	1.8
Flagyl - Risek		MTZ	500	502	0.9998	100.4	4.1
		OMZ	20	18.5	0.9992	92.5	0.85
HELI-CURE® Tablet	TNZ-OMZ	TNZ	500	497.9	0.9995	98.6	3.7
		OMZ	20	19.3	0.9998	96.5	1.3

The results indicated very good recoveries and relative standard deviation (RSD) for the simultaneous determination of two medicaments in pharmaceutical formulations in the range of 92.5-100.4 % and 0.85-4.1% respectively (Table 3 ). The results showed that there was no significant difference between the calculated and real values of the analytes in medicament samples.

## CONCLUSIONS

The proposed method was found to be simple, precise, accurate and rapid for simultaneous determination of metronidazole with omeprazole as well as tinidazole and omeprazole in model solutions, spiked urine samples and pharmaceutical formulations. It can be easily and conveniently adopted for routine quality control analysis.

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