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# Validation of the spectrophotometric determination of omeprazole and pantoprazole sodium via their metal chelates

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**Abstract**

Spectrophotometric procedures for the determination of two irriversible proton pump inhibitors, omeprazole (OMZ) and pantoprazole (PNZ) sodium have been developed, the procedures are based on the formation of 2:1 chelates of both drugs with different metal ions. Pantoprazole sodium is quantified by a stability-indicating procedure through chelation with iron (III) in aqueous-ethanol medium to form an orange chelate picked at 455 nm. The procedure retains its accuracy in presence of up to 70% of its degradate, sulfenic acid prepared by degrading the pure drug in borate buffer of pH 8 at 37 °C for 5 days. The colored chelates of OMZ in ethanol are determined spectrophotometrically at 411, 339 and 523 nm using iron (III), chromium (III) and cobalt (II), respectively. Regression analysis of Beer's plots showed good correlation in the concentration range of 15–95, 10–60 and 15–150 μg $ml^{-1}$ of pure OMZ using iron (III), chromium (III) and cobalt (II), respectively, and in the range of 30–300 μg $ml^{-1}$ of PNZ sodium using iron (III). The limits of detection are 0.22–3.65 μg $ml^{-1}$ while limits of quantitation range between 0.74 and 12.17 μg $ml^{-1}$. The optimum assay conditions are investigated and the recovery of the cited drugs from their dosage forms ranges from 97.2 to 100.3%. Good values of precision are obtained, intraday R.S.D. are 0.93–1.75% and the inter day R.S.D. are 0.51–3.29%.


*Keywords:* Omeprazole; Pantoprazole sodium; Spectrophotometry; Iron (III); Chromium (III); Cobalt (II); Metal chelates; Validation

## 1. Introduction

$H^+/K^+$ ATPase inhibitors, omeprazole (OMZ) and pantoprazole (PNZ) sodium are effective in the treatment of gastric ulcers [1–3]. Both drugs are decomposed in acid media to yield two main products sulfonamide and sulfenic acid [4,5]. OMZ was also found to be unstable in neutral and weak alkaline media where its maximum stability was at pH 11 [6,7].

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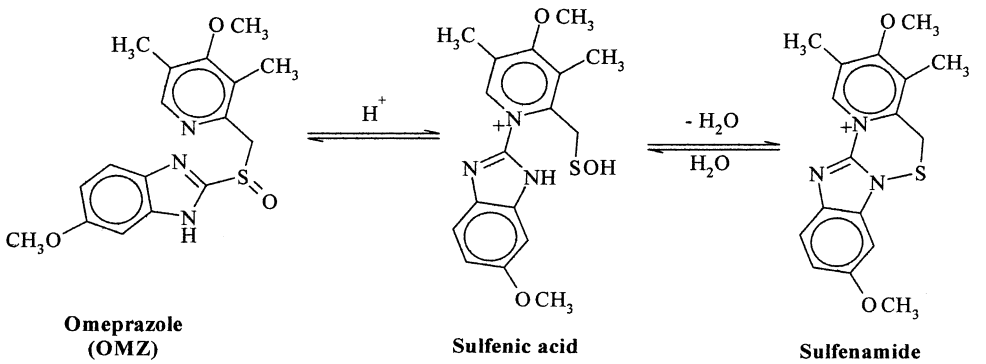



OMZ is officially listed in the British Pharmacopoeia [2]. The reported methods for the determination of OMZ and PNZ include HPLC [5–10], HPTLC [11,12], polarography [4,13], electrophoresis [14] and UV spectrophotometry [15,16]. Concerning visible spectrophotometry, very few methods have been reported [17–19] for the determination of both drugs. Hence, sensitive and accurate visible spectrophotometric methods have been viewed as essential. The purpose of this study is to (a) develop stability indicating spectrophotometric procedure for the selective determination of PNZ-Sodium in presence of its degradation products. (b) develop procedures capable of quantitating OMZ and PNZ separately in presence of each other, (c) describe and validate the structural ability of both drugs to chelate certain metal ions, which essentially present in biological fluids which have not been previously studied except for the ternary complex formed between PNZ, Cu (II) and eosin [18]. A prospective work will be a bioavailability study using the proposed chelation procedures.

## 2. Experimental

### 2.1. Apparatus

UV–vis spectrophotometer (Shimatzu 1601).

### 2.2. Materials

#### 2.2.1. Pure samples

Omeprazole-kindly supplied by Sedico, 6 October City, Egypt. The purity of the sample was checked by TLC and melting point [3].

Pantoprazole sodium sesquihydrate (Byk Golden) konstanz, Germany. Its purity was checked by TLC and melting point [3].

#### 2.2.2. Market samples

The exact composition of the formulations studied are given in Table 1.

