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Original Article

DETERMINATION OF PIOGLITAZONE IN BULK AND PHARMACEUTICAL FORMULATIONS BY EXTRACTIVE SPECTROPHOTOMETRIC METHOD USING ION – PAIR FORMATION

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ABSTRACT

Simple, accurate and good sensitive extractive spectrophotometric method have been developed for the rapid determination of Pioglitazone (PIO) in pure form and pharmaceutical formulations. The spectrophotometric method was based on the formation of binary complex (ion-pair complex) between the (PIO) and Chromotrope 2R (C2R) in acidic buffer, giving purple color, the absorbance of dichloromethan extracted complex was measured at 514 nm.

The effects of analytical parameters on the reported system were investigated. The complexation reaction was extremely rapid at room temperature and the absorption values remains unchanged up to 24h. Beer's law was obeyed in the concentration range of 1.0 – 65.0 µg/ml, detection limit was 0.16 µg/ml and the molar absorptivity coefficients were 9.934×10^3 L .mol^{-1}.cm^{-1}. Recoveries were between 99.13 – 102.17%. Interferences of the other ingredients and excipients were not observed.

Keywords: Extractive Spectrophotometry, Complex formation, Pioglitasone, Chromotrope 2R.

INTRODUCTION

Pioglitazone (PIO), (RS)-5-(4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl) thiazolidine-2,4-dione, molecular weight 356.44 g mol^{-1} (Fig.1.). Pioglitazone is used for the treatment of diabetes mellitus type 2 (previously known as non-insulin-dependent diabetes mellitus, NIDDM) in monotherapy and in combination with a sulfonylurea, metformin, or insulin. Pioglitazone has also been used to treat non-alcoholic steatohepatitis (fatty liver), but this use is presently considered experimental[1]. Pioglitazone has also been found to reduce the risk of conversion from prediabetes to diabetes mellitus type 2 by 72%[2].

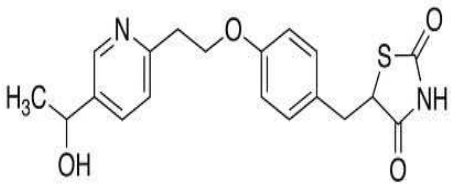

Fig. 1: Chemical structure of Pioglitazone

Few methods have been described for the determination of pioglitazone in pharmaceutical preparation, by extractive spectrophotometric method[3], high performance liquid chromatography HPLC[4-6], RP-HPLC[7-8], Potentionetric sensors[9], UV derivative[10-11], TLC densitometry[12], and determined in human plasma, urin, serum, and biological fluids by HPLC[13-16], LC-MS/MS[17-18], HPLC-MS [19]. Many materials have been determined by using chromotrope 2R for example Spectrophotometric determination meclozine HCl and papaverine HCl in their pharmaceutical formulations [20], sildenafil citrate in pure form and in pharmaceutical formulation [21]. many extractive spectrophotometric procedures are popular for their sensitive in the assay of drugs. Therefore, ion-pair extractive spectrophotometry has received considerable attention for the quantitative determination of many pharmaceutical compounds.

In the present work, new simple, rapid and accurate analytical method was developed for the determination of pioglitazone (PIO). The method was applied for the analysis of local pharmaceutical products samples.

Research Highlights

The proposed the formation of binary complex (ion-pair complex) between the (PIO) and Chromotrope 2R (C2R) was found to be useful in the Extractive spectrophotometric determination of PIO in pure solutions and was successfully applied for the determination of PIO in pharmaceutical dosage forms with average recovery of 99.02 to 101.87% with RSD less than 0.84%.

