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Ratio spectrum derivative quantitative analysis of propranolol and diazipam in combind pharmaceutical mixtures

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ABSTRACT

Two new spectrophotometric methods were developed for the simultaneously estimation of DZP and PRO using the first ratio derivative method (DD1) and the second ratio derivative (DD2). The two methods were succeeded to the estimation of both drugs with a range of concentrations from (5-50 μg.ml^{-1}), depending on Peak to baseline, peak area, peak to peak at specific wavelengths for each compound. The analytical results and of the estimate of The DZP and PRO showed that Rec% values ranged from 95.04-104.97% and 96.30-104.69, and RSD% were between 0.00948-4.87736 % and 0.1163-3.37655%, for the first and second ratio derivative respectively. The method has been successfully applied to the estimation of both PRO and DZP in its pharmaceuticals forms.

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INTRODUCTION

Propranolol Hydrochloride PRO showed in Figure 1 A, (Rani *et al.*, 2011). Chemically is (1-ispropylamino-3-(1-naphthyloxy)-2-propranolol hydrochloride). The Molecular formulation and Molecular mass are $C_{16}H_{21}NO.HCL$, and 295.8 g/mol, respectively (Patel *et al.*, 2011a). It is sold on beneath the trademark names among others Inderal, It is used to remedy hypertension, thyrotoxicosis, capillary hemangiomas, a number of types of irregular heart rate, It is applied as to prohibit migraine headaches, and to prohibit heart attacks (Ghaibi *et al.*, 2015; Davidson, 2006; Chinnadurai *et al.*, 2016). Propranolol is a widely used beta-blocker (Al-Majed *et al.*, 2017).

Diazepam DZP as in Figure 1 B Chemically (7-Chloro-1, 3-dihydro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2-one). The Molecular formulation and Molecular mass are $C_{16}H_{13}CIN_2O_1$, and 284.75g/mol, respectively (Srivastava, 2016). Diazepam, utmost usually known by its trade name valium, It is usually used to remedy a wide range of terms including disquiet, insomnia (Pharmacopoeia, 2009). It is routinely prescribed as the standard first-line remediation for acute convulsions and prolonged condition epilepticus (Shorvon *et al.*, 2015). The combination of Diazepam and Propranolol hydrochloride has been shown to be efficient in the administration of chronic disquiet (Sweetman, 2009). There are many methods used to simultaneously estimation of both drugs. These methods are first derivative spectroscopy (Patel *et al.*, 2011b). RP-HPLC Pydiratnam *et al.* (2013). Ratio absorbance method (Q absorbance) (Patel *et al.*, 2011a). One of both drugs combined with other components was estimated simultaneously, like partial least squares for determination of DZP with Carfelol, furosemide and carbamazepine (Mohammed and Alassaf, 2016).UPLC-MS/MS for the determination of DZP with Bromazepam and Clonazepam (Musaab *et al.*, 2018). Quantitative estimation of PRO in pure