- Gastrazole® capsules (Ameria Pharm. IND-Alexandria, Egypt) BN 533116. Each capsule is labeled to contain 20 mg OMZ.
- Gasic gastrocaps® (Medical Union Pharmaceuticals Abu Sultan, Ismalia, Egypt in cooperation with Mepla Pharma, Egypt, SAE). BN. 010096. Each cap is Labelled to contain 20 mg OMZ.
- Napizole® enteric coated pellets (Global Napi pharmaceuticals GNP. Egypt.) BN. 16803. Each pellet is labeled to contain 20 mg OMZ.
- Controloc® tablets (BYK, konstanz, Germany) BN, 100291. Each tablet is labeled to contain 45.1 mg PNZ sodium sesquihydrate equivalent to 40 mg PNZ.
- Pantoloc-20 tablets (Medical Union Pharmaceuticals, Abu-sultan, Ismalia, Egypt) BN

Table 1
Composition of the formulations studied[a]

| Gastrazole capsules | | Gasic gastrocaps | | Napizole pellets | | Controloc tablets | |
|---|---|---|---|---|---|---|---|
| Omeprazole | 20 mg | Omeprazole | 20 mg | Omeprazole | 20 mg | Pantoprazole | 40.0 mg |
| Methylacryl copolymer | 240 mg | Lactose | 150 mg | Methylhydroxypropyl cellulose phthalate | 23.9 mg | $Na_2CO_3$ | 10.0 mg |
| Shell | | Ovicel | 40 mg | Anhydrous lactose | 8 mg | Mannitol | 42.7 mg |
| Gelatin | 61.1 mg | Talc | 20 mg | Methylhydroxypropylcellulose | 8 mg | Crospovidone | 50.0 mg |
| Titanium dioxide | 0.6 mg | Stearic acid | 2.5 mg | Microcrystalline cellulose | 6 mg | Polyvidone k90 | 4.0 mg |
| Carmoisine | 0.28 mg | Eudra gitel | 17.5 mg | Cetylalcohol | 1.3 mg | Calcium stearate | 3.2 mg |
| Ponceau | 0.012 mg | | | Anhydrous $Na_2HPO_4$ | 0.8 mg | Hydroxylpropylmethyl cellulose 2910 | 19.0 mg |
| Brilliant blue | 0.0026 mg | | | Sod. Lauryl $SO_4$ | 0.5 mg | Polyvidonek 25 | 0.38 mg |
| | | | | | | Titanium dioxide | 0.34 mg |
| | | | | | | Yellow ferricoxide | 0.03 mg |
| | | | | | | Propylene glycol | 4.25 mg |
| | | | | | | Eudragit L30 D-55 | 14.56 mg |
| | | | | | | Triethylcitrate | 1.45 mg |
| | | | | | | Printing ink | 0.016 mg |
| | | | | | | Dry residue | - |

[a] Obtained from the manufacturers by personal communication.

011589. Each tablet is labeled to contain 20 mg PNZ (as PNZ sodium sesquihydrate).

#### 2.2.3. Reagents and chemicals

All reagents and chemicals used were of analytical grade and solvents were of spectroscopic grade.

- $FeCl_3 \cdot 6H_2O$ (Adwic, M.W. 279.3) 0.8% and $1.5 \times 10^{-3}$ M solution in ethanol, standardized against standard $KMnO_4$ after reduction [20].
- $CrCl_3 \cdot 6H_2O$ (Avondale lab, M.W. 266.44) 0.8% and $0.75 \times 10^{-3}$ M in ethanol, standardized iodometricaly after oxidation to dichromate [2].
- $CoCl_2 \cdot 6H_2O$ (M&B lab, M.W. 291.04) 0.9% and $0.75 \times 10^{-3}$ M solution in ethanol, standardized against standard EDTA [20].

#### 2.2.4. Standard solutions

- OMZ, 0.5 mg $ml^{-1}$ in ethanol.
- OMZ, $0.75 \times 10^{-3}$ M solution prepared by dissolving 26 mg in 100 ml ethanol.
- PNZ sodium, 2 mg $ml^{-1}$ in water.
- PNZ sodium, $1.5 \times 10^{-3}$ M solution prepared by dissolving 116 mg in 100 ml water.

OMZ solutions in ethanol are stable for 48 h however, PNZ-sodium solutions in water are freshly prepared and used within 3 h.

#### 2.2.5. Laboratory-degraded pantoprazole sodium

Weigh 100 mg of PNZ sodium and dissolve in borate buffer of pH 8 to prepare 0.5 mg $ml^{-1}$ solution of the drug and keep in a thermostatic oven at 37 °C for 5 days. Filter from the reddish brown precipitate of the sulfinamide degradate. Evaporate filtrate to dryness under vacuum, extract the residue with 20 ml ethanol, three times. Evaporate the combined ethanolic extracts to dryness under vacuum and dissolve the residue in water to make 50 ml. The obtained solution is labeled to contain the sulfenic acid degradate derived from 2 mg $ml^{-1}$ PNZ-sodium.

