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REVIEW PAPER

Pioglitazone: A review of analytical methods

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Abstract Pioglitazone is an oral anti-hyperglycemic agent. It is used for the treatment of diabetes mellitus type 2. It selectively stimulates nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-gamma). It was the tenth-best-selling drug in the U.S. in 2008. This article examines published analytical methods reported so far in the literature for the determination of pioglitazone in biological samples and pharmaceutical formulations. They include various techniques like electrochemical methods, spectrophotometry, capillary electrophoresis, high-performance liquid chromatography, liquid chromatography–electrospray ionization-tandem mass spectrometry and high-performance thin layer chromatography.

1. Introduction

The active moiety of pioglitazone hydrochloride (PIO) (5-[[4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione) is a thiazolidinedione (Fig. 1), a potent and highly selective agonist for the nuclear receptor, peroxisome proliferator-activated receptor gamma (PPAR-γ). PPARs are found in tissues like adipose tissue, skeletal muscle and liver, which are critical to insulin action. Activation of PPAR-γ modulates the transcription of a number of insulin-responsive genes involved in the control of glucose and lipid metabolism [1,2]. It is not chemically or functionally related to the alpha-glucosidase inhibitors, the biguanides, or the sulfonylureas. It addresses main pathophysiological defect i.e., insulin resistance, so it is used alone or in combination with insulin, metformin, or a sulfonylureas (glimepride and glibenclamide) as an agent to treat diabetes. PIO reduces peripheral and hepatic resistance to insulin, resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output [3,4]. It has one chiral center and two enantiomers are available but no differences are found in their activities. Hence racemic mixture is pharmacologically used. Physically the hydrochloride salt of PIO is a white crystalline powder with no odor and has a molecular formula of $C_{19}H_{20}N_2O_3S \cdot HCl$. The molecular weight is 392.90 Da. It is administered orally; insoluble in water and ether; slightly soluble in acetone, acetonitrile and alcohol; and soluble in dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) [5,6]. In the present review we have compiled the published analytical methods reported so far in the literature for determination of PIO in biological samples and pharmaceutical formulations. Techniques like potentiometry, spectrophotometry, capillary electrophoresis (CE), high-performance liquid chromatography (HPLC), liquid chromatography–mass spectrometry (LC–MS) and high-performance thin layer chromatography (HPTLC) have been used for analysis, from which HPLC methods are used most extensively. Overview of these methods for determination of PIO is shown in Fig. 2.

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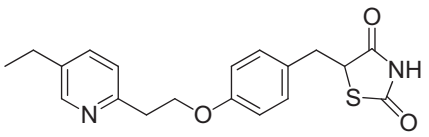

Fig. 1 Structure of pioglitazone.

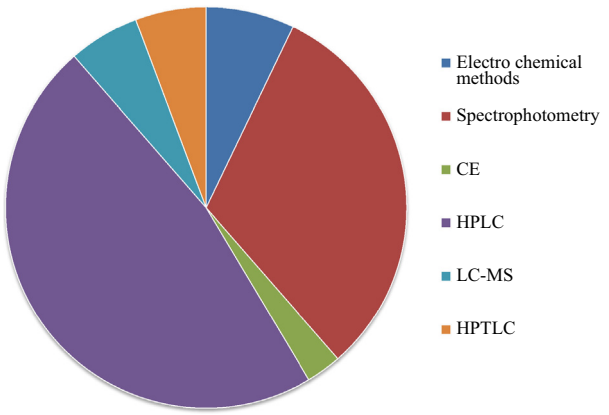

Fig. 2 Overview of analytical methods for estimation of pioglitazone in biological and pharmaceutical samples.