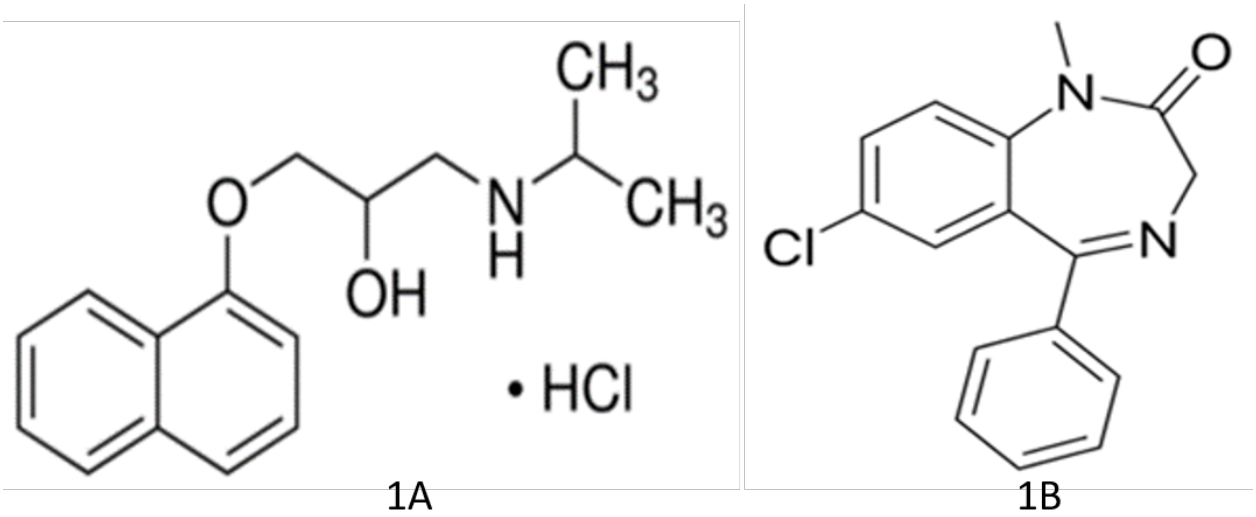

Figure 1: A) Structure of Propranolol Hydrochloride; B) Structure of Diazipam

form and in human urine conducted by using the Ultraviolet spectrum (Araujo *et al.*, 2019). A new spectrophotometric mode depending on the oxidative coupling reaction was developed (Mohammed *et al.*, 2018). Ion Pair method was proposed for estimation of various Drugs include PRO with Bromocresol green and Bromothymol Blue (Mahesh *et al.*, 2019), RP-HPLC mode for the Simultaneous Estimation of Propranolol and Hydralazine was conducted (El-Didamony *et al.*, 2015).This research aims to develop a simalteuous spectrophotometric mode for determination of PRO and DZP in their pharmaceutical mixtures depending on Ratio spectrum derivative, especially as there is not like work through the investigation in the available literatures.

MATERIALS AND METHODS

Practical part

Instruments

To record the absorption spectra for all measurements, the ultraviolet-visible double-beam instrument produced by Shimadzu model 1650, equipped with1cm quartz cells, using a wavelength of 190-400 nm, medium scan speed, a sampling interval 0.1 nm and slight width 2 nm and Ultrasound water bath produced by Lab Tech-Korea.

Chemicals

Pure Materials

The pure analytical grade Propranolol was obtained from Hubei-china company, Diazepam from The Dijla Pharmaceutical Company Samarra - Iraq of Indian Origin, Pure Ethanol C_2H_5OH from Local markets of French origin.

Pharmaceutical Preparations

Indicardin pharmaceutical was10 mg produced by The Arab Pharmaceutical Company M.M. Salt – Jordan. Valiapam 5 mg produced by the state company for the drugs industry and Medical Appliances (SDI) Samarra. Iraq were used in this study.

Stored Standard Solutions

1000 μg.ml^{-1} of the standard material for both PRO and DZP was prepared by dissolving 0.1 g of each substance in a 100 ml volumetric flask using ethanol as a solvent and completed the volume to the mark with the solvent itself, and then the working solutions were prepared with sequential dilution as needed.

Procedure

After the preparation of the standard concentrated work's solution (100 μg.ml^{-1}) of a storage solution (1000 μg.ml^{-1}), a set of concentrations ranging from (5-50μg.ml^{-1}) was prepared by a sequential dilution in the presence of a constant concentration of PRO (15 μg.ml^{-1}). In the same procedure (5-50 μg.ml^{-1}) of PRO were prepared in the presence of a constant concentration of DZP (7 μg.ml^{-1}), using 10 ml volumetric flask. The zero spectrum was recorded between 190-400 nm and kept on the computer. The spectra of the mixtures were divided into the spectrum of the devisor to obtain the relative spectrum of each drug. PRO and DZP. Then the ratio derivative spectrum was derived to the first and second ratio derivatives at $\Delta\lambda$= 20 nm, scaling factor = 8 nm, the width of slit =2 and Sampling interval at 2 nm.

Absorption Spectrum

A set of solutions 1-100 μg ml^{-1} for DZP and 5-75

μg.ml^{-1} of PRO were prepared. A wavelength survey of 190-400 nm to draw its zero spectrum was conducted. The maximum wavelength of DZP was 315nm and 292 nm for PRO. The spectra of their mixtures containing either (5-50 μg.ml^{-1}) of PRO and a constant concentration of 7 μg.ml^{-1} of DZP divided by spectrum of 7 μg.ml^{-1} or 5-50 μg.ml^{-1} DZP and a fixed concentration of 15 μg.ml^{-1} of PRO divided by spectrum of 15 μg.ml^{-1} to obtain the ratio spectra for both PRO and DZP respectively. Then the ratio spectra were derived to obtain the first and second ratio derivative spectra of both compounds.