Experimental

Apparatus

Measurements were made on a Jasco V-650 model spectrophotometer UV-VIS (Japan Spectroscopic Co. Ltd., Tokyo) with a scanning speed of 400 nm/min and a bandwidth of 2.0 nm, equipped with 10 mm matched quartz cells. All absorption spectra were made for electronic spectral measurements between (190-1100nm). The pH measurements were made with CRISON pH meter Model GLP21 made in EU

Reagents and solutions

Stock standard solution of PIO (1.10^{-3} M) was prepared by dissolving 39.37 mg of pioglitazone hydrochloride equivalent to 35.64 mg of pioglitazone base (considering the purity) in 7 mL of hydrochloric acid (2N) and diluted with double distilled water to the mark in 100 ml volumetric flask. The standard solution was prepared by dilution of the stock standard solution with double distilled water to reach concentration (2.10^{-4} M) of PIO. This solution was stored in well-closed vessel, the solution is stable. Solutions of reagent Chromotrope 2R (C2R) were prepared with a concentration of (1.10^{-3} M) by dissolving suitable weight of the reagent in double distilled water and diluted to the mark in 100 ml volumetric flasks separately. The chromotrope 2R dye aqueous solutions were stable for several months. Spectroscopic grade Dichloromethan was used for extraction from SCP (Surchem product Ltd, England).

Procedure for the assay of bulk sample

Aliquots of the standard PIO solutions were transferred into a series of 50 ml separating funnels, 3 ml of (HCl+KCl) (0.1M) buffer pH=1.6 and 4.5ml of reagent C2R were added and mixed well, a 10 ml amount of dichloromethan was added with three portions and the mixture was shaken well. The formed ion associates were extracted

with 3ml by shaking for 5 min, then repeating the extraction step twice by using new 3ml aliquots of the extractant for every extraction. The reaction mixture was allowed to separate into two phases. The organic layer was collected into 10 ml calibrated measuring flask and the volume was made up to the mark with the extractant solvent. The absorbance of the separated dichloromethan layer was measured at a maximum 514 nm, for the complex C2R-PIO, against the reagent blank. The standard calibration plot was prepared to calculate the amount of the analyzed drug in bulk samples. All measurements were carried out at room temperature (25±2°C).

Procedure for formulations

The contents of twenty tablets of PIO drugs were weighed, powdered, and an accurately weighed portion equivalent to 4 mg of the drug was dissolved in methanol, shaken in mechanical shaker for 5 min and then filtered. The filtrate was made up to 100ml volumetric flask. The suitable aliquot was analyzed using the procedure described earlier.

RESULTS AND DISCUSSION

Preliminary investigations have been shown that PIO react with C2R in (HCl+KCl) (0.1M) buffer to give dichloromethan-soluble ion-association complexes. The optimum reaction conditions for quantitative determination of the ion pair complexes were established via a number of preliminary experiments. Several parameters such as acidity, type and amount of buffer added, reagent concentration, sequence of addition and effect of extracting solvent were optimized to achieve high sensitivity, low blank reading and reproducible results.

Effect of Extracting Solvent

Several organic solvents (ethyl ether, chloroform, dichloromethane, ethyl acetate, carbon tetra chloride) were examined for their ability to extract PIO-Dye ion-pair complexes. The dichloromethan was found to be the most suitable solvent for quantitative extraction of the complex.

Effect of kind and pH buffer

The effect of pH was studied by extracting the colored complex in the presence of various buffers such as Briton, Citrate, (HCl+KCl) (0.1M). It was observed that the maximum color intensity and constant absorbance were found in HCl&KCl (0.1M) of pH 1.6 for PIO-C2R system using 3 ml of (HCl+KCl) (0.1M) as shown in (Fig.2).

Effect of amount of (HCl+KCl) (0.1M) buffer (pH 1.6)

The optimum of amount of (HCl+KCl) (0.1M) buffer for the assay of drugs was studied. 3 ml of buffer HCl&KCl (0.1M) pH 1.6 was sufficient for complete color development for PIO- dye complex as shown in (Fig.3).

