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Effect of Non-Aqueous Solvents on Direct Spectrophotometric Determination of Pioglitazone Hydrochloride in Bulk and Pharmaceuticals Using Bromocresol Purple

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Abstract

Effect of non-aqueous solvents (dichloromethane, dichloroethane, chloroform and acetonitrile) on direct spectrophotometric determination of pioglitazone hydrochloride (PGZ) in pure form and pharmaceutical formulations using bromocresol purple (BCP) was studied. The method is based on ion-pair complex between PGZ and BCP. The absorption spectra of these complex's occurs at wavelengths from 402 to 408 nm. The absorbance's were proportional to the concentration of PGZ at range 1.00 to 100.00 µM (0.3929 to 39.290 µg.mL^{-1}) for first three solvents and at 2.00 to 100.00 µM (0.7858 to 39.290 µg.mL^{-1}) for acetonitrile in present 5.0x10^{-4} M of BCP. The method was validated for linearity, precision and accuracy, repeatability and robustness. The method was successfully applied for determination of PGZ in pure and pharmaceutical formulations samples with relative standard deviations did not exceed 3.8% for the concentrations of PGZ (0.3929 µg.mL^{-1}) in dichloromethane as example.

Keywords: Pioglitazone hydrochloride, Direct spectrophotometric method, Ion-pair complexes, Bromocresol purple.

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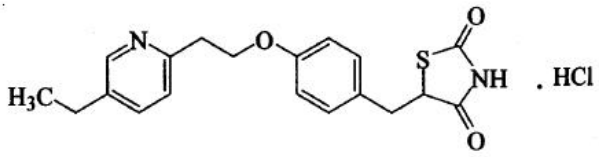
Introduction

The active moiety of pioglitazone hydrochloride (PGZ): (*RS*)-5-(4-[2-(5-ethyl pyridin-2- yl) ethoxy] benzyl) thiazolidine- 2,4-dione hydrochloride (Scheme 1) is an oral antidiabetic agent that has been shown to affect abnormal glucose and lipid metabolism associated with insulin resistance by enhancing insulin action on peripheral tissues in animal models [1-4].



Scheme 1: Chemical structure of pioglitazone hydrochloride (PGZ)

Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S$.HCl and a molecular weight of 392.90 g. It is soluble in N,N- dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether [1, 5].

Bromocresol purple $C_{21}H_{16}Br_2O_5S$ (BCP) acts as a weak acid in solution. It can thus be in protonated or deprotonated form, appearing yellow or purple, respectively, mol. mass 540.22 g [6], see Scheme 2.

Scheme 2: Chemical structure of bromocresol purple (BCP).

No monographs are available in any pharmacopeia for assay of this drug. Various analytical methods developed for its determination in pharmaceuticals and biological samples have recently been reviewed [7]. Various techniques such as UV-spectrophotometry [8-22], electrochemical methods [23-27] and high-performance liquid chromatography (HPLC) [28-36], have been reported for the determination of PGZ in bulk sample and tablets.

Simple, rapid and extractive spectrophotometric method was developed for the determination of pioglitazone hydrochloride in pure and pharmaceutical formulations. This method is based on the formation of yellow ion-pair complex between the basic nitrogen of the drug and bromocresol green (BCG) in phthalate buffer of pH 2.4. The formed complexes were extracted with chloroform and measured at (419 nm) [37]. Various spectrophotometric methods have been reported for the determination of pioglitazone hydrochloride in pure as well as in dosage forms.

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Most spectrophotometric methods employ extraction procedures [38-40]. The complex extraction technique has some difficulties and inaccuracies due to incomplete extraction or the formation of emulsions between the hydrocarbon solvent and the basic compound-containing solution. In response to the problems resulting from the extraction of the complex, it is better to determine formed complex without extraction. Direct methods reported in the literature are based on the formation of a complex between BCG and PGZ [41]. Also none of the methods reported in the literatures is based on the formation of complex between BCP and PGZ.

In the present work, effect of non-aqueous solvents (dichloromethane, dichloroethane, chloroform and acetonitrile) on direct spectrophotometric determination of pioglitazone hydrochloride (PGZ) in pure form and pharmaceutical formulations using bromocresol purple (BCP) was developed.

Materials and Methods

Instruments and apparatus

Spectrophotometric measurements were made in T90+UV-VIS with 1.0 cm quartz cells. The diluter pipette model DIP-1 (Shimadzu), having 100 µL sample syringe and five continuously adjustable pipettes covering a volume range from 10 to 5000 µL (model Piptman P, GILSON). SARTORIUS TE64 (0.01 mg) electronic balance was used for weighing.

Reagents

Pioglitazone hydrochloride (99.37%) was supplied by Doshil Group Company (India), (Mfg. 10/2017, Exp. 9/2022). Bromocresol purple (99%) of analytical grade, all solvents and reagents were analytical grade chemicals from Sigma-Aldrich.