This degradate solution was examined by TLC using silica gel 60 $F_{254}$ plates and a mobile phase of chloroform–methanol (10:0.6) and no undegraded PNZ-sodium observed.

### 2.3. Procedures

#### 2.3.1. General procedures

*2.3.1.1. Chelation of pantoprazole sodium with iron (III).* Accurately transfer volumes of the standard drug solution in water (2 mg $ml^{-1}$) equivalent to 0.3–3.0 mg PNZ-sodium into a series of 20-ml test tubes. Complete to 2 ml with water, add 0.7 ml of 0.8% ethanolic $FeCl_3$ solution followed by 6 ml ethanol. Heat in a thermostated water bath at 60 °C for 30 min. Cool at room temperature and transfer quantitatively, the contents of each tube to a 10-ml volumetric flask and complete to volume with ethanol. Measure the absorbance of orange chelate at 455 nm against a reagent blank.

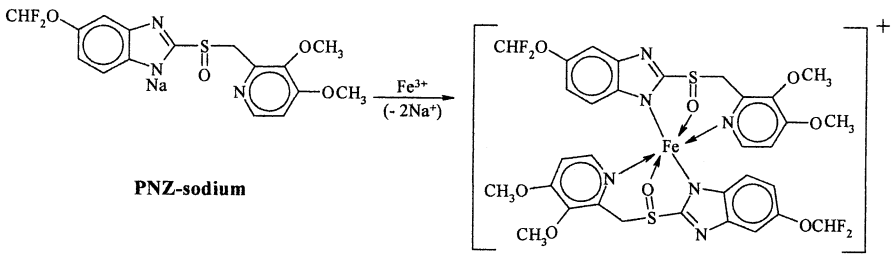
*2.3.1.2. Chelation of Omeprazole with Fe (III), Cr (III) and Co (II).* Into a series of 20-ml test tube, introduce volumes of standard drug solution in ethanol (0.5 mg $ml^{-1}$) corresponding to 0.15–0.95, 0.1–0.6 or 0.15–1.5 mg OMZ. Complete to 5 ml with ethanol, add 0.6 of 0.8% $FeCl_3$, 1.2 ml of 0.8% $CrCl_3$ or 0.3 ml of 0.9% $CoCl_2$ solution in ethanol, and heat in a water bath at $65 \pm 5$ °C for 15, 10 or 35 min, respectively. Cool, transfer to 10-ml volumetric flasks and complete to volume with ethanol. Measure the absorbance of the orange and purple chelates of OMZ with Fe (III) and Co (II) at 411 and 523 nm, respectively, against a reagent blank. And measure that of OMZ-Cr (III) chelate at 339 nm against a blank containing the same amount of the drug but omitting the metal ion.

#### 2.3.2. Determination of mixtures of imtact and degraded PNZ-sodium

Transfer volumes of pure PNZ-sodium (2 mg $ml^{-1}$ in water) equivalent to 2.7–0.3 mg of the intact drug into a series of 20 ml test tubes. Mix with volumes of the laboratory-degraded solution, corresponding to 0.3–2.7 mg degraded PNZ-sodium. Proceed as detailed under "Section 2.3.1.1".

*2.3.3. Application to dosage forms*

*2.3.3.1. Omeprazole.* Weigh the contents of 20 gastrazole capsules, gasec caps or napizole pellets, finely grind them and mix well, weigh an amount of the fine powder equivalent to 25 mg OMZ into a 50 ml volumetric flask. Dissolve in about 40 ml ethanol by shaking for 15 min and complete to volume with ethanol, then filter. Analyze the clear alcoholic filtrate claimed to contain 0.5 mg $ml^{-1}$ OMZ by chelation with, Fe (III), Cr (III) and Co (II), following the details under "Section 2.3.1".




*2.3.3.2. Pantoprazole sodium.* Weigh 20 controloc or pantoloc tablets and finely grind them. Weigh an amount of the powder equivalent to 100 mg PNZ sodium and dissolve in about 40 ml water by shaking for 10 min, complete to volume with water then filter. Analyze the clear aqueous filtrate labeled to contain 2 mg $ml^{-1}$ of PNZ-sodium sesquihydrate by chelation with iron as described under "Section 2.3.1".

## 3. Results and discussion

The formation of metal complexes with organic compounds have long been recognized. However, the binary complexes of the cited drugs with metal ions have not been studied yet, although they may be an area of interest. This is because they may affect the bioavailability of these drugs as certain metal ions are present in relatively appreciable concentration in biological fluids.