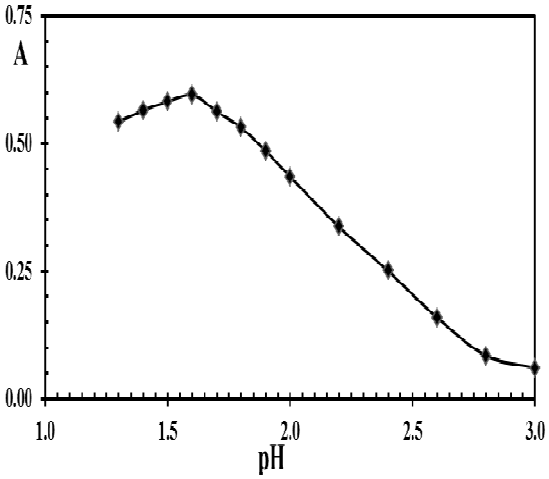

Fig. 2: Effect of the pH value on absorption of PIO-dye complex

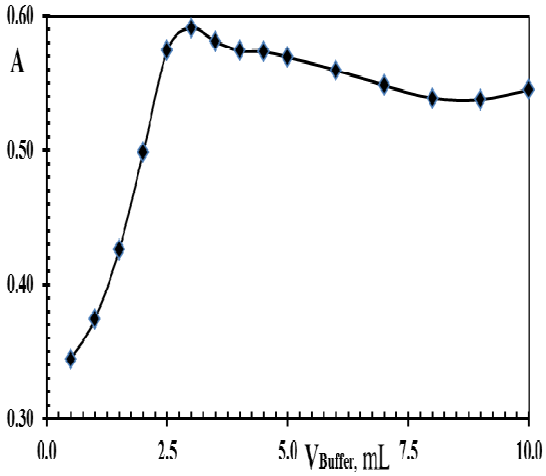

Fig. 3: Effect of the (HCl+KCl) (0.1M) volume (pH=1.6) on absorbance of PIO-dye complex.

Effect of the amount of dye

The optimum of amount of dye for the assay of drugs was studied. 4.5 ml of dye was sufficient for complete color development for PIO-dye complex as shown in (Fig.4).

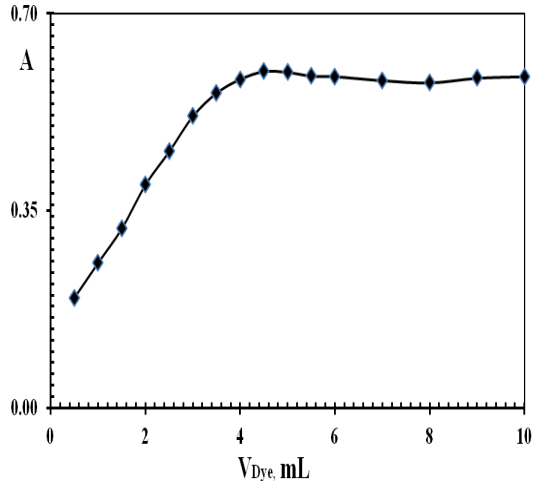

Fig. 4: Effect of the amount of dye on absorbance of PIO-dye complex.

Effect of time and temperature

The effect of time on the formation and stability of the ion-associates was studied by measuring the absorbencies of the extracted ion-associates at increasing time intervals, the results show that the ion-associates were formed almost instantaneously in the cases at room temperature(25±2°C). The color of the PIO-C2R remained stable for 24-48 h. after these intervals, a slight decrease in color intensity occurred.

Molar Ratios Determination of PIO-Dye complexes

The molar ratio of the drug to dye of the colored complex was determined using the molar ratio [22] and continuous variation [23] methods. the ratio were found to be 1:1 for PIO:C2R (Fig. 5), (Fig. 6).The Beer's law limits, molar absorptivity, linear regression equation, correlation coefficient and detection limit determined for method is given in TABLE-1. A linear relationship was found between the absorbance at λ_{max} and the concentration of the drug in the ranges 1.0-65.0 µg/ml for C2R.

Table 1: Spectral characteristics of PIO-dye complexes

Parameters	Extraction method with PIO-C2R
Buffer pH	1.6
λ_{max} (nm)	514
Stoichiometric relationship	1:1
Beer's law limit (µg. ml^{-1})	1.0-65.0
Molar absorptivity ($L.mol^{-1}.cm^{-1}$)	9.934×10^3
Linear Regression equation	A= 0.0280C +0.0012
Correlation coefficient, r	0.9999
LOD (µg.ml^{-1})	0.16
LOQ (µg.ml^{-1})	0.49
Range of Error	±4.96%

Table2: Evaluation of precision and accuracy of the proposed methods for determination of PIO in pure form.