A stock standard solution of pioglitazone hydrochloride ($1x10^{-3}$ $mol.L^{-1}$)

Dissolving 98.85 mg of pioglitazone hydrochloride (purity 99.37%) with studding solvent into volumetric flask (25 mL) and diluting to mark by same solvent ($1x10^{-2}$ $mol.L^{-1}$). We extend this solution ten times and get a concentration $1x10^{-3}$ $mol.L^{-1}$.

Stock standard solution of bromocresol purple (BCP) $1x10^{-2}$ $mol.L^{-1}$

Accurately weighed 136.42 mg of BCP was dissolved in studding solvent into a volumetric flask (25 mL) and diluted up to mark with solvents.

Working solutions

The stock solutions were further diluted to obtain working solutions daily just before use in the ranges of PGZ: 1.00, 2.00 , 5.00, 10.00, 20.00, 30.00, 40.00, 50.00, 60.00, 80.00 and 100.0 $\mu mol.L^{-1}$ (0.3929, 0.7858, 1.965, 3.929, 7.858, 11.787, 15.716, 19.645, 23.574, 31.432 and 39.290 $\mu g.mL^{-1}$) by dilution of the volumes: 0.010, 0.020, 0.050, 0.100, 0.200, 0.300, 0.400, 0.50, 0.60, 0.80 and 1.00 mL from stock standard solutions of pioglitazone hydrochloride ($1x10^{-3}$ $mol.L^{-1}$) into 10 mL volumetric flask, then added 500 µL from stock standard solution of bromocresol purple ($1x10^{-2}$ $mol.L^{-1}$) and diluted to 10 mL with studding solvent.

Sample preparation:

Commercial formulations (as a tablet) were used for the analysis of PGZ. The pharmaceutical formulations subjected to the analytical procedure were:

(1) ***Pioglit*** tablets, Barakat pharmaceutical industries, Aleppo–Syria, each tablet contains 15 and 30 mg of pioglitazone hydrochloride (Mfg. 06/2018, Exp. 06/2022.

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(2) ***Actazone Asia*** tablets, Asia pharmaceutical industries, Aleppo–Syria, each tablet contains 30 mg of pioglitazone hydrochloride (Mfg. 07/2018, Exp. 07/2021).

(3) ***Defast*** tablets, Unipharma pharmaceutical industries. Damascus -Syria, each tablet contains 30mg of pioglitazone hydrochloride (Mfg. 07/2019, Exp. 07/2022).

Stock solutions of pharmaceutical formulations

Twenty tablets of each studied pharmaceutical formulation were weighed accurately, finely powdered and mixed well. An amount of the powder equivalent to the weight of third of the tablet was solved in suitable solvent using ultrasonic for 15 min, 8 mL of solvent was added, filtered over a 10 mL flask and washed by the same solvent, then diluted to 10 mL with same solvent. This solution contains the following: 0.5 and 1.0 mg.mL^{-1} of PGZ (stock solution A and B, respectively) for all studied pharmaceutical formulations contain 15 and 30 mg/tab, respectively.

Working solutions of pharmaceuticals

Five solutions were prepared daily by diluting 400 µL from stock solution A and 200 µL from stock solution B, then 500 µL from stock standard solution of bromocresol purple (1x10^{-2} mol.L^{-1}) and diluted to 10 mL with studding solvent (these solutions contain 20 µg.mL^{-1} of PGZ and 5x10^{-4} mol.L^{-1} of BCP; test solutions).

Results and Discussion

The effect of solvent

The effect of the solvents (dichloromethane, dichloroethane, chloroform, acetonitrile, acetone and ethylacetate) on absorbance of reagent (BCP), formed complex [PGZ]:[BCP] and the difference between them. It was found that favorite solvents are in series dichloromethane, dichloroethane, chloroform and acetonitrile. As for acetone and ethylacetate, it is not appropriate, see Figure 1.