Calibration Curves Construction

Calibration curves were constructed using peak to baseline, peak area and peak to peak at the wavelengths assigned in the first and second relative spectrum derivative versus concentration (5-50 μg.ml^{-1}) for both PRO and DZP.

Accuracy and Precision

The accuracy and precision of the proposed methods were tested on the basis of the international council for Harmonization ICH (Araujo, 2009). By calculating the Rec% recovery percentage value and the relative standard deviation value RSD% respectively for concentrations of calibration curves.

Limit of Detection and Limit of Quantification

Detection limit LOD values and quantification limit LOQ values were calculated as follows (Ingram, 1970).

$$L\,O\,D\ = \frac{3.3 \times S \times conc.}{\bar{X}} \qquad (1)$$

$$L\,O\,Q\ = \frac{10 \times S \times conc.}{\bar{X}} \qquad (2)$$

Where

S: Standard Deviation, X: mean of seven readings (n=7), and Conc: The lowest concentration in the calibration curve.

Analysis of Pharmaceutical Mixtures

Twenty tablets were weighted of each of the pharmaceutical drugs indicardin 10 mg were produced by the Arab Pharmaceutical Company M.M. Salt - Jordan and valiapam 5 mg pharmaceutical products produced by the state company for drugs industry and Medical Appliances (SDI) Samarra. In a ceramic mortar, the equivalent of one tablet of each product is 0.1495 g of PRO, and 0.1208 g of DZP was dissolved in a quantity of ethanol using 100 ml volumetric flasks, and completed the volumes of to the mark with ethanol, and was filtrated using Whatman no. 42 filter paper to get rid of non-dissolved substances to become the concentration of PRO and DZP 100μg.ml^{-1}and 50 μg.ml^{-1}Respectively. The proposed methods are applied to the estimation of PRO and DZP in their solutions with concentrations (40, 35, 30, 25) μg.ml^{-1}for PRO and (30, 25, 20) μg.ml^{-1} for DZP. All the measurements were k-repeated seven times (n=7).

RESULTS AND DISCUSSION

Solvent Selection

Many solvents, namely distilled water, methanol, and ethanol, have been used, as well as their mixtures in an acid or basic medium to complete the dissolving process. The results showed that ethanol in the equivalent is the best solvent because it completely dissolved both drugs and gave regular spectra that can be used in the simultaneous quantitative assessment of them**.**

Absorbance Spectrum

Based on the rules of ratio derivative of the spectrum (Salinas, 1990). The Absorption spectra of the concentrations 5-50 μg.ml^{-1} for both PRO and DZP individually and for their mixtures at wavelengths between 400-190 nm were recorded. Figure 2 represents the zero spectrum of DZP at a concentration of 20μg.ml^{-1}, which gave the maximum absorption at 315 nm and B represents the zero spectrum of PRO at a concentration of 20μg. ml^{-1} which gave the maximum absorption at 292 nm and C represents the spectrum of the mixture of 35 μg.ml^{-1} DZP +15 μg. ml^{-1}PRO. Figure 3 is a ratio spectrum of 5-50 μg.ml^{-1}PRO, which gave the maximum peak at 294.46 nm. Figure 4 represents the ratio spectrum of DZP for concentrations of 5-50 μg.ml^{-1} and its maximum peak at 332.244 nm.

Figure 5 represents the first ratio derivative (DD1)(a) and the second ratio derivative (DD2)(b) of PRO in the presence of DZP. Figure 6 represents the first ratio derivative(DD1)(a) and the second ratio derivative (DD2)(b) of DZP in the presence of PRO. All spectra were obtained at $\Delta\lambda$=20 nm and scaling factor = 8 nm

Calibration Curves

The calibration curves were constructed using the peak to the baseline, peak area and peak to peak, which were found to be propotional with concentrations of both drugs at specific wavelengths as in Table 1 and Table 2. R^2 values ranged between 0.997 -0.9998 and Slope between 0.0002-2.8749 μg.ml^{-1}for DZP and PRO. The linearity of two drugs ranged from 5 μg.ml^{-1}as a minimum, and