Dye	PIO, µg. ml^{-1}			RSD%	Recovery%	Confidence limit
	Taken	Found*	SD			
C2R	1.00	0.99	0.049	4.96	99.36	0.99±0.06
	3.00	3.07	0.0110	3.59	102.17	3.07±0.14
	5.00	4.96	0.160	3.23	99.13	4.96±0.20
	10.00	9.97	0.311	3.12	99.72	9.97±0.39
	20.00	20.04	0.552	2.75	100.20	20.04±0.69
	30.00	30.34	0.663	2.19	101.14	30.34±0.82
	40.00	40.69	0.690	1.70	101.71	40.69±0.86
	50.00	50.01	0.770	1.54	100.02	50.01±0.96
	60.00	59.92	0.797	1.33	99.86	59.92±0.99
	65.00	64.81	0.802	1.24	99.70	64.81±1.00

*****Average of five determinations.

Table 3: Results of the estimation of PIO in tablets

Formulation (Tablets)	PIO	C2R (µg/ml)					
		Taken	found*	SD	Content determined (mg/tab)	RSD%	R*%
ACTAZONE ASIA	15	20	20.25	0.07	15.19	0.33	101.25
ASIA pharma	(mg/tab)	30	30.33	0.17	15.16	0.57	101.10
		40	40.66	0.20	15.25	0.49	101.66
Mean R*% ±RSD%				101.33±0.46			
ACTAZONE ASIA	30	20	19.78	0.05	29.67	0.28	98.89
ASIA pharma	(mg/tab)	30	29.64	0.44	29.64	1.48	98.80
		40	39.92	0.07	29.94	0.18	99.80
Mean R*% ±RSD%				99.16±0.64			
DEFAST	30	20	19.86	0.09	29.79	0.44	99.30
UNIPHARMA pharma	(mg/tab)	30	29.42	0.24	29.42	0.82	98.07
		40	39.88	0.05	29.91	0.13	99.69
Mean R*% ±RSD%				99.02±0.46			
PIOGLIT	15	20	20.18	0.09	15.13	0.42	100.88
BARAKAT pharma	(mg/Ctab)	30	30.34	0.33	15.17	1.10	101.14
		40	40.23	0.05	15.08	0.11	100.57
Mean R*% ±RSD%				100.86±0.54			
PIOGLIT	30	20	20.15	0.09	30.23	0.45	100.76
Barakat pharma	(mg/Ctab)	30	30.25	0.05	30.25	0.15	100.85
		40	40.30	0.01	30.22	0.02	100.75
Mean R*% ±RSD%				100.78±0.21			
PIOGLIT	45	20	20.32	0.15	45.71	0.73	101.58
Barakat pharma	(mg/Ctab)	30	30.70	0.29	46.05	0.95	102.33
		40	40.68	0.35	45.76	0.85	101.70
Mean R*% ±RSD%				101.87±0.84			
PLIZONE	30	20	20.01	0.04	30.01	0.22	100.04
ELSaad pharma	(mg/tab)	30	30.29	0.05	30.29	0.17	100.96
		40	40.68	0.04	30.51	0.09	101.69
Mean R*% ±RSD%				100.90±0.16			

*Average of five determinations.

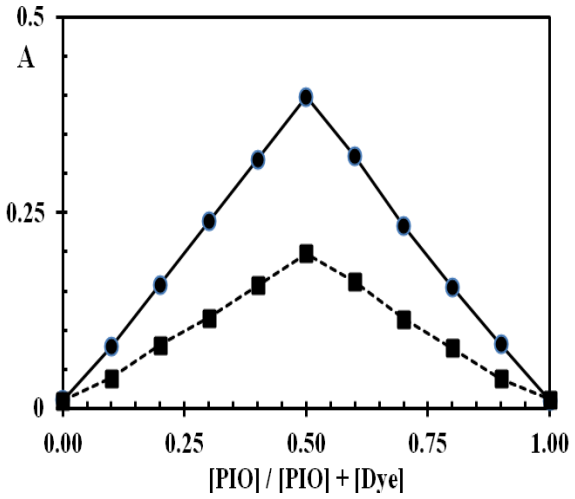

Fig. 5: Continuous Variations plots for PIO-Dye.

