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First-order UV-derivative spectrophotometry in the analysis of omeprazole and pantoprazole sodium salt and corresponding impurities

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Abstract

The first-order UV-derivative spectrophotometry, applying zero-crossing method was developed for the determination of omeprazole (OM), omeprazole sulphone (OMS), pantoprazole sodium salt (PANa), and *N*-methylpantoprazole (NPA) in methanol–ammonia 4.0% v/v, where the sufficient spectra resolutions of drug and corresponding impurity were obtained, using the amplitudes $^1D_{304}$, $^1D_{307}$, $^1D_{291.5}$ and $^1D_{296.5}$, respectively. Method showed good linearity in the ranges (μg ml^{-1}): 1.61–17.2 for OM; 2.15–21.50 for OMS; 2.13–21.30 for PANa and 2.0–20.0 for NPA, accuracy and precision (repeatability and reproducibility). The experimentally determined values of LOD (μg ml^{-1}) were 1.126; 0.76; 0.691 and 0.716 for OM, OMS, PANa and NPA, respectively. The obtained values of 2.91% w/w for OMS and 3.58% w/w for NPA in the presence of their parent drug, by applying the method of standard additions, point out the usage of the proposed method in stability studies. Zero-crossing method in the first-order derivative spectrophotometry showed the impurity–drug intermolecular interactions, due to the possible intermolecular hydrogen bonds, confirmed by divergences of experimentally obtained amplitudes for impurities OMS and NPA in comparison to expected values according to regression equations of calibration graphs.

Keywords: First-order derivative UV spectrophotometry; Zero-crossing method; Omeprazole; Pantoprazole sodium; Impurities; Intermolecular interactions

1. Introduction

The final step in the pathway for acid secretion from the parietal cell into the gastric lumen is the so-called 'proton pump'. The proton pump is an active transport system that is powered by the enzyme H^+/K^+-ATPase, which catalyzes the

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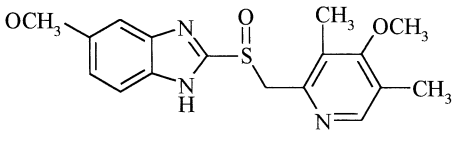
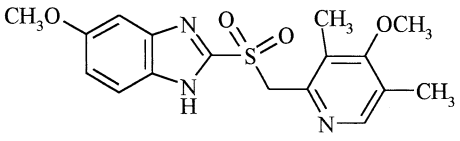
exchange of intra-cellular hydrogen ions for extracellular potassium ions. The inhibition of the proton pump will prevent acid secretion from the parietal cell [1].

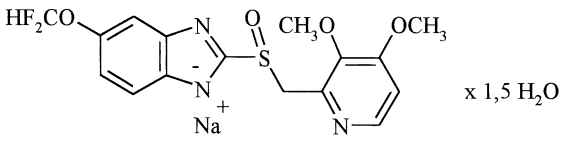
Omeprazole (OM) 5-Methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole and pantoprazole 5-(Difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole, in the form of pantoprazole sodium sesquihydrate (PANa) presented in Fig. 1, are two irreversible proton pump inhibitors (PPIs). The benzimidazole PPIs are essentially the prodrugs, that in the acidic biophase of the parietal cell form an active metabolite that irreversibly interact with an essential thiol (SH) function on ATPase of the pump.



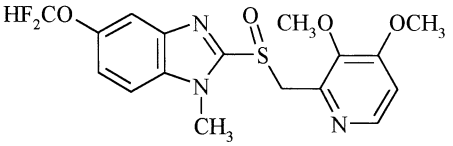
omeprazole (OM)



omeprazole sulphone (OMS)



pantoprazole sodium (PANa)



N-methylpantoprazole (NPA)

Fig. 1. Chemical structures of investigated PPIs and corresponding impurities.

OM is an amphoteric compound (pyridine N, pK_a 3.97, benzimidazole N–H, pK_a 8.70), it is acid labile, formulated as delayed-release capsules containing enteric coated granules or as gastro-resistant tablets. The review of pharmacology and clinical efficacy in the control of ulcer, reflux oesophagitis and Zollinger–Ellison syndrome has been published [2].