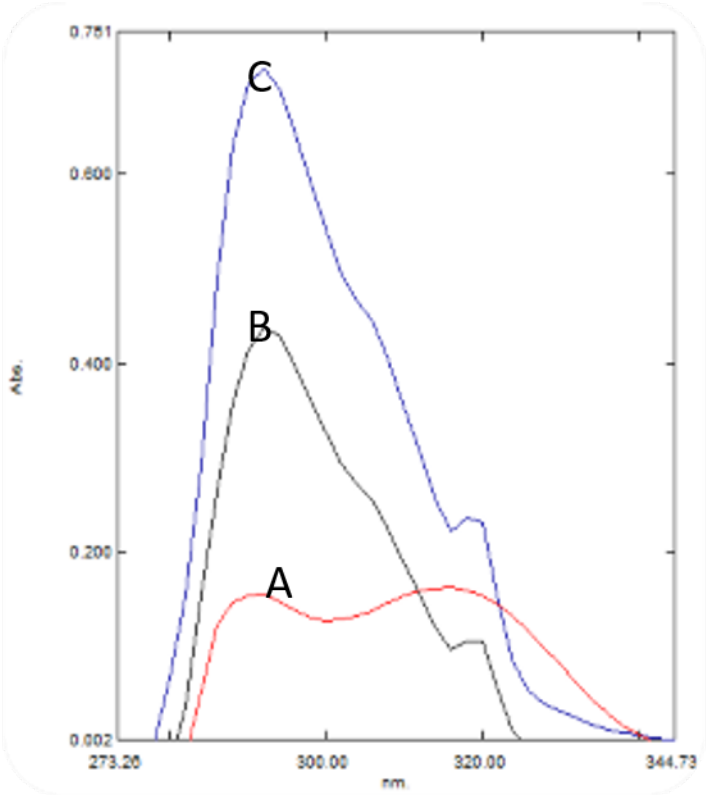

Figure 2: A represents the zero spectrum of diazipam and B the zero spectrum of Propranolol and C the spectrum of the mixture

