



**VISUAL, POTENTIOMETRIC AND CONDUCTOMETRIC ACID-BASE
TITRATIONS FOR DETERMINATION OF ANTIDIABETIC
PIOGLITAZONE-HCl****MOHAMMED AL BRATTY¹, HISHAM HASHEM^{1,2*}, SAFEENA
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University, Egypt***Correspondence author: Dr. Hisham Hashem; E-mail address:****hisham413@yahoo.com; Tel.: +20552303266; Fax: +20552303266****ABSTRACT**

Each molecule of the antidiabetic pioglitazone-HCl (PGZH) includes in its structure one HCl; so this HCl can be titrated using NaOH. There was no previously reported conductometric or potentiometric titration for determination of PGZH; so the main goal of this study was to find simple and precise visual, conductometric and potentiometric acid-base titration methods for determination of PGZH in bulk powder and tablets dosage form. First method is based on visual detection of endpoint during titration of PGZH with standard NaOH in presence of phenolphthalein as indicator. In the second and third methods electrochemical techniques were applied to detect the endpoint of titration. Potentiometric titration using pH-meter and applying standard NaOH as a titrant is the main principle of the second method. Third method depends on conductometric determination of the HCl content of PGZH using NaOH as a titrant.

The results of the proposed methods indicate that the proposed methods are precise and accurate. Good recovery is obtained reflecting high accuracy of the method while the low relative standard deviation ensured the good precision of the method.

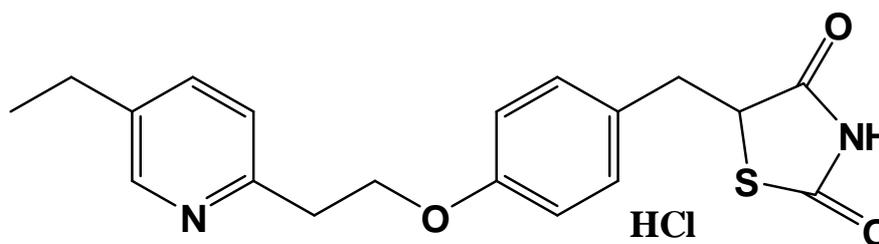
The three proposed methods are found to be simple and low expensive. They were successively used for quantitative analysis of PGZH in its tablets dosage form. Statistical analysis ensured that there was no significant difference between the results of established methods and those of the previously reported one.

Keywords: Conductometry; Potentiometry; Acid-base; Titration; Pioglitazone-HCl

1. INTRODUCTION

Pioglitazone-HCl, which is a thiazolidine-dione oral anti-diabetic similar to rosiglitazone, can be applied in the management of type 2 diabetes mellitus. It can be given orally, especially in case of patients who are

overweight. It is prescribed also for patient for whom metformin is not tolerated or contra-indicated [1]. Chemically, Pioglitazone-HCl is (\pm) -5-{p-[2-(5-ethyl-2-pyridyl) ethoxy] benzyl}-2,4-thiazolidine dione hydrochloride (scheme 1) [1].



Scheme 1: Chemical structure of PGZH

Several spectrophotometric methods have been reported for estimation of PGZH including ion pair complex formation with bromothymol blue, bromophenol blue and bromocresol purple [2], chlorophenol red [3] fast green and orange G [4] as well as interaction with diazotized sulphanilic acid [5]. Derivative spectrophotometry [6] has been also applied. Another spectrophotometric method was found which is based on oxidation of PGZH with excess n-bromosuccinimide and then oxidation of metol through unreacted amount of n-

bromosuccinimide followed by coupling between oxidation product of metol and sulphanilic acid. The coloured compound produced in acidic medium was finally measured at 520 nm [7]. Atomic absorption spectrometric methods for determination of PGZH have been reported which are based on its reaction with disodium edetate calcium, sodium chloride [8] and bismuth (III) tetraiodide [4]. Other methods include electrochemical techniques [9-14] such as flow injection analysis [9] and voltametry [10]. Chromatographic

methods [7,15,16] have also been reported such as a very rapid separation and quantitation of PGZH in presence of metformin-HCl on monolithic column [7] as well as TLC methods [16, 17]. Adding to those previously mentioned techniques, capillary electrophoresis was also applied for determination of PGZH [18, 19].