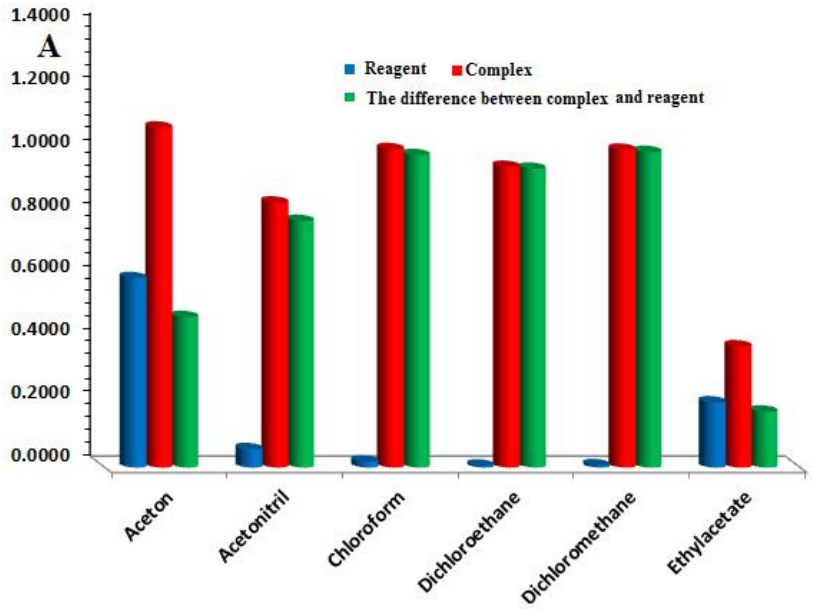

Fig. 1: Absorbance of reagent (BCP), formed complex [PGZ]:[BCP] and difference between them (C_{BCP} 2.5x10^{-4} M, $C_{Complex}$ 5x10^{-5} M, Blank is solvent, ℓ =1 cm).

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Spectrophotometric results

UV-Vis spectra of PGZ, BCP and the formed complex PGZ:BCP solutions in favorite solvents were obtained. PGZ solutions do not absorb in the range 300-600 nm. BCP solutions have small absorption at λ_{max} 400 to 410 nm ($\varepsilon \approx 28, 24, 76, 232, 2396$ and 844 $L.mol^{-1}.cm^{-1}$ in dichloromethane, dichloroethane, chloroform, acetonitrile, acetone and ethylacetate, respectively). [PGZ]:[BCP] complex solutions have maximum absorption at λ_{max} 402 to 408 nm, ε for the complex was 20000, 18900, 19700, 15700, 9520 and 3540 $L.mol^{-1}.cm^{-1}$, in mentioned solvents, respectively. However, the difference between the absorption of the complex and the absorption of the reagent is very small for acetone and ethylacetate and therefore they are not suitable for determining PGZ using this method, see Figure 1.

The effect of time and temperature

The effect of time and temperature on the complex [PGZ]:[BCP] formation was studied within the ranges 5-120 min and 15-45^{o}C. It was found that the formed complex was not affected by time or temperature at those ranges.

The effect of BCP concentration

The effect of BCP concentration on complex [PGZ]:[BCP] formation was investigated. It was observed that the absorbance of the formed complex increased coinciding with increasing the ratio of C_{BCP}:C_{PGZ} until the ratio (5:1), then it becomes almost fixed.

Stoichiometric Relationship

The composition of PGZ:BCP complex were determined by [39]. It confirmed that the binding ratio of PGZ:BCP complexes are equal to (1:1).

Mechanism of reaction

Anionic dyes such as BCP form ion-pair complexes with the positively charged nitrogen-containing molecule. The color of such dyes is due to the opening of lactoid ring and subsequent formation of quinoid group (deprotonated). Pioglitazone hydrochloride is dissolved in solvent and forms yellow ion-pair complex with the dye at pH<3.8; (in pH>5.4 and alkaline solution BCP gives blue color). Each drug-dye complex with two oppositely charged ions (positive on the drug and negative on the dye) behaves as a single unit held together by an electrostatic binding [42-45]. The suggested mechanism of PGZ:BCP ion-pair complex formation is shown in Scheme 3.

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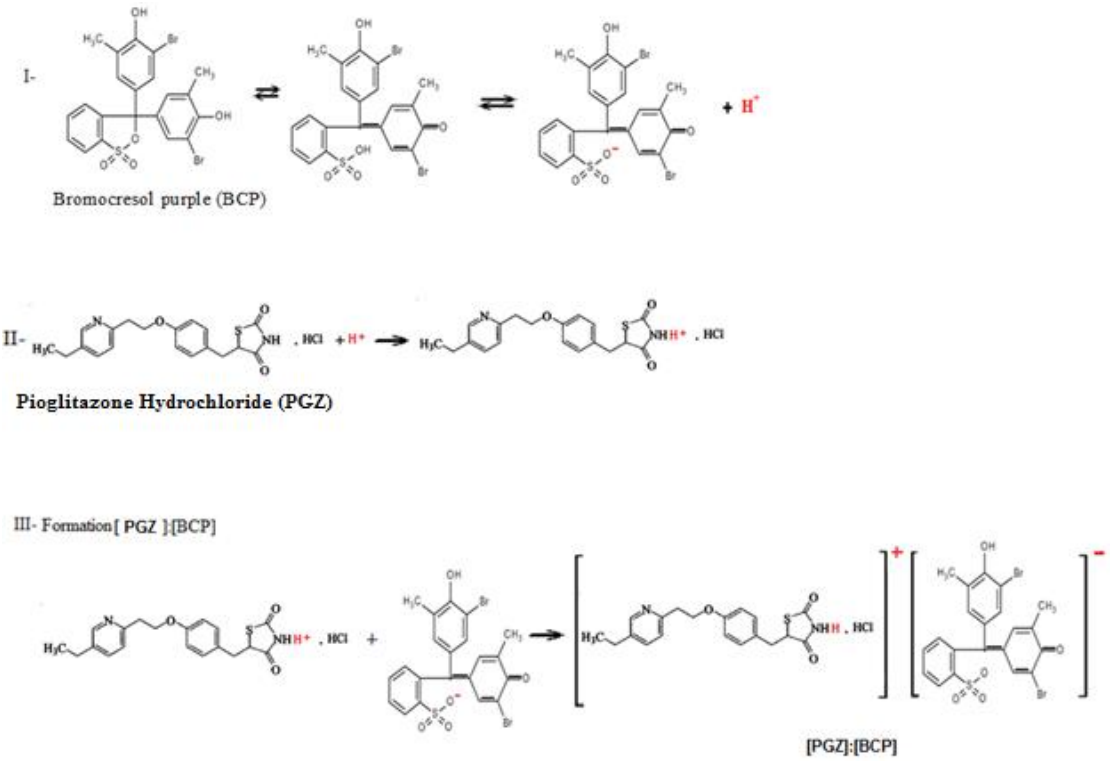