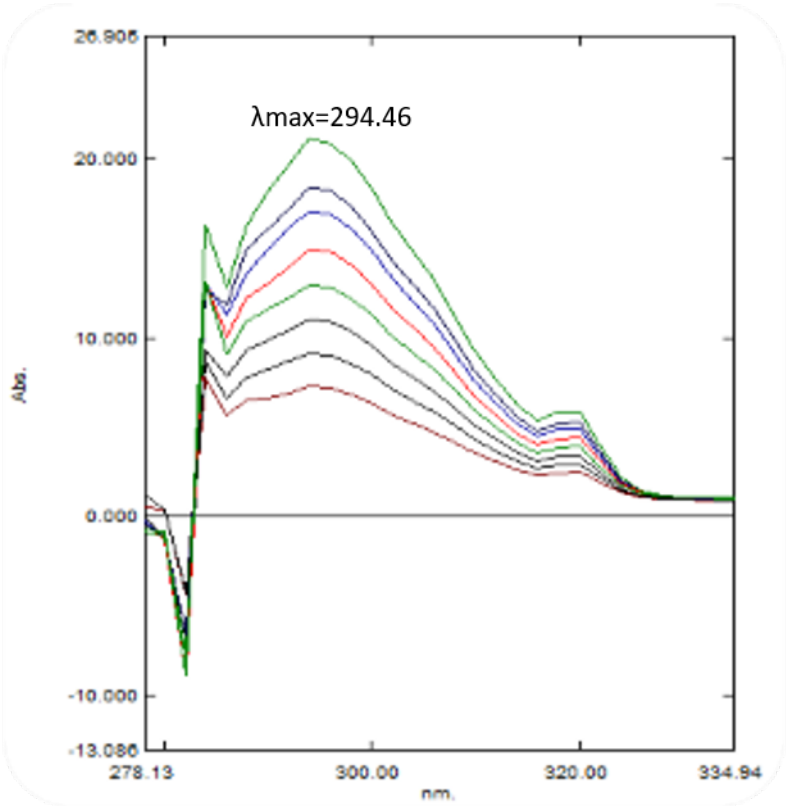

Figure 3: is a ratio spectrum of 5-50 μg.ml^{-1} Propranolol

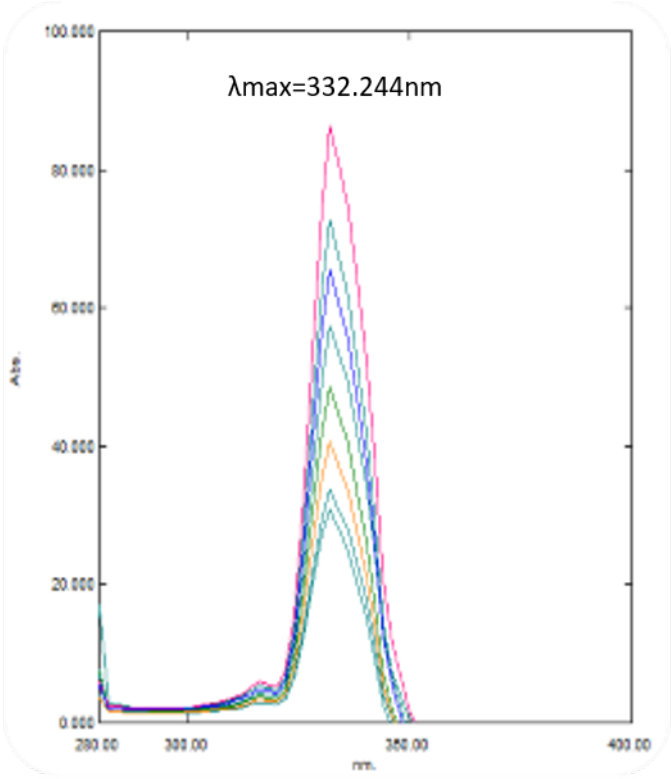

Figure 4: Represents the ratio spectrum of diazipam for concentrations of 5-50μg.ml^{-1}

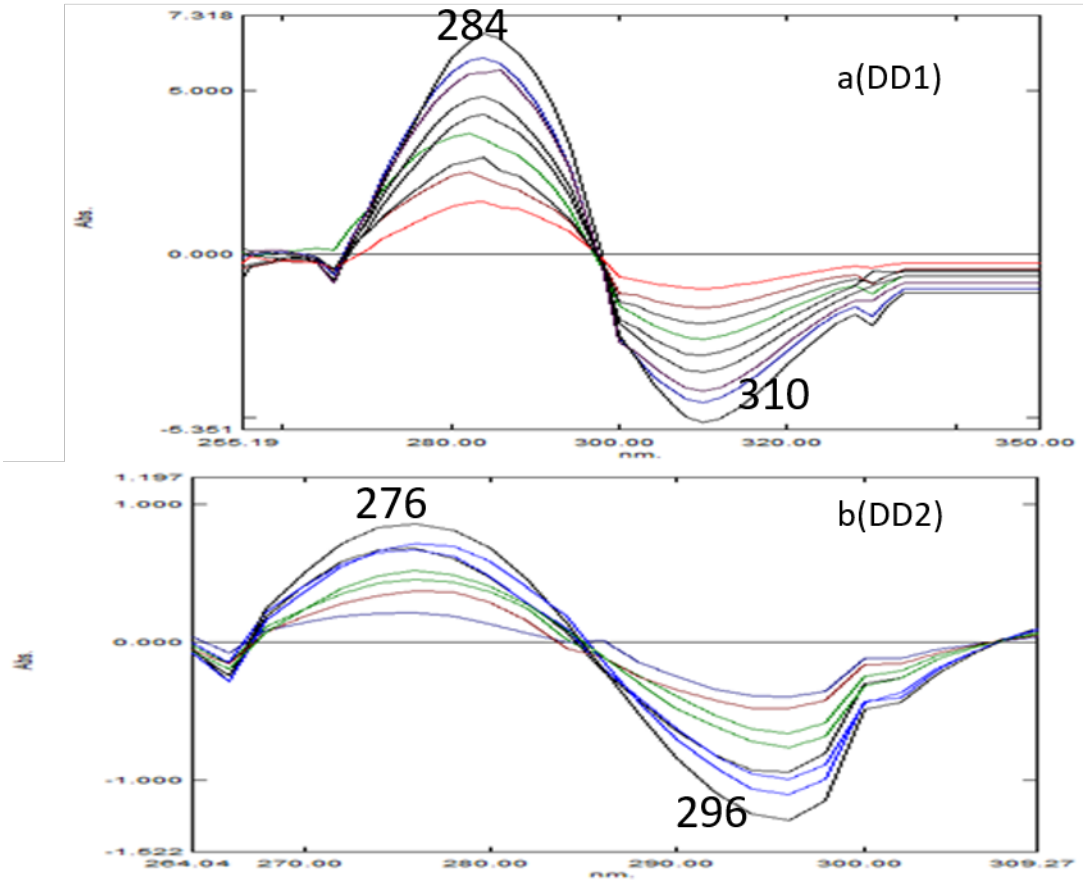

Figure 5: The first(a) and second (b) ratio derivative of 5-50 μg.ml^{-1} Propranolol in the presence of 7μg.ml^{-1}of DZP