Studying the structural formulae of OMZ and PNZ, showed that they are promising in forming metal chelates between the imidazole-NH group, the oxygen of the sulfur dioxide side chain, and the N of the pyridine ring to yield a six-membered ring chelate as follow:

OMZ and PNZ-sodium are labile drugs of the benzimidazole derivatives used in treatment of GIT ulcers. They are acid-sensitive and hence formulated as enteric coated tablets, pellets or capsules [2,4–7]. It has also been reported that OMZ was degraded at pH 8 using borate buffer at 37 °C for 4 days [21]. Analogous to OMZ, PNA-sodium was degraded at pH8 at 37 °C using borate buffer where complete degradation was observed after 5 days to yield two degradation products, sulfenamide (I) which is insoluble in aqueous media and separated by filtration, and a soluble sulfenic acid derivative (II). These degradation products were tested by TLC using silica gel 60 $F_{254}$ plates ($5 \times 10$ cm) and $CHCl_3$–methanol (10:0.6) as a mobile phase. Then visualized under UV lamp at 254 nm. Each degradate gave a single spot at $R_f$ values of 0.76 and 0.25 for (I) and (II), respectively, however the $R_f$ value corresponding to the intact drug was 0.53.

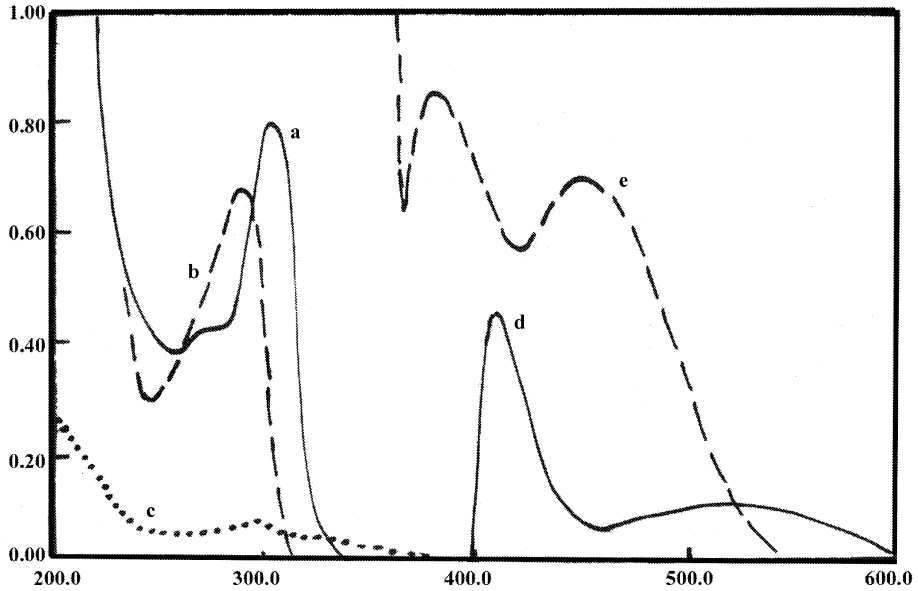



Fig. 1. UV–visible spectra of: (a) OMZ (15 μg ml$^{-1}$). (b) PNZ sodium (20 μg ml$^{-1}$), (c) Sulfenic acid derived from 20 μg ml−1 PNZ sodium. (d) OMZ (30 μg ml$^{-1}$)–Fe(III) chelate, in ethanol. (e) PNZ (200 μg ml$^{-1}$)–Fe(III) chelate, in water–ethanol (2–8).

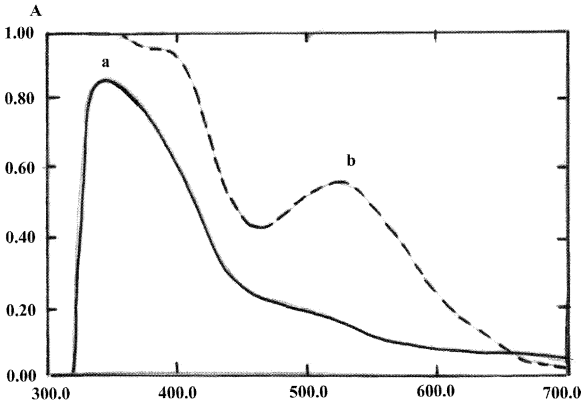



Fig. 2. UV–visible spectra of: (a) OMZ (50 μg ml$^{-1}$)–Cr(III) chelate and (b) OMZ (90 μg ml$^{-1}$)–Co(II) chelate in ethanol.

### 3.1. Absorption spectra

The UV spectra of the solution of sulfenic acid derivative of PNZ-sodium has shown some band overlapping with the principle maximum of the intact drug at 290 nm. Chelation of PNZ-sodium with iron (III) in water–ethanol mixture lead to the appearance of two new bands at 385 nm at 455 nm (Fig. 1). Upon mixing its degradate (sulfenic acid) aqueous solution with iron no evidence of complexation was observed. Accordingly, this procedure can be advantageously used for the selective determination of intact PNZ-sodium in its dosage forms at 455 nm; the peak at 385 nm gave unreliable results.

On the other hand OMZ is insoluble in water and hence it was determined by chelation with Fe (III), Cr (III) and Co (II) in ethanol in which its sulfenamide degradate is soluble and greatly interfere with the absorbance of the formed chelates.