Scheme 3: The possible reaction mechanism of [PGZ]:[BCP] complex formation.

Calibration curve

The calibration curve of pioglitazone hydrochloride in pure form through complexation with bromocresol purple showed excellent linearity over concentration range of 1.00 – 100.00 µmol.L^{-1} (0.3929 to 39.290 µg.mL^{-1}) for first three solvents (dichloromethane, dichloroethane and chloroform) and at 2.00 to 100.00 µM (0.7858 to 39.290 µg.mL^{-1}) for acetonitrile in presence of 5.0×10^{-4} mol.L^{-1} of bromocresol purple with good correlation coefficient in studied solvents. Regression equation at λ_{max} was as the follows: $y_1=0.0508x+0.0005$ ($R^2=$ 0.9998), $y_2=0.0481x+0.0001$ ($R^2=$ 0.9998), $y_3=0.0502x+0.0009$ ($R^2=$ 0.9990) and $y_4=0.0395x+0.0036$ ($R^2=$ 0.9987), in dichloromethane, dichloroethane, chloroform and acetonitrile. Figures 2-5 showed the spectra of [PGZ]:[BCP] complex in presence of 5.0×10^{-4} M of BCP. The spectra characteristics of the method such as the molar absorptivity (ε, Beer's law, regression equation at λ_{max} (y=a.x+b); where y=absorbance, a=slope, x=concentration of PGZ by µg.mL^{-1}, b=intercept, the correlation coefficient, limit of detection (LOD) and limit of quantification (LOQ) and the optimum conditions for spectrophotometric determination of PGZ through ion-pair complex formation using BCP in mentioned solvents is summarized in Table 1.

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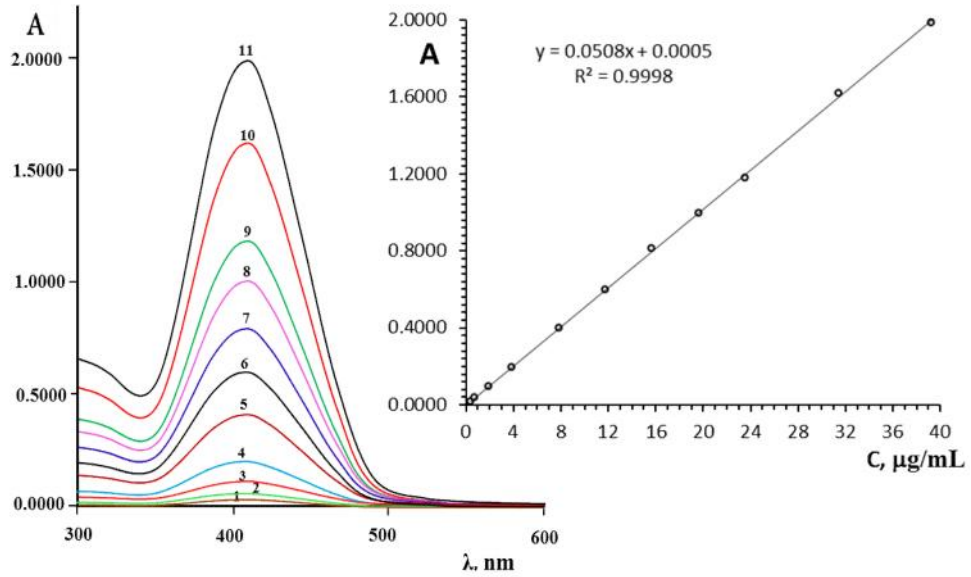

Fig. 2: Spectra and calibration curve of PGZ: BCP complex in presence of 5.0×10^{-4} M of BCP in dichloromethane; where concentration of PGZ as the follows: 1- 0.3929, 2- 0.7858, 3- 1.965, 4- 3.929, 5- 7.858, 6- 11.787, 7- 15.716, 8- 19.645, 9- 23.574, 10- 31.432 and 11- 39.290 µg.mL^{-1} (ℓ = 1.0 cm , blank is 5.0×10^{-4} M of BCP in dichloromethane).