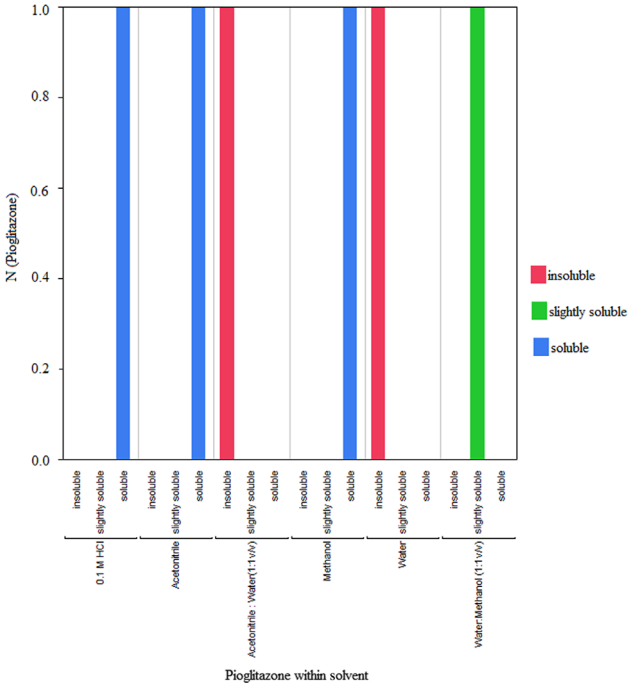

Fig. 3 Solubility chart of pioglitazone (generated using JMP software).

2. Sample preparation

2.1. *Solubility*

According to Biopharmaceutics Classification System (BCS), classification of PIO falls under BCS class-II [7], meaning it has low solubility and high permeability. The solubility of the drug was tested in solvents routinely used for analytical methodology [8]. The solubility chart is shown in Fig. 3. To enhance aqueous solubility of the drug, various strategies like co-solvent solubilization [9], micellar solubilization [10], and cyclodextrin inclusion complexes [11] have been proposed.

2.2. *Sample preparation strategies*

Sample preparation is an integral part of analytical methodology, and it was reported that about approximately 30% error generated in sample analysis was due to sample preparation [12]. Fig. 4 shows various diluents used for the analysis of PIO. In major cases methanol was used as a diluent. The sample preparation techniques for the extraction of PIO from biological matrices (plasma, serum and urine) include protein precipitation with acetonitrile, liquid–liquid extraction using diethyl ether, dichloromethane, ethyl acetate, methyl *t*-butyl ether and *n*-butyl ether; hollow fiber liquid phase micro-extraction using di n-hexyl ether; and solid phase extraction.

3. Analytical methods

3.1. *Electrochemical methods*

Mostafa et al. [13] constructed a new composite and classical potentiometric sensor for the determination of PIO, in which the authors used polyvinyl chloride (PVC) membrane sensors. These membrane sensors incorporate ion association complexes of PIO cation and sodium tetraphenylborate (NaTPB) or phosphomolybdic acid (PMA) or phosphotungstic acid (PTA) as electroactive materials. Direct determination showed an average recovery of 98.5%, 99.0% and 98.4% correspondingly. These sensors were applied for direct determination of PIO in some pharmaceutical preparations and have been used as indicator electrodes for potentiometric titration. In another study El-Ghobashy et al. [14] applied the above proposed principle i.e. membrane selective electrodes for the determination of PIO. The proposed method showed a linear response over the concentration range $3.16 \times 10^{-5} - 1 \times 10^{-2}$ M for PIO. The authors have applied this method for the determination of PIO in tablets and plasma. Potentiometric sensor for quantitative analysis of PIO was developed by Faridbod et al. [15] who selected pioglitazone–tetraphenyl borate as a suitable ion-pair reagent in making potentiometric PVC membrane sensor for PIO. The proposed method showed a wide linear range of 10^{-5}–10^{-2} M and detection limit of 6.0×10^{-6} M. Badawy et al. [16] quantified rosiglitazone, PIO, glimepiride and glyburide conveniently and economically using cyclic voltammetry and differential pulse voltammetry. The authors used carbon paste and glassy carbon electrodes as sensors for these drugs in Briton–Robinson as buffer solution. The proposed technique was found to be orthogonal to the standard HPLC method. Ion selective electrodes were prepared by construction of 10% standard drug ionpair with reineckate or tungstophosphate imbedded as electroactive material. Al-Arfaj et al. [17] used square-wave adsorptive cathodic stripping voltammetry to determine PIO in Britton–Robinson buffer of pH 5. The adsorptive cathodic peak was observed at −1.5 V vs. Ag/AgCl. The detection limit was 8.08×10^{-9} M (3.17 ng/mL) using 300 s pre-concentration time. This method was applied to assay in pharmaceutical formulations and biological fluids. The samples were extracted by liquid–liquid extraction procedure using dichloromethane. The pharmacokinetic parameters of PIO in human plasma were estimated as C_{max} = 785.8 ng/mL, t_{max} = 1.5 h, K_e = 0.125 h^{-1} and $t_{1/2}$ = 8 h.