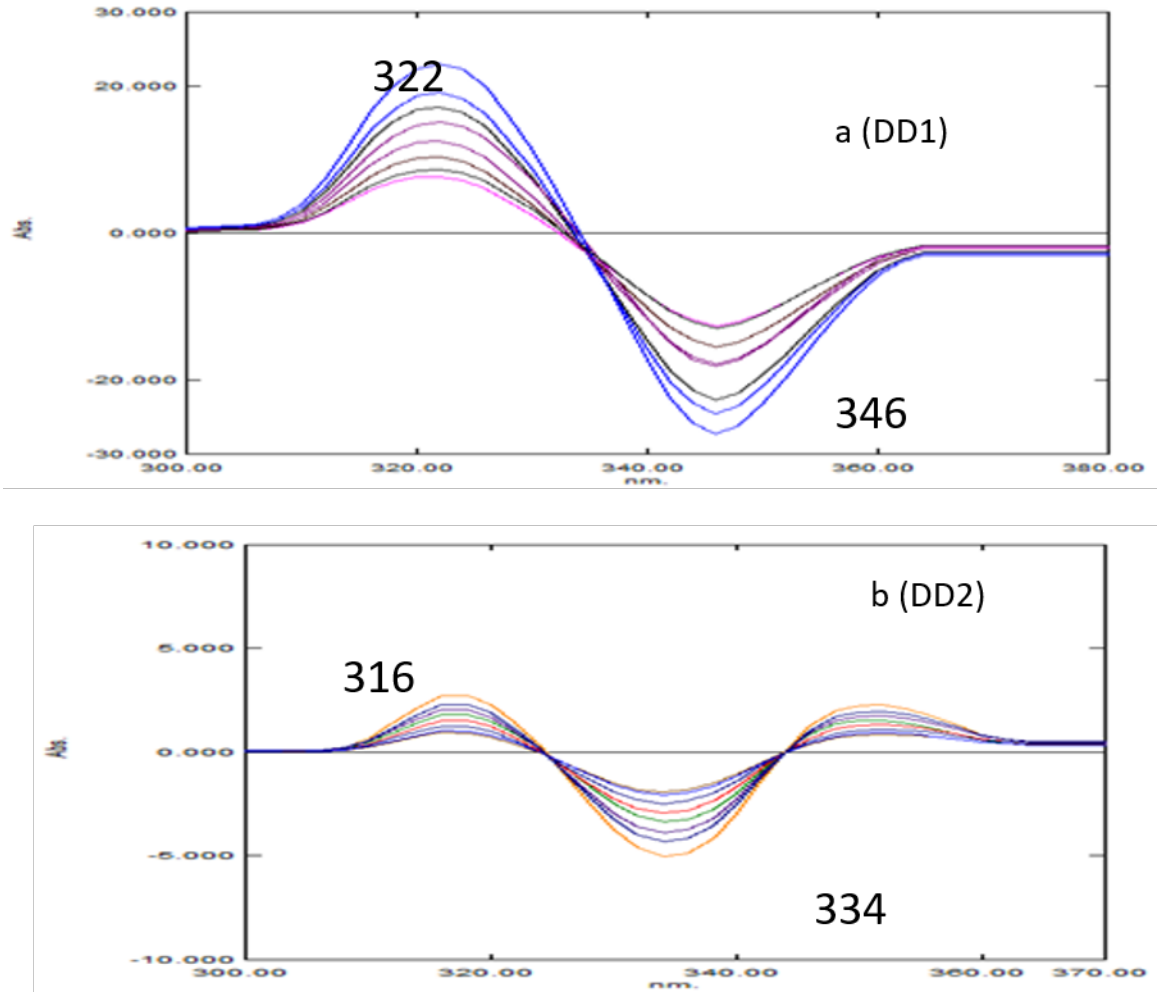

Figure 6: The first(a) and second (b) ratio derivative of 5-50 μg.ml^{-1} diazipam in the presence of 15μg.ml^{-1}of Propranolol

50 μg.ml^{-1} as a maximum, for the first and second ratio derivatives. Limit of detection LOD for all modes of analysis were between 0.12548 - 2.2143 μg.ml^{-1}and 0.0598 - 2.52338 μg.ml^{-1}for DZP and PRO respectively, while the Limit of quantification LOQ was between 0.381181- 6.71037 μg.ml^{-1}and 7.64662 - 0.181407 mcg.ml-1for DZP and PRO, respectively.