In ethanol, OMZ has a sharp peak at 301 nm, when reacting with iron (III) in ethanol an orange-colored chelate has a new sharp peak at 411 nm together with a peak of much lower sensitivity at 530 nm were obtained (Fig. 1). Also, OMZ forms a yellow and purple chelates with Cr (III) and Co (II) absorbs at 339 and 523 nm, respectively; Fig. 2. Neither the drugs, nor the metal ions show significant absorbance at these new bands. This was motivational to use the latter bands for the spectrophotometric determination of OMZ in bulk powder and in dosage forms.

It should be pointed out that no spectroscopic evidences for the chelation of PNZ-sodium with Cr (III) and Co (II) were observed. This may be

Table 2
Effect of temperature and time of heating on the absorbance of the chelates of OMZ and PNZ sodium with different metal ions

| Time in min | Temperature | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A of OMZ-Fe (III) $\lambda_{max}$ 411 nm | | | A of OMZ-Cr (III) $\lambda_{max}$ 339 nm | | | A of OMZ-Co (II) $\lambda_{max}$ 523 nm | | | A of PNZ-Fe (III) $\lambda_{max}$ 455 nm | | |
| | 50 °C | 60 °C | 70 °C | 80 °C | 50 °C | 60 °C | 70 °C | 80 °C | 50 °C | 60 °C | 70 °C | 80 °C | 50 °C | 60 °C | 70 °C | 80 °C |
| 5 | – | – | – | – | 0.750 | 0.823 | 0.821 | 0.830 | – | – | – | – | – | – | – | – |
| 10 | 0.528 | 0.607 | 0.602 | 0.592 | 0.721 | 0.843 | 0.819 | 0.809 | 0.376 | 0.415 | – | – | 0.275 | 0.271 | 0.280 | 0.121 |
| 15 | – | – | – | – | 0.720 | 0.841 | 0.839 | 0.757 | – | – | – | – | – | – | – | – |
| 20 | 0.535 | 0.596 | 0.599 | 0.607 | 0.694 | 0.628 | 0.672 | 0.669 | 0.405 | 0.621 | – | – | 0.392 | 0.359 | 0.368 | 0.279 |
| 25 | – | – | – | – | 0.479 | 0.449 | 0.511 | 0.521 | – | – | – | – | – | – | – | – |
| 30 | 0.521 | 0.592 | 0.612 | 0.617 | 0.416 | 0.440 | 0.352 | 0.373 | 0.436 | 0.659 | 0.657 | 0.649 | 0.410 | 0.402 | 0.397 | 0.311 |
| 40 | 0.532 | 0.589 | 0.592 | – | – | | | | 0.433 | 0.660 | 0.652 | 0.659 | 0.409 | 0.400 | 0.391 | 0.302 |
| 50 | 0.530 | 0.551 | – | – | – | | | | 0.435 | 0.659 | 0.661 | 0.651 | 0.406 | 0.405 | – | 0.329 |
| 60 | 0.529 | 0.543 | – | – | – | | | | | | | | 0.391 | 0.387 | – | |

– Conc. of the drug taken was: 50 μg $ml^{-1}$ of OMZ for OMZ-Fe (III) and OMZ-Cr (III); 100 μg $ml^{-1}$ of OMZ for OMZ-Co (II) chelate; 120 μg $ml^{-1}$ of PNZ for PNZ-Fe (III) chelate.

ascribed to the powerful electron withdrawing effect of $-OCHF_2$ group in the para-position to the $-N^- Na^+$ group of the imidazole ring, that rinder the negative charge on nitrogen atom is resonating with the adjacent benzene ring rather than forming a bond with the metal ion in a chelate form.

### 3.2. Optimization of the reaction conditions

Ethanol was found to be the solvent of choice in which OMZ and the metal ions are stable and freely soluble. Although PNZ-sodium was dissolved in water however, the diluting solvent for PNZ-iron (III) chelate was also ethanol to stabilize iron and the chelate formed. The ethanolic OMZ solutions is stable for 48 h and those of metal ions for 1 week. However, the aqueous solution of PNZ-sodium must be freshly prepared.

At room temperature, the chelation reactions were very slow and up to 2 h were required to attain maximum absorbance at the relevant maxima thus, different temperature were tried (50–80 °C) using thermostated water bath. Optimum heating time was found to be 10–30, 5–15 and 30–50 min at 65 ± 5 °C for chelation of OMZ with Fe (III), Cr (III) and Co (II), respectively. However, for PNZ-iron (III) chelate, maximum color intensity was obtained upon heating at 50–60 °C for 30–50 min. Below and above the mentioned temperature and time of heating, decreased absorbance at the relevant maxima were obtained (Table 2). In addition, the color of the obtained chelates were stable for 30, 30, 60 and 40 min for OMZ-Fe (III), OMZ-Cr (III), OMZ-Co (II) and PNZ Fe (III), respectively.