Different analytical methods, several HPLC procedures for determination of OM in biological fluids [3–6], HPLC with coulometric detection [7], spectrophotometry [8], polarography [9–11], voltammetry [12], capillary electrophoresis [13] and thin-layer chromatography [14,15] have been developed for the determination of OM.

For pantoprazole sodium, which is a non-official drug substance [16], the review of pharmacology, clinical efficacy and tolerability [17], as well as the similarities and differences between pantoprazole and other PPIs: OM, lansoprazole and rabeprazole [18] have been published recently. Several literature data concerning HPLC determination of pantoprazole in serum and plasma [19] and in tablet dosage forms [20], enantioselective separation of OM and three analogues on different chiral stationary phases [21], as well as chiral resolution of pantoprazole sodium and related sulfoxides by capillary zone electrophoresis using bovine serum albumin as the chiral selector [22] and enantiomeric determination of pantoprazole by multidimensional. HPLC [23] have been reported. Recently, pantoprazole sodium and lansoprazole have been determined by spectrophotometric procedures: two methods based on charge transfer complexation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and iodine, and the third method depending on ternary complex formation with eosin and copper(II) [24].

In the last years, derivative techniques in UV spectrophotometry have been used as separative methods for the analysis of drug mixtures, determination of degradation products, as well as in stability studies. The first literature data, on the determination of OM in pharmaceuticals by second-order UV-derivative spectroscopy in borate buffer (pH 10.0; 0.1 M) has been reported by Özaltin and Koçer [25] and later for lansoprazole [26]. Castro et al. [27], used first-order derivative

spectrophotometric method for the determination of OM in aqueous solutions during stability studies. OM has also been determined in presence of its photodegradation products by derivative spectrophotometry and complex formation [28]. Wahbi et al. [29] recently reported the compensation method and other chemometric methods (derivative, orthogonal function and difference spectrophotometry) for determination of OM, lansoprazole and pantoprazole in pharmaceutical formulations and the assay of drugs in presence of acid induced degradation products.

Since the previously published data [27–29] concerned the determination of OM and pantoprazole in the presence of their degradation products, the goal of this paper was to investigate the application of derivative spectrophotometry, using zero-crossing method, in the first-order spectra for the analysis of impurities—degradation products in the presence of their parent drug. The impurities (Fig. 1) omeprazole sulphone (OMS) 5-methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulphonyl]-1*H*-benzimidazole is defined as impurity D in Ph. Eur. 4th (specification allow 0.1% w/w) and *N*-methylpantoprazole (NPA) (B8810-044) specification allow 0.2% w/w, have been investigated.

2. Experimental

2.1. Apparatus

Absorption and derivative spectra were recorded over the wavelength range 230–430 nm in 1 cm quartz cells using a GBC UV/Visible spectrophotometer Cintra 20 (GBC Scientific Equipment Pty Ltd, Dandenong, Australia) with data processing Spectral Software Ver. 1.70a, The zero-order spectra were recorded at a scan speed 120 nm min^{-1} and the fixed values of slit width and data interval of 1 and 0.5 nm, respectively, The first-order derivative spectra were calculated using Savitzky–Golay algorithm.

2.2. Reagents and solutions

The OM reference standard was obtained from pharmaceutical company Alkaloid, Skopje, Macedonia, and for the impurity OMS pharmacopoeias standard catalog No. O0151000 Strasburg, France was used. The pantoprazole sodium salt and impurity NPA (B8810-044) reference standards were purchased from BYK Gulden-Konstanz, Germany, HPLC grade methanol and ammonia solution, concentrated (25%) were purchased from Merck (Darmstadt, Germany).

Freshly prepared stock solutions in methanol of OM (0.1075 mg ml^{-1}); OMS (0.215 mg ml^{-1}); PANa (0.1065 mg ml^{-1}) and NPA (0.10 mg ml^{-1}) were used in the procedures for calibration cures.