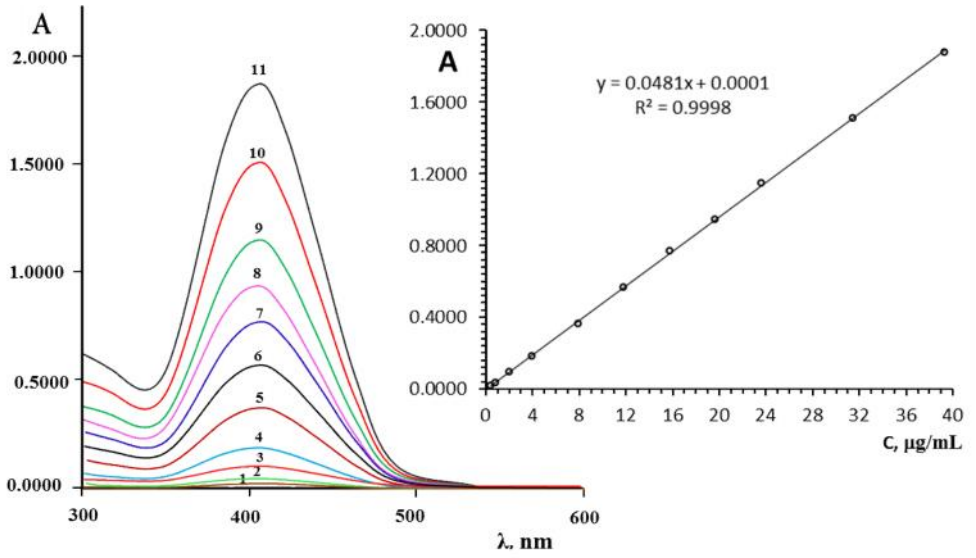

Fig. 3: Spectra and calibration curve of PGZ:BCP complex in presence of 5.0×10^{-4} M of BCP in dichloroethane; where concentration of PGZ as the follows: 1- 0.3929, 2- 0.7858, 3- 1.965, 4- 3.929, 5- 7.858, 6- 11.787, 7- 15.716, 8- 19.645, 9- 23.574, 10- 31.432 and 11- 39.290 µg.mL^{-1} (ℓ = 1.0 cm , blank is 5.0×10^{-4} M of BCP in dichloroethane).

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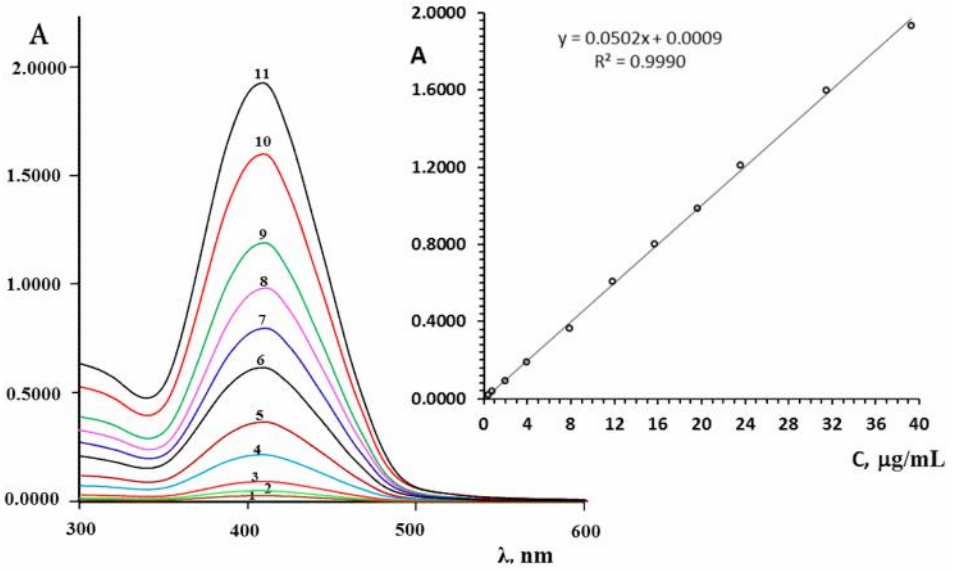

Fig. 4: Spectra and calibration curve of PGZ:BCP complex in presence of 5.0×10^{-4} M of BCP in chloroform; where concentration of PGZ as the follows: 1- 0.3929, 2- 0.7858, 3- 1.965, 4- 3.929, 5- 7.858, 6- 11.787, 7- 15.716, 8- 19.645, 9- 23.574, 10- 31.432 and 11- 39.290 µg.mL^{-1} (ℓ = 1.0 cm , blank is 5.0×10^{-4} M of BCP in chloroform).