Investigation of metal ion concentration revealed that 0.6–0.7 ml or 0.5–0.7 ml of 0.8% $FeCl_3$ solution were optimum for maximum color intensity of the chelates of OMZ or PNZ-sodium, using 100 and 150 μg $ml^{-1}$ of OMZ and PNZ, respectively. Also 1.0–1.4 ml of 0.8% $CrCl_3$ solution and 0.2–0.4 ml of 0.9% $CoCl_2$ solution were found to be optimal for chelation of 50 and 100 μg $ml^{-1}$ of OMZ with Cr (III) and Co (II), respectively (Fig. 3).

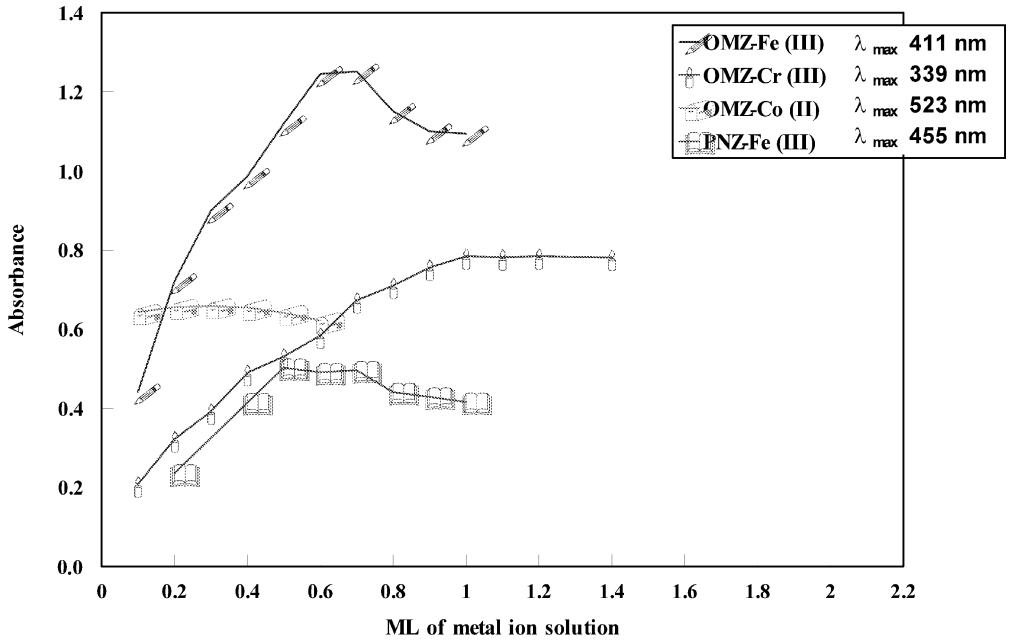



Fig. 3. Effect of metal ion cone on the absorbance of drug–metal chelate using: 0.8% $FeCl_3$ solution and 100 μg $ml^{-1}$ of OMZ and 150 μg $ml^{-1}$ of PNZ; 0.8% $CrCl_3$ solution and 50 μg $ml^{-1}$ of OMZ; 0.9% $CoCl_2$ solution and 100 μg $ml^{-1}$ of OMZ.

### 3.3. Determination of chelates stability and composition

The composition of the chelate of each drug with metal ions used was studied by Job's method [22,23], chelates of 2:1 ratio were obtained between each drug and metal ion. The stability constants of the formed chelates β were calculated [22,23] and the values of log β were around 8; Table 3.

### 3.4. Linearity range and quantification of the procedures

Beer's law was found to be obeyed in the ranges of 15–95, 10–60 and 15–150 μg $ml^{-1}$ of pure OMZ at 411, 339 and 523 nm, upon chelation with Fe (III), Cr (III) and Co (II), respectively. A (1%, 1 cm) were calculated to be 124, 167 and 63 with the previously mentioned metal ions, respectively,

Table 3
Stability constants of OMZ and PNZ sodium chelates with metal ions in ethanol by Job's method [22,23]

| | OMZ-Fe (III) $\lambda_{max}$ 411 nm | OMZ-Cr (III) $\lambda_{max}$ 339 nm | OMZ-Co (II) $\lambda_{max}$ 523 nm | PNZ-Sodium–Fe (III) $\lambda_{max}$ 455 nm |
|---|---|---|---|---|
| Total molar conc | $0.75 \times 10^{-3}$ | $0.75 \times 10^{-3}$ | $0.75 \times 10^{-3}$ | $1.5 \times 10^{-3}$ |
| N | 1.985 | 1.900 | 2.280 | 1.630 |
| A/Aex | 0.883 | 0.931 | 0.980 | 0.970 |
| β* | $3.85 \times 10^{8}$ | $3.00 \times 10^{8}$ | $1.04 \times 10^{8}$ | $2.53 \times 10^{8}$ |
| Log β | 8.59 | 8.48 | 8.02 | 8.40 |

$\beta^* = \frac{A/AeXC_x}{[C_M - A/A_{ex}C_x][C_L - nA/A_{ex}C_x]^n}$, where, M, metal ion; L, ligand; $n = \frac{X_{max}}{1 - X_{max}}$, X, mole fraction of the ligand at the maximum of the Job's plot; $A/A_{ex}$, The ratio of the observed absorbance to that indicated by the tangent for the same λ, $C_M$ and $C_L$, conc of the metal ion and ligand, respectively, $C_X = C_M$ (when $X > X_{max}$).