2.3. Procedure for calibration curves

In each of seven volumetric flasks of 10 ml, 0.40 ml of ammonia solution, concentrated was transferred, the aliquots: OM (0.15–1.60 ml); OMS (0.10–1.00 ml); PANa (0.20–2.00 ml) and NPA (0.20–2.00 ml) were added and solutions diluted to the mark with methanol. Zero-order spectra were recorded using aforementioned instrumental parameters. First-order derivative spectra were calculated using selected value of 15 for smoothing points. The values of the analytical amplitudes $^1D_{304}$, $^1D_{307}$, $^1D_{291.5}$ and $^1D_{296.5}$ for OM; OMS; PANa and NPA, respectively, were read out.

3. Results and discussion

Due to the structural similarity of the impurities to the corresponding parent drug, particular consideration was paid to the selection of solvent in which the sufficient spectra resolution could be obtained for the application of zero-crossing method. The spectra of OM and OMS in methanol entirely overlap, as well as their first- and second-order derivative spectra. The corresponding zero-order spectra of PANa and NPA in methanol showed insufficient resolution, that was confirmed with the same wavelengths of the zero-crossing (λ_{zc}) in the first-order derivative spectra. It has been confirmed, that in higher order derivative

spectra resolution enhancement is obtained with more λ_{zc} points [30,31]. The second-order derivative spectra of PANa and NPA showed better resolution, but the amplitude at λ_{zc} points were too low for quantitative analysis for the further studies, For all mentioned reasons, methanol as an amphiprotic solvent was eliminated.

The previously reported results by Lagerström and Persson [3] showed in the stability studies of OM that it could be stored at pH 7.5–10.0 for 4 days at room temperature without any degradation. The results of Castro et al. [27] demonstrated that the application of amplitude $^1D_{313}$, due to its decrease, could be used for quantitation of OM after 10% of its degradation (presence of NaOH, further addition of Borate buffer pH 8, and storage at 37 °C for 6 h), but no resolution of spectra of OM standard and 10% decomposed OM solution has been obtained.

Regarding these investigations our further experiments in the selection of solvent for spectra resolution were to evaluate the addition of ammonia to methanol solutions of drugs and corresponding impurities. Three different methanol–NH_3 v/v% (1.8; 4.0 and 8.0%) have been investigated. The best resolution and maximal stability (up to 48 h) for both OM and PANa, as well as of their impurities have been obtained in methanol–NH_3 4.0% v/v (pH* 9.0), and thus this solvent was defined as the working solvent. Addition of ammonia caused bathochromic shift of 6 nm for both OM and PANa (Fig. 2(A)) and the shift for OMS was 3 nm, in comparison to spectra in methanol, since the substances are in ionic form. No shift for NPA (Fig. 2(B)) was observed, probably due to the presence of methyl group on position N-1, which with its positive inductive effect resonantly stabilized the molecule. The overlaid zero-order spectra (A), as well as the first-order derivative spectra (B) of OM and OMS (Fig. 3) in the working solvent showed the resolution of 3 nm. This resolution was sufficient regarding the selected values of slit width 1.0 nm and data interval of 0.5 nm for accurate amplitude recording. The higher difference of 5 nm between the wavelengths of zero-crossing points (λ_{zc}) for PANa and NPA was obtained (Fig. 2(C)). In the first-order derivative UV spectra the selectivity of the proposed method is defined according to λ_{zc} of investigated drugs and corresponding impurities OM, OMS, PANa and NPA as 307, 304, 296.5 and 291.5 nm, respectively. The used analytical amplitudes in accordance to λ_{zc} with notation proposed by Fasanmade and Fell [30], for OM, OMS, PANa and NPA were $^1D_{304}$, $^1D_{307}$, $^1D_{291.5}$ and $^1D_{296.5}$, respectively.