3.2. Spectrophotometry

In the literature about 22 methods were reported for the estimation of PIO using spectrophotometry [8,18–34], of which 8 methods are for determining PIO alone, while the others are for quantifying PIO in combination with other drug substances. Table 1 shows the summary of the reported spectrophotometric methods indicating the basic principle, λ_{max}, solvent and limit of detection (LOD).

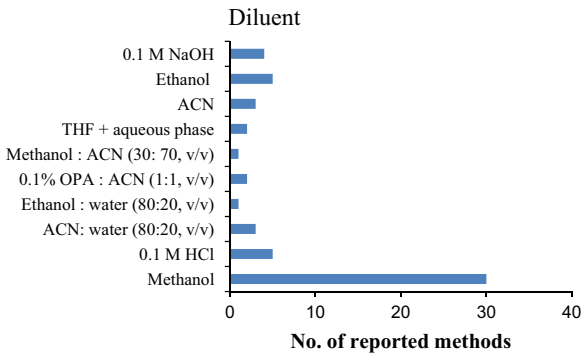

Fig. 4 Various diluents used for the analysis of pioglitazone.

3.3. Capillary electrophoresis (CE)

CE methods have excellent performance for separation of pharmaceuticals, which makes it the first-choice technique for separation of stereoisomers. For PIO analysis few authors have used CE as a separation and determination technique. HPLC and micellar electrokinetic chromatographic (MEKC) methods were developed by Radhakrishna et al. [35] for the determination of PIO and its unsaturated impurity was separated in less than 7 min using an uncoated fused-silica capillary (43 cm × 50 μm i.d.) with extended light path for better sensitivity (25 kV at 30 °C) and a background electrolyte consisting of 20% acetonitrile (v/v) in 0.02 M sodium borate buffer pH 9.3 containing 0.05 M sodium dodecyl sulfate. LOD and limit of quantification (LOQ) were found to be 0.29 μg/mL and 0.74 μg/mL, respectively.

Calixto et al. [36] proposed an alternative electrophoretic method for PIO and its main metabolites determination in rat liver microsomal fraction. It was carried out on an uncoated fused-silica capillary (48 cm × 50 μm i.d.) using 50 M sodium phosphate buffer solution (pH 2.5). Using hydrodynamic injection (0.05 bar, 15 s), samples were introduced into the capillary and detected at 190 nm. The method demonstrated LOQ of 200 ng/mL.

Table 1 Representative spectrophotometric methods for the analysis of PIO.