Table 4
Results of assay validation of the proposed chelation procedures

| Parameter | Omeperazole-Fe (III) | Omeprazole-Cr (III) | Omeparzole-Co (II) | Pantoprazole sodium-Fe (III) |
|---|---|---|---|---|
| Linearity range (μg ml$^{-1}$) | 15–95 | 10–60 | 15–150 | 30–300 |
| LOD (μg ml$^{-1}$) | 0.70 | 1.98 | 0.22 | 3.65 |
| LOQ (μg ml$^{-1}$) | 2.34 | 6.59 | 0.74 | 12.17 |
| Slope (b) | 0.0123 | 0.0168 | 0.0063 | 0.0034 |
| Intercept (a) | 0.004 | 0.0027 | 0.0035 | 0.0002 |
| Correlation coefficient (r) | 0.9999 | 0.9994 | 0.9999 | 1.000 |
| Accuracy% | 100.3 | 99.1 | 100.4 | 100.6 |
| *Precision (R.S.D.%)* | | | | |
| [a]Repreatability | 0.93 | 1.75 | 1.27 | 1.52 |
| [b]Reproducibility | 3.29 | 1.48 | 0.51 | 1.38 |

[a] n = 6.
[b] n = 4.

indicating that OMZ-Cr (III) is the most sensitive chelate and OMZ-Co (II) is the least.

However, the linearity of PNZ-Fe (III) chelate covered the range of 30–300 μg ml$^{-1}$ of the drug with A (1%, 1 cm) equals 33.5.

The drug chelate absorbances were plotted against the corresponding concentrations. Data were fitted to the equation Y = a + bx, where Y, is the absorbance at the relevant maximum; x, is the drug concentration in μg ml$^{-1}$; b, is the slope and a, is the intercept of the calibration curve. The regression parameters are shown in Table 4; the correlation coefficients "r" ranged from 0.9991 to 1.000 indicating perfect linearities.

The accuracy of the proposed procedures were found to be 99.1–100.6% (Table 4). Repeatability was evaluated by determining different concentrations of each drug for three times within the same day, where R.S.D. values were 0.93–1.75%. Also the reproducibility was evaluated over a period of 6 months and interday precision range from 0.51 to 3.29%.

The limit of detection (LOD) does not exceed 3.65 μg ml$^{-1}$ for all the proposed chelates, whereas the limit of quantitation (LOQ) was between 0.74 and 12.17 μg ml$^{-1}$ (Table 4).

### 3.5. Rugedness

Peaks shape remained visually acceptable throughout the assay and the interday R.S.D. did not exceed 3.3% over a period of 6 months, proving that the proposed chelation procedures were precise and accurate.

Table 5
Determination of PNZ-sodium in laboratory-prepared mixtures with its degradate, sulfenic acid derivative by the proposed Fe-chelation procedure

| Intact taken (μg ml$^{-1}$) | Degraded taken (μg ml$^{-1}$) | Degraded (%) | Found (μg ml$^{-1}$) | Recovery of intact (%) |
|---|---|---|---|---|
| 270 | 30 | 10 | 275.4 | 102.0 |
| 240 | 90 | 30 | 207.7 | 98.9 |
| 180 | 120 | 40 | 179.8 | 99.9 |
| 150 | 150 | 50 | 180.2 | 100.1 |
| 90 | 210 | 70 | 91.7 | 101.9 |
| 60 | 240 | 80 | 65.7 | 109.5[a] |
| Mean + S.D. | | | 100.6 ± 1.35% | |

[a] Rejected.

Table 6
Results of the determination of OMZ and PNZ-sodium by the proposed chelation procedures in their dosage forms compared with reference methods (16,18)[a]