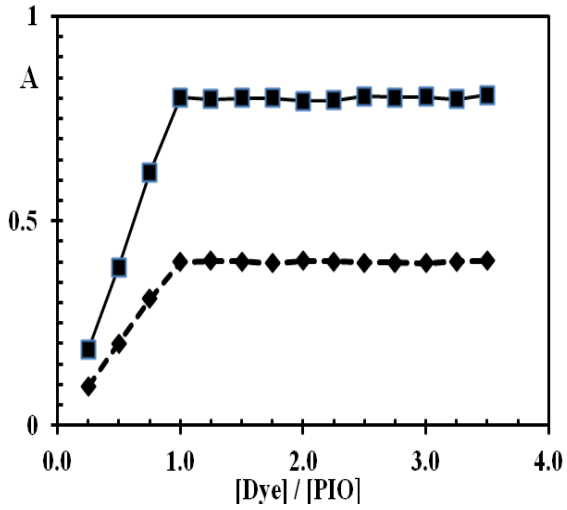

Fig. 6: Molar ratio plots for PIO-Dye

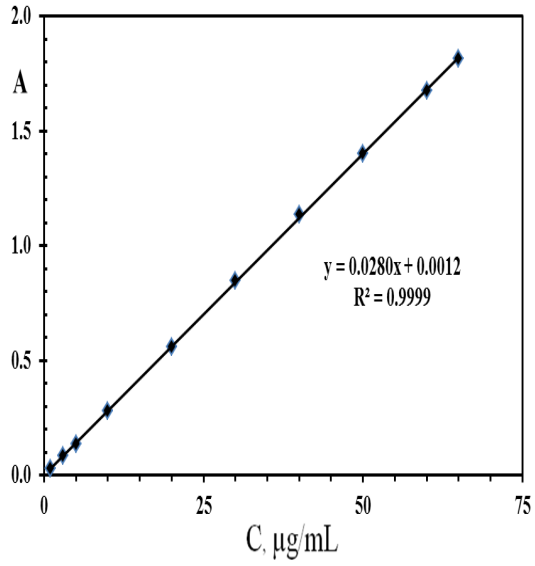

Fig. 7: Calibration plot of PIO using C2R

Linearity and range

The graphs show negligible intercept and are described by the regression equation, A= mC + b (where A is the absorbance of 1 cm layer, m is the slope, b is the intercept and C is the concentration of the measured solution in µg.ml^{-1}) obtained by the least-squares method [24]. The high molar absorptivity of the resulting colored complexe indicate the good sensitivity of the method (Fig. 7).

Accuracy and Precision

The results obtained are summarized in TABLE-2. The low values of relative standard deviation (RSD) indicate good precision and reproducibility of the method. The average percent recoveries obtained were 99.13 – 102.17% for C2R, indicating good accuracy of the methods

Application to the pharmaceutical dosage forms

The proposed method have been successfully applied to the determination of PIO in pharmaceutical preparations TABLE-3. The ingredients in the tablets did not interfere in the experiments.

CONCLUSION

The proposed method for the estimation of PIO using chromotrope 2R are advantages over many of the reported methods. The method are rapid, simple and have good sensitivity and accuracy. Proposed method makes use of simple reagent, which an ordinary analytical laboratory can afford. The high recovery percentage and low relative standard deviation reflect the high accuracy and precision of the proposed method. The method are easy, applicable to a wide range of concentration, besides being less time consuming and depend on simple reagent which are available, thus offering economic and acceptable method for the routine determination of pioglitazone in its formulations.

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