Compounds	Method	λ_{max}	Solvent/procedure	LOD (μg/mL)	Ref.
PIO, SIT	Vierodt's method	267, 269	0.1 M HCl	0.009	[8]
PIO, MET, GLP	Three wavelength method	236.5, 226.4, 227.3	Acetonitrile:methanol:water (5:4:1)	0.18	[18]
	Multi-wavelength method	236.5, 226.4, 227.3, 254		0.18	
PIO	Extractive spectrophotometric method	419	0.1 M HCl drug+BCG in pthalate buffer pH 2.4 and extracted into chloroform	–	[19]
PIO, MET, GLM	Second order derivative	265.4	Methanol	0.06	[20]
PIO, MET, GLB	Absorption correction method	268	Ethanol (95%)	0.08	[21]
PIO, GLM	First order derivative	250	Methanol	4	[22]
PIO, ATS	Vierodt's method	210, 225	Ethanol	0.7	[23]
PIO, GLP	Vierodt's method	216, 225	0.1 M NaOH	0.04	[24]
	Absorption ratio method	216, 228		0.05	
PIO	–	269	0.1 M HCl	0.66	[25]
PIO	–	224.4	Ethanol	–	[26]
PIO	–	269	0.1 M HCl	0.03	[27]
PIO, MET, GLM	Vierodt's method	227, 233, 265.5	0.1 M NaOH:Water (50:50)	0.007	[28]
PIO	Met. A	267	Ethanol:methanol:water	–	[29]
	Met. B	297	Ion pair complex with methyl orange and bromo cresol green (0.05%)	–	
PIO, MET	Vierodt's method	233, 265.5	0.1 M NaOH	0.007	[30]
PIO	–	238	Phosphate buffer pH 7.4	0.0002	[31]
PIO, GLM	Multi-wavelength spectroscopy	238, 280	0.1 M NaOH	–	[32]
PIO, MET	Difference spectrometric method	225.8	Ethanol+0.1 M NaOH	–	[33]
PIO, MET	Vierodt's method	225, 237	Methanol	0.9	[34]
	Absorption correction method	267		3	

3.4. Chromatography

3.4.1. HPLC

3.4.1.1. Biological samples. Various methods for the determination of PIO in biological samples like plasma, serum and urine [37–43] are listed in Table 2.

3.4.1.2. Pharmaceutical samples. Analytical methods for the determination of PIO in pharmaceutical dosages forms using HPLC [35,44–67] are shown in Table 3, while Fig. 5 shows the best HPLC methods for the analysis of PIO.

3.5. LC–MS

Ramulu et al. [68] have discussed the identification, isolation and characterization of potential degradation products using LC–MS, ^{1}H NMR, ^{13}C NMR, MS and IR. Oxidative degradation impurity and base degradation impurity were characterized as pioglitazone N-oxide, 3-(4-(2-(5-ethylpyridine-2yl)ethoxy) phenyl)-2-mercapto-propanoic acid and 2-(1-carboxy-2-{4-[2-(5-ethylpyridine-2yl)-ethoxy]phenyl}-ethyldisulfanyl)-3-{4-[2-(5-ethylpyridine-2yl)-ethoxy] phenyl} propanoic acid respectively. The method consists of water:trifluoroacetic acid in the ratio of 100:0.05 (v/v) as mobile phase–A and acetonitrile:trifluoroacetic acid in the ratio of 100:0.05 (v/v) as mobile phase–B using gradient/elution (T/%B: 0/10, 12/62, 16/65,17/10) at a flow rate of 1.0 mL/min and the eluents are monitored at 225 nm. The separation was carried out on a Zorbax Bonus RP18 column (150 mm × 4.6 mm, 3.5 μm). Zero air was used as nebulizer gas and high pure nitrogen was used as curtain gas and collision assisted dissociation gas. The MS parameters include Nebulizer 8.00 psi, curtain gas 8.00 psi, ion spray voltage 4500 V, temperature 0 °C, declustering potential 70 V, focusing potential 180 V, and entrance potential 10 V.