| | Recovery + S.D.% | | | | |
|---|---|---|---|---|---|
| | OMZ-Fe (III) | OMZ-Cr (III) | OMZ-Co (II) | PNZ Sodium Fe (III) | Reference methods[a] |
| Gastrazole capsules | 97.2 ± 1.09<br>F = 1.35 (6.39)<br>t = 1.34 (2.31)<br>(n = 5) | 99.7 ± 1.78<br>F = 3.58 (6.39)<br>t = 1.78 (2.31)<br>(n = 5) | 98.7 ± 1.58<br>F = 2.83 (6.39)<br>t = 0.73 (2.31)<br>(n = 5) | | 98.1 ± 0.94 (16)<br>(n = 5) |
| Standard addition | 100.1 ± 1.05 | 98.9 ± 1.15 | 99.5 ± 0.26 | | |
| Gasec Caps. | 99.6 ± 1.89<br>F = 5.44 (6.39)<br>t = 0.34 (2.31)<br>(n = 5) | 100.3 ± 1.14<br>F = 1.98 (6.39)<br>t = 0.15 (2.31)<br>(n = 5) | 98.9 ± 1.41<br>F = 3.03 (6.39)<br>t = 1.79 (2.31)<br>(n = 5) | | 100.2 ± 0.81 (16)<br>(n = 5) |
| Standard addition | 100.0 ± 0.71 | 99.6 ± 0.86 | 100.3 ± 1.03 | | |
| Napizole pellets | 98.0 ± 1.79<br>F = 3.02 (6.39)<br>t = 2.17(2.31)<br>(n = 5) | 98.8 ± 0.49<br>F = 4.60 (6.39)<br>t = 1.98 (2.31)<br>(n = 5) | 98.7 ± 1.49<br>F = 2.09 (6.39)<br>t = 1.61 (2.31)<br>(n = 5) | | 100.0 ± 1.03 (16)<br>(n = 5) |
| Standard addition | 99.3 ± 0.87 | 98.4 ± 1.07 | 100.0 ± 1.06 | | |
| Controloc tablets | | | | 98.5 ± 0.61<br>F = 3.25 (9.28)<br>t = 2.08 (2.45)<br>(n = 4) | 99.6 ± 1.10 (18)<br>n = 4 |
| Standard addition | | | | 99.6 ± 0.80 | |
| Pantoloc tablets | | | | 97.8 ± 1.34<br>F = 1.48 (6.59)<br>t = 2.28 (2.37)<br>(n = 5) | 99.6 ± 1.10 (18)<br>n = 4 |
| Standard addition | | | | 97.6 ± 0.84 | |

The figures in parentheses are the tabulated F and t values at 95% confidence level.
[a] A direct UV measurements of OMZ (16) in NaOH at λmax 305 nm or charge transfer complexation of PNZ sodium with DDQ (18) in acetonitrile and measuring the absorbance of the product at 457 nm.

### 3.6. Specificity and selectivity

The selectivity of the proposed procedure for PNZ-Sodium was vertified by direct determination of the intact drug in mixtures with its degradate, sulfenic acid in different ratios. It is clear from Table 5 that chelation of PNZ-sodium with Fe (III) can be used for stability indication, were an accuracy of 100.6 ± 1.35% was obtained in presence of up to 70% sulfenic acid degradate.

Also, no interference was observed from OMZ or lansoprazole (other benzimidazole related drugs) since they are water insoluble.

In addition the determination of OMZ through chelation with Cr (III) and Co (II) was free of interference by PNZ-sodium which gave negative reaction with these two metal ions. Unfortunately the procedure of OMZ chelation in ethanol is non-specific concerning the presence of its degradation product (sulfenamide) which is ethanol soluble and interferes with the absorbance of the formed chelates.

Moreover, the selectivity of the proposed procedures was checked by direct analysis of each drug is its dosage forms the results obtained for OMZ and PNZ-sodium confirm non-interference by excipients and additives (Table 6).

### 3.7. Application of the proposed procedures

The proposed chelation procedures have been successfully applied to quantitate OMZ and PNZ-

sodium in their different dosage forms (capsules, pellets or tablets) where the percentage recovered ranged between 97.2 and 100.3%. The validity of the proposed procedures was further assessed by applying the standard addition technique; good recoveries of added were obtained (Table 6). Compared with reference methods [16,18]), the results were of equal accuracy and precision and no significant differences were observed within a probability of 95% of being correct; (Table 6).

## 4. Conclusion

Only OMZ is official by non-selective titrimetic method with standard NaOH In B.P. [2]. Most of the reported methods are HPLC [5–10] which require elaborate and sophisticated instrumentation. The electrochemical methods are less sensitive [4,13]. In addition the conventional UV methods [15,16] suffer from interference due to UV absorbing compounds in the determination of the cited drugs. The few reported visible spectrophotometric methods are mainly concerned with charge transfer complexation with different electron acceptors, which give similar reaction with all basic compounds or concerned with the reducing activity of OMZ [17–19].

However, the proposed procedure for PNZ sodium is a stability-indicating one which can be used for evaluating the extent of its degradation in dosage forms. Moreover, it can be used to determine PNZ-Sodium in presence of related drugs, OMZ and lansoprazole without interference; the latter two drugs being water-insoluble. For OMZ, although it cannot be used for stability indication, yet it can be considered as more selective than the reported ones in determining the structural ability of the studied drugs to chelate certain metal ions.

In addition, such chelation may be of special importance as it may affect the bioavailability of the cited drugs through complexation with metal ions in biological fluids [24].

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