3.1. Linearity

Linearity was evaluated separately for each investigated drug and separately for corresponding impurity, using the defined analytical amplitudes, with appropriate seven standard solutions. Statistical analysis of the experimental data: regression equations from the calibration graphs, along with standard error of the intercept (S_a) and slope (S_b) are summarized in Table 1. The precision of the slope relative to its size was also evaluated by calculating the relative standard error of the slope (Sb_{rel} (%) Table 1) according to the following equation: $Sb_{rel}(\%) = S_b/b \times 100$, where S_b is the standard error of the slope. Proportionality was achieved since zero was between the confidence limits $a \pm tS_a$ for intercept (t value at $P = 0.01$ two-tailed values, and with $n-2$ degree of freedom). The high values of the determination coefficients (r^2) indicated good linearity of the calibration graphs for all investigated substances.

3.2. Precision and accuracy

Repeatability was calculated by assaying 10 samples of the 100% standard concentrations μg ml^{-1}) of 8.60; 10.75; 10.65 and 10.00 for OM, OMS, PANa and NPA, respectively, The recoveries ranged from 99.44 to 100.84% and the RSD values for the analytical amplitudes were in the range 0.72–1.07%. The reproducibilities were calculated by comparing the results obtained for two different concentrations ($n = 6$) within 3 days (Table 2). The RSD values obtained using the proposed analytical amplitudes were similar to the ones reported for the first derivative spectrophotometric method developed for OM determination during stability studies [27] and to those accomplished in other derivative spectrophotometric