A simple, high throughput, direct-injection (LC/MS/MS) method was developed for the determination of PIO in human serum. Extraction of samples was achieved on an Oasis HLB column (50 mm × 1 mm, 30 μm) with a 100% aqueous loading mobile phase consisting of 0.005 M ammonium acetate (pH 4.0). The extracted samples were eluted using a mobile phase consisting of 0.005 M ammonium acetate and acetonitrile. The separation was carried out on a Luna C18 column (50 mm × 4.6 mm, 5 μm). Detection was achieved by positive ion electrospray tandem mass spectrometry. The lower limit of quantitation of the method was 9 ng/mL. The linearity ranged from 9 to 1350 ng/mL. The authors have successfully applied the proposed method to analyze PIO concentrations in human serum samples for a bioequivalence study [69].

LC/MS/MS method was developed by Lin et al. [70] for simultaneous determination of PIO and its two metabolites in human plasma. Samples were extracted by single step liquid–liquid extraction procedure using 1:1 (v/v) of methyl *t*-butyl ether:*n*-butyl chloride. The extraction tubes were shaken at high speed for 20 min. Elution of three components was done isocratically on a C18 column, ionized using a positive ion atmospheric pressure electrospray ionization source, and analyzed using multiple reactions monitoring mode.

Another LC/MS/MS study was reported by Kumari Karra et al. [71] for simultaneous determination of PIO and candesartan in human plasma in which Irbesartan was used as an internal standard. Solid phase extraction was used for extracting the analytes from plasma. The samples were separated on a C18 column using a mixture of acetonitrile and 0.1% formic acid (80:20, v/v) with a flow rate of 0.8 mL/min. The proposed method was linear in the range of 15–3000 ng/mL for PIO and was successfully applied to human pharmacokinetic study.

3.6. HPTLC

Dhirender Singh et al. [72] developed an HPTLC method for PIO. They carried out separation on aluminum plates precoated with silica gel using the mixture of toluene:ethyl acetate:formic acid (10:3:1, v/v) as the mobile phase. The detection of spot was carried

Table 2 Summary of HPLC methods to determine PIO in biological samples.

Matrix	IS	Sample preparation	Mobile phase	Column	Detection	λ_{max}	Flow rate (mL/min)	LOD/ LLOQ (ng/mL)	Ref.
Human serum	AD-4875	Solid-phase and liquid–liquid extraction	MP-A; 0.05 M phosphate buffer (pH 6.0)–methanol (9:1, v/v)	Inertsil ODS-2 (150 mm × 4.6 mm, 5 μm)	UV	269	1	10	[37]
Human urine		Liquid–liquid extraction	and MP-B; 0.05 M phosphate buffer (pH 6.0)–methanol–ACN (4:2:4, v/v/v).					100	
Human plasma	Rosaglitazone	Solid-phase extraction	Methanol:ACN:phosphate buffer (pH 2.6; 0.01 M) (40:12:48, v/v/v)	Apollo C18 (250 mm × 4.6 mm, 5 μm)	UV	269	1.2	50	[38]
Human urine	–	Hollow fiber liquid phase micro-extraction	0.05 M ammonium acetate (pH 4.6) and acetonitrile (20/80, v/v)	ODS-3 (150 mm × 4.0 mm, 3 μm)	UV	270	0.7	1000	[39]
Rat serum	Rosaglitazone	Protein precipitation using ethyl acetate	Methanol and ammonium acetate (0.03 M; pH 5) (60:40, v/v).	Phenomenex C18 (250 mm × 4.6 mm, 5 μm)	UV	269	1	50	[40]
Rat plasma	–	Liquid–liquid extraction	Methanol and ammonium acetate buffer (pH 3.5) (55:45)	Phenomenex C18 (150 mm × 4.6 mm, 5 μm)	UV	252	0.5	4	[41]
Human plasma	–	Protein precipitation	Phosphate buffer (pH 2.6; 0.01 M):methanol:ACN: perchloric acid	Shimpack VP-ODS (150 mm × 4.6 mm, 5 μm)	UV	269	1.5	50	[42]
Human serum	Glibenclamide	Protein precipitation	Methanol–water–acetonitrile (80:10:10, v/v/v)	Purospher STAR RP-18 (250 mm × 4.6 mm, 5 μm)	UV	230	0.7	5000	[43]

Table 3 Reported analytical HPLC methods for determination of PIO either alone or in combination with other drugs like metformin (MET), glimepiride (GLM), atorvastatin (ATS), glibenclamide (GLB), and gliclazide (GLC) in pharmaceutical dosage forms.