Accuracy and Precision

The accuracy and precision of the method were tested using the Rec% and the RSD% for the concentrates of calibration curves by seven repetitions for each measurement either for the first and or second ratio derivative. The values of Rec% were ranged between 95.040 - 104.79% for DZP and 97.0285 - 104.36% for PRO. RSD% values were ranged between 0.1163- 3.7030% and 0.1206 - 4.945% for DZP and PRO, respectively.

Additives Effect

The effect of additives (Lactose, Aerasil, Mg.stearte, Maize starch, Talc, PHB, MHB) was studied by adding each additive to the pure substance as its percentage in the drug. The results obtained showed that the additives had no significant effect when the two Drugs were analyzed using the proposed methods throw recovery percentage Rec% of 30μg.ml^{-1}of DZP and PRO which was 95.02 - 104.87% and 95.03 -104.99% and the relative standard deviation of RSD% for DZP and PRO which was 0.4397 - 4.558% and 1.2601 -4.7626%, respectively.

Method Application

The ratio derivative proposed methods were used in the estimation of both pharmaceutical forms (Valiapam 5 mg and Indicardin 10 mg) by repeating each measurement seven times (n=7) for different concentrations within the calibration curve concentrations of 20, 25, 30 μg.ml^{-1}of the valipam 5 mg in the presence of 7 μg.ml^{-1} indicardin 10 mg. The concentrations of 25,30,35,40 μg.ml^{-1} were selected from the indicardin 10 mgin the presence of 15 μg.ml^{-1} valipam 5 mg using three modes of measurements (Peak to Base Line, Peak Area, Peak to

Table 1: Represents the results of the DZP analysis using the first and second relative derivatives

LOQ μg.mL-1	LOD μg.mL^{-1}	λ nm	Linearty μg.mL^{-1}	Mode of Analysis	Order of Derivative	Compound
4.96296	1.63777	322	25-50	Peak to Base Line	DD1	DZP in present of PRO 15μg.ml^{-1}
3.0675	1.012295	346	10-50			
2.0516	0.67705	306-334	5-50	Peak Area		
2.80597	0.92597	334-362	10-50			
4.6273	1.52623	322 + 346	20-50	Peak to Peak		
6.71037	2.21433	316	20-50	Peak to Base Line	DD2	
0.381181	0.12548	334	5-50			
1.64868	0.54401	304-324	5-50	Peak Area		
2.97148	0.98059	324-344	10-45			
6.71037	2.21433	316+334	20-50	Peak to Peak		

Table 2: Represents the results of the analysis of PRO using the first and second relative derivatives

LOQ μg.mL^{-1}	LOD μg.mL^{-1}	λ(nm)	Linearty μg.mL^{-1}	Mode of Analysis	Order of Derivative	Compoun
0.181407	0.05986	284	5-50	Peak to Base Line	DD1	PRO in present of DZP 7μg.ml^{-1}
1.790701	0.590931	310	5-50			
1.73785	0.387005	266-298	5-50	Peak Area		
1.73785	0.57345	298-334	5-50			
7.64662	2.52338	284+310	25-50	Peak to Peak		
3.82887	1.263529	276	10-50	Peak to Base Line	DD2	
4.34242	1.432999	296	10-50			
1.39471	0.460256	286-308	5-50	Peak Area		
1.743071	0.575213	286-308	5-50			
6.26759	2.068306	276-296	15-50	Peak to Peak		

Peak). The values of Rec% were between 95.41-104.92% and RSD% values were between 0.00116 – 1.36587 % for DZP while Rec% and RSD% for PRO were 96.53- 104.46% and 0.16260- 4.75101% respectively.

CONCLUSION

Two spectrophotometric methods for estimation of PRO and DZP were developed in pure mixtures and pharmaceutical forms. These methods are based on the first ratio derivative and the second ratio derivative. Where the height of the peak to the baseline, peak area and the peak to peak were found to be proportional to the concentrations of PRO and DZP. Therefore, the three modes of analysis were used in the quantitative estimation of the above drugs were able to used in the routine analysis of the Drugs in the quality controls of the factories of Drugs.

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