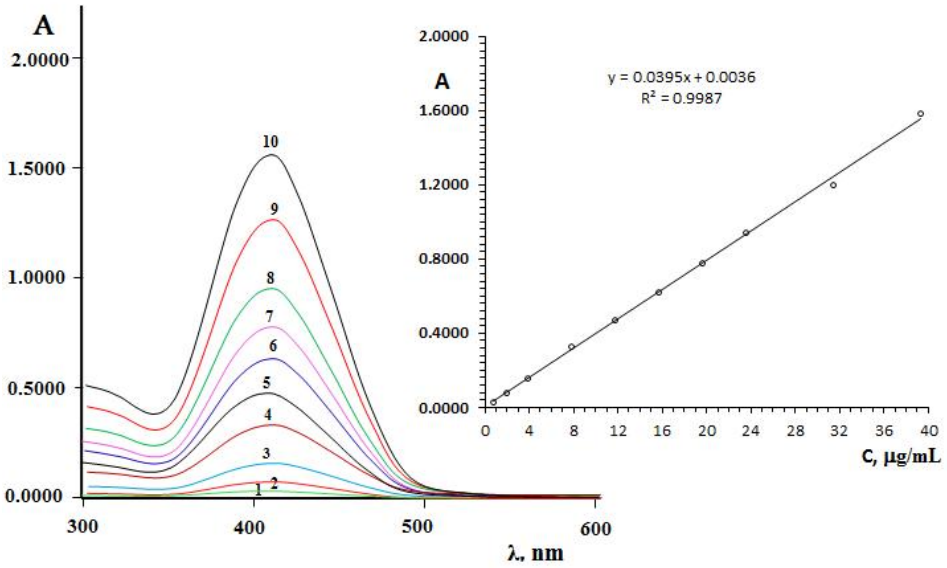

Fig. 5: Spectra and calibration curve of PGZ:BCP complex in presence of 5.0×10^{-4} M of BCP in acetonitrile; where concentration of PGZ as the follows: 1- 0.7858, 2- 1.965, 3- 3.929, 4- 7.858, 5- 11.787, 6- 15.716, 7-19.645, 8- 23.574, 9- 31.432 and 10- 39.290 µg.mL^{-1} (ℓ = 1.0 cm , blank is 5.0×10^{-4} M of BCP in acetonitrile).

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Table 1. The parameters established for spectrophotometric determination of PGZ by complex formation with BCP in studied solvents.

Parameters	Operating values			
	Dichloromethane	Dichloroethane	Chloroform	Acetonitrile
λ_{max} of PGZ:BCP complex, nm	404	402	408	408
Beer's Law Limit by µmol.L^{-1}	1.00-100.00			2.00-100.00
Beer's Law Limit by µg.mL^{-1}	0.3929–39.290			0.7858-39.290
ε of complex (L.mol^{-1}.cm^{-1})	20000	18900	19700	15700
Y=a.x+b for complex at λ_{max}:	y=0.0508x+0.0005	y=0.0481x+0.0001	y=0.0502x+0.0009	y=0.0395x+0.0036
Slope	0.0508	0.0481	0.0502	0.0395
Intercept	0.0005	0.0001	0.0009	0.0036
Correlation coefficient (R^2)	0.9998	0.9998	0.9990	0.9987
C_{BCP}:C_{PGZ}, M	≥5			
Stability	24 h			
Temperature of solution	25±5^{o}C			

n=5, t=2.776.

Analytical results

Spectrophotometric determination of pioglitazone hydrochloride through complexation with BCP in solvents (dichloromethane, dichloroethane, chloroform and acetonitrile) within optimal conditions using calibration curve was applied. The results, summarized in Table 2, showed that the determined concentration of PGZ was rectilinear over the range of 1.00 to 100.00 µM (0.3929 to 39.290 µg.mL^{-1}) for first three solvents and at 2.00 to 100.00 µM (0.7858 to 39.290 µg.mL^{-1}) for acetonitrile, with relative standard deviation (RSD) not more than 3.8% for the concentrations of PGZ (0.3929 µg.mL^{-1}) in dichloromethane as example. The results obtained from the developed method have been compared with the official RP-HPLC method [36] and good agreement was observed between them.