Study aim	Mobile phase	Column	Detection	λ_{max} (nm)	Flow rate (mL/min)	LOD (μg/mL)	Ref.
In bulk and pharmaceutical formulations by HPLC and MEKC methods	0.01 M potassium dihydrogen phosphate buffer (pH 6.0):ACN (50:50, v/v)	Symmetry C18 (250 mm × 4.6 mm, 5 μm)	UV	225	1	–	[35]
SIAM by RP-HPLC	Phosphate buffer (pH 4.0), ACN and methanol (55:30:15, v/v)	Prontosil C8 (250 mm × 4.6 mm, 5 μm)	UV	245	1.5	–	[44]
Study of stressed degradation behavior in bulk and pharmaceutical formulation	0.01 M potassium dihydrogen phosphate buffer (pH 3.5):methanol (55:45, v/v)	Phenomenex Luna C18 (250 mm × 4.6 mm, 5 μm)	UV	241	1.5	1.69	[45]
Assay of tablets	Ammonium formate buffer (pH 3):ACN (75:25, v/v)	Nova-Pak C18 (150 mm × 3.9 mm, 5 μm)	UV	225	1	–	[46]
Purity test and assay of tablets	Ammonium formate buffer (pH 4.1):ACN (44:55, v/v)	Symmetry C18, (250 mm × 4.6 mm, 5 μm)	UV	266	1	0.042	[47]
SIAM	ACN:(0.15, v/v) triethylamine (pH 4.6) (40:60, v/v)	Hypersil C-8 (250 mm × 4.6 mm, 5 μm)	UV	220	1.5	0.6	[48]
Simultaneous determination with GLM	0.01 M triammonium citrate (pH 6.95): ACN: methanol (45:35:20, v/v/v)	Cosmosil C18 (250 mm × 4.6 mm, 5 μm)	UV	228	1	–	[49]
Simultaneous with MET	ACN:potassium dihydrogen phosphate buffer (pH 3) (50:50, v/v)	Hypersil BDS C18 (250 mm × 4.6 mm, 5 μm)	UV	238	1	–	[50]
SIAM for determination of impurities	ACN:0.05 M potassium dihydrogen orthophosphate buffer of pH 3.0 (50:50, v/v)	Gemini C18 (250 mm × 4.6 mm, 5 μm)	UV	225	1	0.005	[51]
Simultaneous determination with GLM	ACN:0.02 M ammonium acetate (pH 4.5) (60:40, v/v)	Inertsil ODS (250 mm × 4.6 mm, 5 μm)	UV	230	1	0.2	[52]
Simultaneous determination with MET and GLM in tablet formulation	Methanol:phosphate buffer (pH 4.3) (75:25, v/v)	Inertsil-ODS-3 C-18 (250 mm × 4.6 mm, 5 μm)	UV	258	1	–	[53]
Simultaneous estimation with saxagliptin in tablets	ACN:phosphate buffer (pH 7) (60:40, v/v)	Inertsil C18 column (250 mm × 4.6 mm, 5 μm)	UV	260	0.8	0.010	[54]