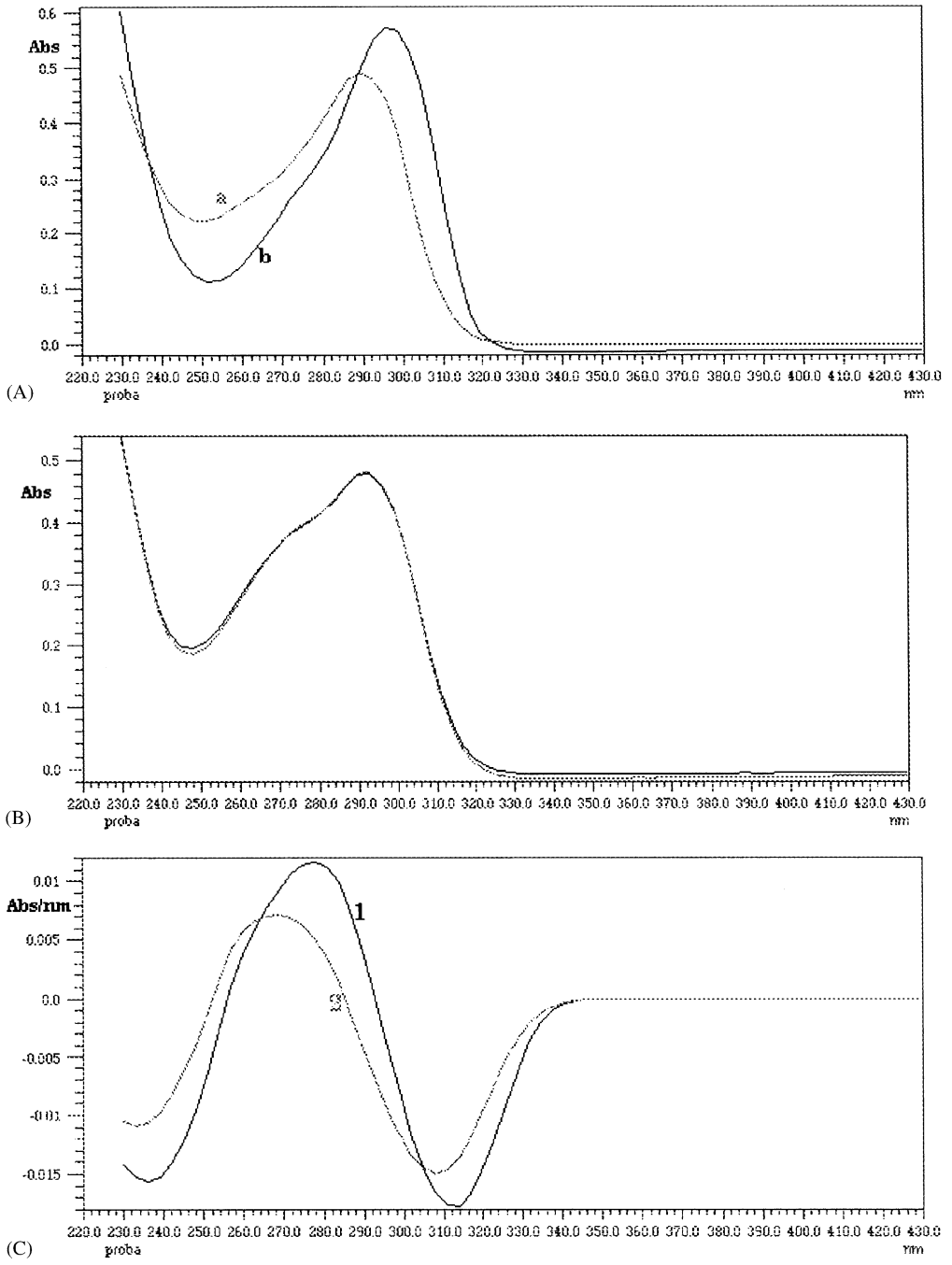


Fig. 2. (A) Zero-order spectra of PANa (12.60 μg ml^{-1}) in methanol (a) and in the working solvent (b); (B) Entirely overlapped zero-order spectra of NPA (12.90 μg ml^{-1}) in methanol and in the working solvent; (C) Overlaid first-order derivative spectra of PANa (curve 1) and NPA (curve 2) at aforementioned concentrations.