Applications

The developed spectrophotometric method was applied to determine pioglitazone hydrochloride (PGZ) in some Syrian pharmaceutical preparations through complex formation by bromocresol purple (BCP) in studied solvents (dichloromethane, dichloroethane, chloroform and acetonitrile) according to the optimal conditions. The amount (m) of PGZ in one tablet was calculated from the following relationship: m=h.m', where: m' is the amount of PGZ in tablet calculated according to the regression equation of calibration curve, h conversion factors are equal to 0.75 and 1.50 for all pharmaceuticals content 15 and 30 mg/tab, respectively. The results of quantitative analysis for PGZ in pharmaceutical preparations were summarized in Table 3 (in dichloromethane as example). The proposed method was simple, direct, specific and successfully applied to the determination of pioglitazone hydrochloride in pharmaceuticals without any interference from excipients. Average assay ranged between 99.2 to 104.0%. The results obtained by this method agree well with the contents stated on the vials and were validated by RP-HPLC method [36].

Table 2: Spectrophotometric determination of PGZ through complex formation with BCP within optimal conditions using calibration curve in studied solvents.

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X_i, µg.mL^{-1} (Taken)	Solvents	*$\bar{x}$ ±SD, µg.mL^{-1} (Found)	$\bar{x} \pm \frac{t.SD}{\sqrt{n}}$ µg.mL^{-1}	RSD%	*$\bar{x}$, µg.mL^{-1} RP-HPLC[36]
0.3929	dichloromethane	0.3927±0.0149	0.3927±0.0185	3.8	not determined
	dichloroethane	0.3928±0.0153	0.3928±0.0190	3.9	
	chloroform	0.3827±0.0157	0.3827±0.0195	4.1	
	acetonitrile	not determined			
0.7858	dichloromethane	0.7864±0.0283	0.7864±0.0351	3.6	not determined
	dichloroethane	0.7860±0.0283	0.7860±0.0351	3.6	
	chloroform	0.7856±0.0306	0.7856±0.0380	3.9	
	acetonitrile	0.7943±0.0381	0.7943±0.0473	4.8	
1.960	dichloromethane	1.962±0.0687	1.962±0.0853	3.5	1.962
	dichloroethane	1.958±0.0685	1.958±0.0851	3.5	
	chloroform	1.962±0.0746	1.962±0.0926	3.8	
	acetonitrile	1.955±0.0860	1.955±0.1068	4.4	
3.929	dichloromethane	3.934±0.1298	3.934±0.1612	3.3	3.934
	dichloroethane	3.928±0.1336	3.928±0.1658	3.4	
	chloroform	3.931±0.1415	3.931±0.1757	3.6	
	acetonitrile	3.930±0.1611	3.930±0.2000	4.1	
7.858	dichloromethane	7.856±0.2435	7.856±0.3023	3.1	7.867
	dichloroethane	7.762±0.2484	7.762±0.3084	3.2	
	chloroform	7.751±0.2635	7.751±0.3272	3.4	
	acetonitrile	8.876±0.3462	8.876±0.4298	3.9	
11.787	dichloromethane	11.785±0.3536	11.785±0.4389	3.0	11.792
	dichloroethane	11.799±0.3658	11.799±0.4541	3.1	
	chloroform	11.867±0.3797	11.867±0.4714	3.2	
	acetonitrile	11.875±0.4275	11.875±0.5307	3.6	
15.716	dichloromethane	15.827±0.4590	15.827±0.5698	2.9	15.799
	dichloroethane	15.848±0.4754	15.848±0.5902	3.0	
	chloroform	15.829±0.4907	15.829±0.6092	3.1	
	acetonitrile	15.516±0.5275	15.516±0.6549	3.4	
19.645	dichloromethane	19.425±0.5051	19.425±0.6270	2.6	19.756
	dichloroethane	19.783±0.5144	19.783±0.6386	2.6	
	chloroform	19.774±0.5339	19.774±0.6628	2.7	
	acetonitrile	19.580±0.5874	19.580±0.7292	3.0	
23.574	dichloromethane	23.525±0.6352	23.525±0.7885	2.7	23.600
	dichloroethane	23.594±0.6606	23.594±0.8202	2.8	
	chloroform	23.522±0.6821	23.522±0.8469	2.9	
	acetonitrile	23.782±0.7610	23.782±0.9448	3.2	
31.432	dichloromethane	31.540±0.7885	31.540±0.9789	2.5	31.438
	dichloroethane	31.467±0.7867	31.467±0.9766	2.5	
	chloroform	31.562±0.8206	31.562±1.0188	2.6	
	acetonitrile	31.110±0.8711	31.110±1.0814	2.8	
39.290	dichloromethane	39.221±0.9413	39.221±1.1686	2.4	39.308
	dichloroethane	39.184±0.9796	39.184±1.2161	2.5	
	chloroform	39.720±0.9930	39.720±1.2328	2.5	
	acetonitrile	39.984±1.0396	39.984±1.2906	2.6	

n=5, t=2.776.

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Table 3: Determination of pioglitazone hydrochloride in some Syrian pharmaceutical preparations using spectrophotometric method through complex formation with 5.0×10^{-4} M of BCP within optimal conditions using calibration curve in dichloromethane.