Simultaneous determination with GLM	ACN:0.01 M potassium dihydrogen orthophosphate (pH 6.2) (50:50, v/v)	Eurosphere-100 C18 (250 mm × 4.6 mm, 5 μm)	UV	225	1.4	0.00049	[55]
Simultaneous estimation with GLM and rosiglitazone	Dil. orthophosphoric acid (pH 3.0):ACN (80:20, v/v)	Nucleodur C-18 (250 mm × 4.6 mm, 5 μm)	UV	215	0.8	0.19	[56]
Estimation along with MET in tablets	ACN:water:acetic acid (75:25:0.3, v/v/v), pH 5.5	Hypersil ODS C18 (250 mm × 4.6 mm, 5 μm)	UV	230	0.5	0.009	[57]
Simultaneous quantification with GLM and MET	Phosphate buffer:ACN:tetrahydrofuran (40:50:10, v/v/v)	Intersil ODS 3V (250 mm × 4.6 mm, 5 μm)	UV	228	1.7	–	[58]
Simultaneous estimation along with GLM	Phosphate buffer:ACN (40:60, v/v)	Inertsil ODS (150 mm × 4.6 mm, 5 μm)	UV	225	1.5	0.12	[59]
SIAM along with GLM	Solution-A is 0.02 M potassium dihydrogen phosphate, pH 3.2. Solution-B is ACN	Zorbaxcyano (250 mm × 4.6 mm, 5.0 μm)	UV	230	0.8	–	[60]
Simultaneous determination with metformin and GLC in multicomponent formulation	Methanol:0.02 M potassium dihydrogen phosphate (85:15, v/v)	C18 column (250 mm × 4.6 mm, 5.0 μm)	UV	227	1.2	0.1	[61]
Simultaneous estimation with GLM	Methanol:water (72:28, v/v)	Agilent TC – C18 (250 mm × 4.6 mm, 5 μm)	UV	230	1	0.760	[62]
Simultaneous estimation with telmisartan	ACN:ammonium dihydrogen phosphate (pH 4.5; 0.02 M) (65:35, v/v)	Phenomenex C8 (250 mm × 4.6 mm, 5 μm)	UV	210	1	0.82	[63]
Determination of along with metformin and GLM	ACN:phosphate buffer (pH 3) (65:35, v/v)	Phenomenex RP-18 (150 mm × 4.6 mm, 5 μm)	UV	245	0.5	0.061	[64]
Micellar liquid chromatographic analytical method for determination of atorvastatin calcium	Tween-20: n-butanol: phosphate buffer, (pH 4.2) (50:25:25,v/v/v)	Luna C18 (250 mm × 4.6 mm, 5 μm)	UV	322	1.5	–	[65]
SIAM for determination of impurities in PIO	Sol-A: phosphate buffer pH 3.1 and Sol-B: acetonitrile	Inertsil ODS-3V (150 mm × 4.6 mm, 5 μm)	UV	225	1.5	0.033	[66]
HPLC method	0.01 M buffer:methanol (40:60, v/v)	Symmetry – extend – C18 (150 mm × 4.6 mm, 5 μm)	UV	240	1.2	–	[67]