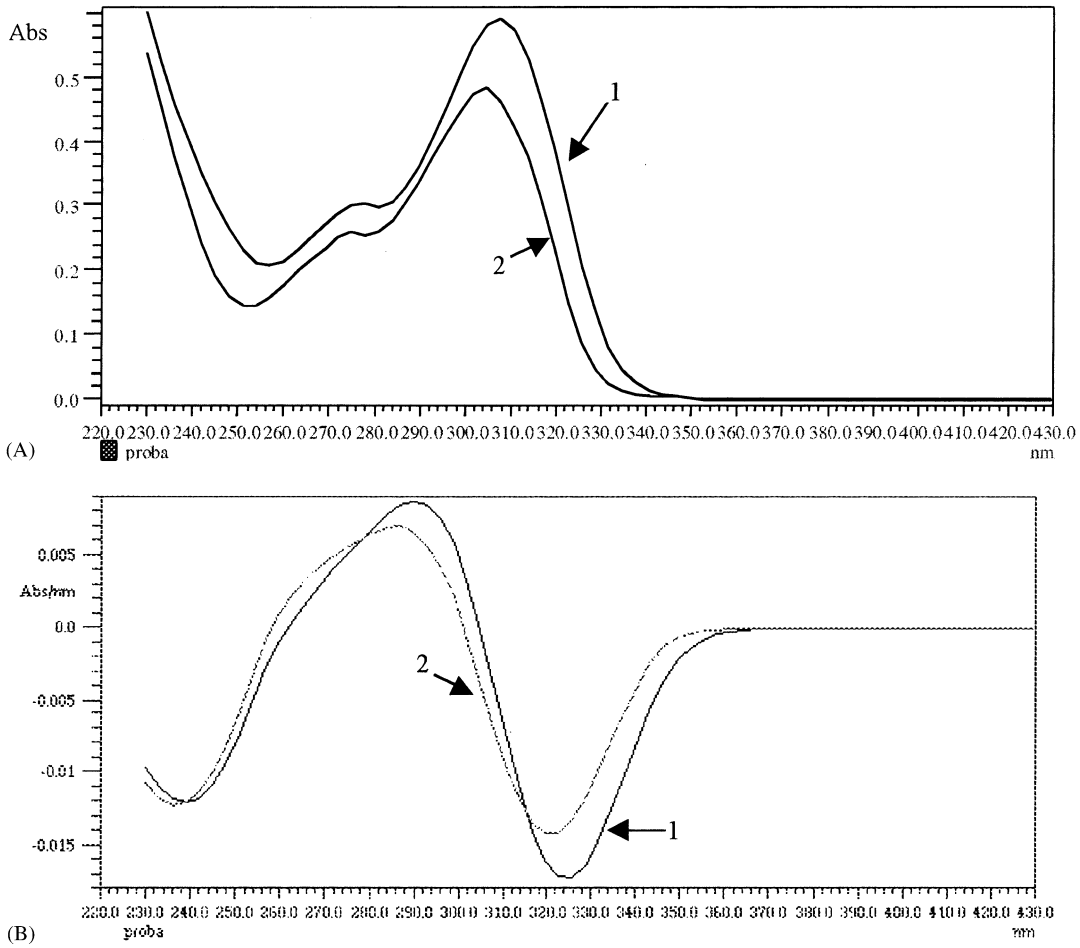


Fig. 3. (A) Overlaid zero-order spectra of OM (curve 1; 8.64 μg ml^{-1}) and OMS (curve 2; 10.75 μg ml^{-1}) in the working solvent. (B) Overlaid first-order derivative spectra of OM (curve 1) and OMS (curve 2) at the same aforementioned concentrations.

Table 1
Analytical data of the calibration graphs

Substance	Linearity range (μg ml^{-1})	Regression equation	S_a	S_b	Sb_{rel} (%)
OM	1.61–17.2	$^1D_{304} = 4.83 \times 10^{-6} + 6.77 \times 10^{-4}$ c ($r^2 = 0.9997$)	4.64×10^{-5}	4.99×10^{-6}	0.74
OMS	2.15–21.50	$^1D_{307} = 2.53 \times 10^{-4} + 8.76 \times 10^{-4}$ c ($r^2 = 0.9998$)	6.56×10^{-5}	4.85×10^{-6}	0.55
PANa	2.13–21.30	$^1D_{291.5} = -1.01 \times 10^{-4} + 0.0011$ c ($r^2 = 0.9999$)	3.71×10^{-5}	3.32×10^{-6}	0.30
NPA	2.0–20.0	$^1D_{296.5} = 2.91 \times 10^{-4} + 7.96 \times 10^{-4}$ c ($r^2 = 0.9994$)	9.87×10^{-5}	9.14×10^{-6}	1.15

Table 2
Inter-day reproducibilities ($n = 6$)

Substance	Taken ($\mu g\ ml^{-1}$)	Found $\pm$ SD ($\mu g\ ml^{-1}$)	RSD (%)
OM	6.45	6.41 $\pm$ 0.05	0.78
	12.90	12.87 $\pm$ 0.08	0.62
OMS	5.37	5.38 $\pm$ 0.05	0.93
	16.13	16.12 $\pm$ 0.09	0.56
PANa	7.45	7.46 $\pm$ 0.06	0.80
	15.97	15.89 $\pm$ 0.12	0.76
NPA	5.00	4.94 $\pm$ 0.05	1.01
	15.00	15.09 $\pm$ 0.13	0.86

methods also applying the zero-crossing technique to the first-order derivative spectra [32].

3.3. Limits of detection and quantification

The experimental detection limits LOD were determined using the following concentrations ($\mu g\ ml^{-1}$) 1.6125 for OM; 2.15 for OMS; 2.10 for PANa and 2.15 for NPA. For the impurities OMS and NPA the signal to noise ratios were found as 8.5 and 9.0, respectively. Experimentally obtained values of LOD ($\mu g\ ml^{-1}$), defined as the analyte signal which is three times higher in comparison to measured noise signal (in λ range 430–340 nm), were: 1.126; 0.76; 0.691 and 0.716 for OM, OMS, PANa and NPA, respectively. The values of LOQ ($\mu g\ ml^{-1}$), calculated as three times LOD values were: 3.378; 2.28; 2.073 and 2.148 for OM, OMS, PANa and NPA, respectively. The experimentally determined LOQ values ($\mu g\ ml^{-1}$) were very close to the calculated ones: 3.225, 2.15; 2.13 and 2.00 for OM, OMS, PANa and NPA, respectively, These LOQ values were confirmed and accepted with the values of RSD ($n = 6$): 2.30, 1.40; 1.66 and 1.21% obtained for the analytical amplitudes $^1D_{304}$, $^1D_{307}$, $^1D_{291.5}$ and $^1D_{296.5}$, respectively, since the obtained values were lower than 2.5%.