Dosage form	Label Claim of PGZ, mg/tab	*Mean ±SD PGZ, mg/tab	RSD %	Assay %	*Mean ±SD PGZ, mg/tab by HPLC [36]	*Assay %, by HPLC [36]
Pioglit tablets, Barakat pharmaceutical industries	15	15.32±0.40	2.6	102.1	15.40±0.51	102.7
	30	31.21±0.76	2.5	104.0	31.24±0.78	104.1
Actazone Asia tablets, Asia pharmaceutical industries	30	31.02±0.74	2.5	103.4	31.00±0.75	103.3
Defast tablets, Unipharma Pharmaceutical Industries	30	29.76±0.74	2.6	99.2	29.82±0.76	99.4

***** n=5.

Method Validation

The developed method for simultaneous estimation of pioglitazone hydrochloride has been validated in accordance with the International Conference on Harmonization guidelines (ICH) [46].

Linearity

Several aliquots of standard stock solution of pioglitazone hydrochloride were taken in different 10 mL volumetric flask and diluted up to the mark with studied solvent such that their final concentrations were 0.3929-39.290 $\mu g.mL^{-1}$ of PGZ. Absorbance was plotted against the corresponding concentrations to obtain the calibration graph, see Figures 2-5 and Table 2. Linearity equations obtained at λ_{max} suitable for used solvent were applied, see Table 1.

Precision and Accuracy

The precision and accuracy of proposed method was checked by recovery study by addition of standard drug solution to pre-analyzed sample solution at three different concentration levels (80%, 100% and 120%) within the range of linearity for pioglitazone hydrochloride. The basic concentration level of sample solution selected for spiking of the pioglitazone hydrochloride standard solution was 11.787 $\mu g.mL^{-1}$. The proposed method was validated statistically and through recovery studies, and was successfully applied for the determination of pioglitazone hydrochloride in pure and dosage forms with percent recoveries ranged from 98.4% to 102.8%, see Table 4 (in dichloromethane as example).

Table 4: Results of recovery studies (in dichloromethane as example).

Level	% Recovery
80%	98.4
100%	99.7
120%	102.8

n=5

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Repeatability

The repeatability was evaluated by performing 10 repeat measurements for 15.716 µg.mL^{-1} of pioglitazone hydrochloride using the studied spectrophotometric method under the optimum conditions. The found amount of pioglitazone hydrochloride ($\bar{x}$ ± SD) 15.845 ± 0.44 µg.mL^{-1} (in dichloromethane as example). The percentage recovery was found to be 100.8 ± 2.8 with RSD of 0.028. These values indicate that the proposed method has high repeatability for pioglitazone hydrochloride analysis.

Sensitivity (LOD and LOQ)

The sensitivity of the method was evaluated by determining the LOD and LOQ. The values of LOD and LOQ for pioglitazone hydrochloride are 0.012 and 0.036 µg.mL^{-1} (in dichloromethane as example).

Robustness

The robustness of the method adopted is demonstrated by the constancy of the absorbance with the deliberated minor change in the experimental parameters such as the change in the concentration of excipients, temperature (25±5^{o}C), stability (23-25 h) and reaction time (5±1 min), see Table 5 which indicates the robustness of the proposed method. The absorbance was measured and assay was calculated for five times (in dichloromethane as example).

Table 5: Robustness of the proposed spectrophotometric method (in dichloromethane as example).

Experimental parameter variation	Average recovery (%)*	
	C_{PGZ}	
	0.7858 µg/ml	23.574 µg/ml
Temperature		
20^{o}C	99.2	99.6
30^{o}C	100.0	100.2
Stability		
23 h	100.0	99.8
25 h	100.1	100.2
Reaction time		
4.0 min	99.6	99.7
6.0 min	100.1	100.2

* n=5.

Conclusion

Effect of non-aqueous solvents (dichloromethane, dichloroethane, chloroform and acetonitrile) on direct spectrophotometric determination of pioglitazone hydrochloride (PGZ) in pure form and pharmaceutical formulations using bromocresol purple (BCP) was studied. The method is based on ion-pair complex between PGZ and BCP. The peak of these complex's occurs at wavelengths from 402 to 408 nm. The absorbance's were proportional to the concentration of PGZ at range 1.00 to 100.00 µM (0.3929 to 39.290 µg.mL^{-1}) for first three solvents and at 2.00 to 100.00 µM (0.7858 to 39.290 µg.mL^{-1}) for acetonitrile in present 5.0x10^{-4} M of BCP. The method was validated for linearity, precision and accuracy, repeatability and robustness. The method was successfully applied for determination of PGZ in pure and pharmaceutical formulations samples with relative standard deviations did not exceed 3.8% for the concentrations of PGZ (0.3929 µg.mL^{-1}) in dichloromethane as example.

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