out at 254 nm. The calibration curve was found to be linear between 100 and 3000 ng/mL. Gumieniczek et al. [73] reported a thin-layer chromatographic behavior of three antidiabetic drugs PIO, rosiglitazone and repaglinide and then they developed stability-indicating HPTLC method for determination of PIO in tablets. The mobile phase consisted of 1,4-dioxane and phosphate buffer of pH 4.4 (5:5). The detection was carried out by densitometry at 266 nm. The proposed method was linear in the range of 0.4–2.4 μg/10 μL. Later Sharma et al. [74] gave an HPTLC method for the determination of PIO and atorvastatin using aluminum plates precoated with silica gel and mobile phase consisting of chloroform:methanol:toluene (6:3:4, v/v). The detection was carried out at 259 nm. The calibration curve was found to be linear between 100 and 400 ng/spot for both drugs. In another study, Anand et al. [75] proposed an HPTLC method for determination of PIO along with telmesartan using the mobile

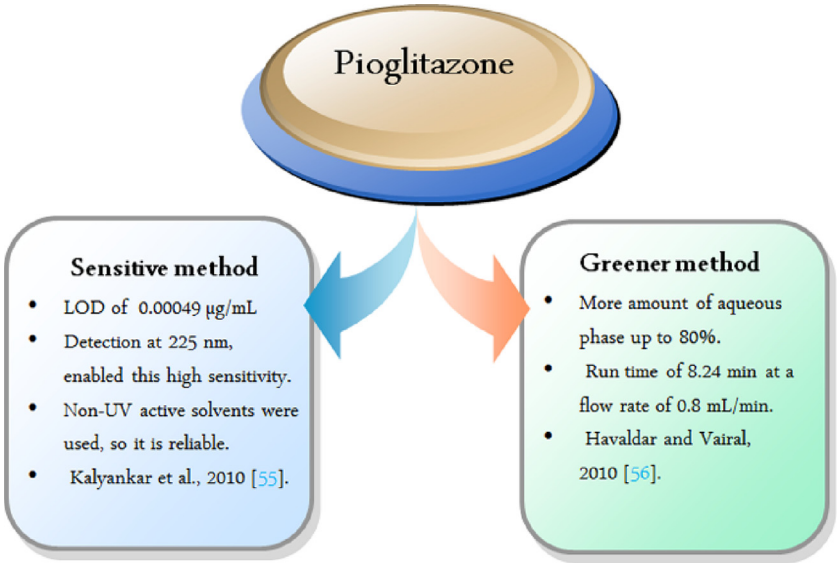

Fig. 5 Sensitive and greener HPLC methods among the reported.

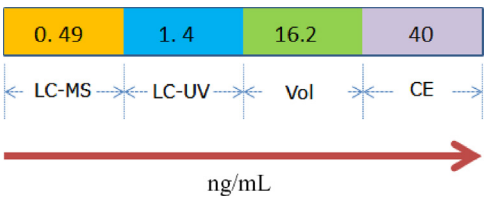

Fig. 6 Comparison of sensitivities of various techniques for estimation of pioglitazone.

phase consisting of toluene:ethyl acetate:methanol (7:2:1, v/v/v). LOD and LOQ were 140.0, 186.7 and 424.4, 1867.5 ng/spot for telmesartan and PIO respectively. Kale et al. [76] proposed a simple HPTLC method for simultaneous estimation of PIO, MET, and GLP using mobile phase consisting of acetonitrile, methanol, propyl alcohol, and ammonium acetate 7:2:1:1 (v/v). Densitometric quantification was performed at 240 nm. The R_f value of PIO was found to be 0.83 and the method was linear in the range of 0.3–1.2 µg/band. The comparative sensitivities of various techniques are shown in Fig. 6.

4. Challenges

As discussed earlier, PIO belongs to BCS class-II and so it is insoluble in water. Selection of the diluents would be a problem in the analysis of PIO as there are concerns with the formation of insoluble precipitate with various compositions of aqueous:organic phases. Furthermore, with more amount of aqueous phase or methanol in the mobile phase, the run times are prolonged with greater tailing factor in HPLC. It was observed that the drug gets slowly degraded in strongly acidic conditions over a period of time. For spectrometric determination, complexity with multicomponent dosage forms includes the presence of multiple entities and excipients, which may cause considerable challenge to the analytical chemist during the development of assay procedure. Estimation of the individual drugs in these multicomponent dosage forms becomes difficult. For such instances like multicomponent dosage forms, chemometric methods can be preferred to routine spectrophotometric methods.

5. Conclusion

In conclusion, a broad range of techniques are available for the analysis of PIO in biological samples and pharmaceutical formulations. The analysis of the published data revealed that the HPLC was extensively used for the determination of PIO in various matrices like plasma, serum and urine. For determination of PIO in biological samples, we recommend the HPLC–MS/MS method, since this method combines the HPLC separation ability with MS sensitivity and selectivity, allowing the unambiguous identification of PIO and its metabolites. For analysis of PIO in pharmaceuticals, HPLC with UV detection is applicable because this method provides accurate results and low cost compared to more advanced detection techniques. This review carried out an overview of the current state-of-art analytical methods for the determination of PIO.

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