The calculated LOD values [33] were obtained according to the regression equations, defined as the concentration of the analyte giving a signal equal to the blank signal $y_B (= a)$, plus three standard deviations of the blank, $S_B (= S_{y/x})$, $y = y_B + 3S_B$. These calculated values ($\mu g\ ml^{-1}$) were significantly lower: 0.31; 0.29; 0.15 and 0.56 for OM, OMS, PANa and NPA, respectively, but they could be considered only as the theoretical values.

3.4. Assay of impurities in the presence of the parent drug and intermolecular drug–impurity interactions

Considering the experimentally determined values of LOD for impurities, the specification for impurity levels of 0.1% w/w for OMS and 0.2% w/w for NPA (reaching the impurity/drug ratios of 1:1000 and 1:500 for OMS and NPA, respectively) and the absorbance values significantly higher than 1.0 in the samples of the mixtures of drug and impurity (LOD), only the application of the method of standard additions [33] could be considered for the impurity determination in the presence of parent drug.

In the presence of constant OM concentration of 17.20 $\mu g\ ml^{-1}$, the standard curve ($n = 5$) for OMS determination with the test mixture sample of untraceable 0.0172 $\mu g\ ml^{-1}$ (0.1% w/w) of OMS and in the next four mixture samples with increasing OMS concentrations in the range 3.672–6.682 $\mu g\ ml^{-1}$ (with constant 0.0172 $\mu g\ ml^{-1}$ of OMS) gave regression equation $^1D_{307} = 3.802 \times 10^{-4} + 7.549 \times 10^{-4}$ c ($r = 0.981$). The concentration that could be detected in the test mixture sample x_c is given by the intercept on the x-axis as the ratio of y-axis intercept and the slope of the regression equation ($x_c = a/b$) was 0.5035 $\mu g\ ml^{-1}$, equivalent to 2.93% w/w of OMS, and was established as the sensitivity of the proposed method. This sensitivity was experimentally confirmed in the next standard curve ($n = 7$) for test OMS concentration of 0.5040 $\mu g\ ml^{-1}$ (2.87% w/w) at constant OM concentration of 17.52 $\mu g\ ml^{-1}$ and the range of OMS increasing concentrations from 2.0265 to 9.5340 $\mu g\ ml^{-1}$ (including tested OMS concentration). The obtained regression equation was $^1D_{307} = 3.268 \times 10^{-4} + 6.415 \times 10^{-4}$ c; $r = 0.985$, and since obtained $x_c = 0.5096$ $\mu g\ ml^{-1}$, with recovery of 101.1%, confirmed value of 2.91% w/w of OMS determination in presence of OM.

The corresponding studies for NPA determination using the method of standard additions were performed in the similar way. The standard curve

($n = 8$) with the constant PANa concentration of 12.78 μg ml^{-1}, test untraceable NPA concentration of 0.026 μg ml^{-1} and with increasing NPA concentrations in the range 2.026–11.026 μg ml^{-1}, gave the regression equation $^1D_{296.5} = 3{,}718 \times 10^{-4} + 8.153 \times 10^{-4}$ c ($r = 0.9993$) and determined sensitivity as the value of $x_c = 0.456$ μg ml^{-1} equivalent to 3.57% w/w of NPA was attained. This value was experimentally confirmed in the next standard curve ($n = 8$), with constant 12.78 μg ml^{-1} of PANa, added NPA to the test mixture sample to reach the concentration of 0.46 μg ml^{-1} (3.60% w/w), and NPA concentrations in the range 2.46–11.135 μg ml^{-1} in the next mixture sample solutions. From the regression equation $^1D_{296.5} = 3.9565 \times 10^{-4} + 8.6364 \times 10^{-4}$ c ($r = 0.9981$) the calculated value for $x_c = 0.4581$ μg ml^{-1}, with recovery of 99.59%, confirmed sensitivity of 3.58% w/w of NPA determination in presence of PANa.

The lower correlation coefficients values, obtained for both OMS and NPA determination in the standard curves using the method of standard additions, could be explained with the performed studies on possible impurity–drug interactions under used experimental conditions. For the both pair of impurity and drug, seven artificial mixtures with different ratios of OMS/OM and NPA/PANa were analyzed and the recorded $^1D_{307}$ and $^1D_{296.5}$ (defined as y_{exp}) were match up to the expected—calculated amplitudes (defined as y_{calc}) for OMS and NPA from their calibration graphs (Table 3). More significant divergences were established for OMS/OM mixtures (even in the mixtures with the ratios between 1:1.60 up to 1:8.70), that is in accordance with higher dispersion obtained for the method of standard additions. Due to the lower divergences for pair NPA/PANa (up to ratio 1:10), better linearity and recovery for NPA determination applying the method of standard additions was accomplished. The differences between y_{exp}, and y_{calc}, particularly for the higher impurity/drug ratios probably could be elucidated due to the positive and negative charges in the resonance structures of parent drug and corresponding impurity that caused intermolecular interactions possible intermolecular hydrogen bonds. It is important to point out, that if such intermolecular interactions are noticed, the signal of the impurity in the dual mixture drug/impurity is not obeying Lambert–Beer law for the whole range of concentration stated as the linearity domain. Due to this it is essential for impurity determination to apply its appropriate increasing concentrations (for the method of standard additions), which are within the calibration range, but these, should be also in the range of drug/impurity ratios where the measured and calculated signal are approximately the same. The application of the method of standard additions could suppress the mentioned interactions by altering the impurity/drug ratios and therefore should be used for OM and PANa stability studies analysis. The determined x_c values in the test mixture sample solutions for OMS and NPA were lower than the experimentally determined LOD of about 33 and 34%, respectively, and were approximate to calculated LOD values, as expected for the mentioned method.

In conclusion it may be considered that the obtained impurity levels of 2.91% w/w for OMS in the presence of OM and 3.58% w/w for NPA in the

Table 3
Intermolecular interactions in artificial mixtures of OMS/OM and NPA/PANa with different concentration ratios

Artificial mixture	Ratios of OMS/OM	Divergences of (y_{exp}) and (y_{calc}) for $^1D_{307}$	Ratios of NPA/PANa	Divergences of (y_{exp}) and (y_{calc}) for $^1D_{296.5}$
1	1:1000	$y_{exp} = 2.50\ y_{calc}$	1:500	$y_{exp} = 1.50\ y_{calc}$
2	1:8.70	$y_{calc} = 3.95\ y_{exp}$	1:280	$y_{exp} = 3.30\ y_{calc}$
3	1:4.40	$y_{calc} = 1.90\ y_{exp}$	1:170	$y_{exp} = 3.50\ y_{calc}$
4	1:3.00	$y_{calc} = 1.70\ y_{exp}$	1:100	$y_{exp} = 3.80\ y_{calc}$
5	1:1.80	$y_{calc} = 1.40\ y_{exp}$	1:10	$y_{exp} = 1.20\ y_{calc}$
6	1:1.60	$y_{calc} = 1.40\ y_{exp}$	1:5	$y_{exp} = 1.20\ y_{calc}$
7	1:1	$y_{calc} = y_{exp}$	1:1	$y_{calc} = y_{exp}$

presence of PANa, by means of the proposed zero-crossing method in the first-order derivative spectrophotometry, applying the method of standard additions, could be used as stability-indicating method of OM and PANa. The achieved results also confirmed that derivative spectrophotometry, using zero-crossing method, could be used to analyze possible pH induced impurity–drug or drug–drug interactions.

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