Titrimetric technique is considered to be one of the simplest analytical techniques applied in drug analysis. Different pharmacopoeias include several titrimetric assay methods [20]. In titration of drugs, the endpoint can be determined visually [21, 22], conductometrically [23- 25] or potentiometrically [21, 22]. There is only one previously reported titrimetric method for determination of PGZH [17]; which was based on non-aqueous titration of PGZH in glacial acetic acid with 0.1 M perchloric acid. This is why this work aimed to establish new simple titrimetric methods for PGZH analysis.

2. MATERIALS AND METHODS

2.1. Instrumentation

All conductometric measurements were done using Jenway 470 model portable conductivity/TDS meter.

For potentiometric titration an Elico 120 digital pH-meter provided with

combined glass-SCE electrode system was applied.

2.2. Chemicals and reagents

All solutions were prepared with analytical-grade chemicals and water was always doubly distilled. The studied drug was of pharmaceutical grade. NaOH, KOH and ethanol were obtained from Merck (Darmstadt, Germany). Phenolphthalein indicator was supplied by S.D's Chem & Industries (Bombay, India). The authentic PGZH was a gift from Unipharma (El-Obour city, Egypt).

0.01 M NaOH solution should be freshly prepared, standardized and stored in tightly capped containers [26]. In a 100 mL volumetric flask, 0.5% phenolphthalein solution was prepared via dissolving of 500 mg of pure phenolphthalein in 50 mL ethanol and then diluted to the mark with bidistilled water [21].

Actos 30[®] tablets containing 30 mg PGZH/tablet (The Arab Pharmaceutical Manufacturing Co. Ltd., Amman, Jordan) were analyzed for their content of PGZH.

2.3. Standard solution

1 mg/mL PGZH stock solution was prepared by dissolving 100 mg PGZH in 50 mL neutralized alcohol and then the volume was completed to 100 mL

with neutralized alcohol. The neutralized alcohol was prepared through addition of dilute alcoholic KOH to ethanol with constant stirring.

2.4. General procedures

2.4.1. Visual titration (method A)

In a 100 mL titration flask 2-4 drops 0.5% phenolphthalein were added to aliquot of the drug solution containing 2-20 mg of PGZH and then the volume was completed to 25 mL with bidistilled water. The contents were titrated against 0.01 M NaOH and the endpoint was indicated with appearance of pink color. The necessary volume correction was made through blank titration [22].

The drug content in the solution was determined from equation (1):

$$\text{Amount (mg)} = \text{VMR/N} \quad (1)$$

Where V is volume of titrant, M is molecular weight of the drug, R is molar concentration of NaOH (0.01 M) and N is number of moles of titrant consumed by one mole of drug.

2.4.2. Potentiometric titration (method B)

Into a 100 mL calibrated flask an aliquot of the standard drug solution equivalent to 2-20 mg of PGZH was transferred and diluted to the mark with bidistilled water. The contents were transferred to a beaker quantitatively

and titrated against 0.01 M NaOH. After each 0.1 mL addition of NaOH, the solution was stirred magnetically for 30 seconds and pH-value was noted. Equivalence point was determined from the plot representing the relation between volume of titrant and pH. The concentration of drug was determined according to equation (1) as mentioned under method A.

2.4.3. Conductometric titration (method C)

An aliquot of the standard drug solution equivalent to 2- 20 mg of PGZH was transferred in to a 100 mL volumetric calibrated flask and diluted to 100 mL by adding bidistilled water. The contents were transferred quantitatively to a conductometric titration cell. The contents were titrated conductometrically against 0.01 M NaOH. The conductance was noticed after each addition of 0.1 mL of NaOH after stirring for 30 seconds. Equation (2) was used for correction of conductance for dilution [27].

$$\Omega\text{-1correct} = \Omega\text{-1obs} [v_1+v_2/v_1] \quad (2)$$

$\Omega\text{-1correct}$ and $\Omega\text{-1obs}$ are the corrected electrolytic conductivity and the observed electrolytic conductivity, respectively. v_1 represents the initial

volume and v_2 represents the volume of NaOH added [28].

A plot of corrected conductivity versus the volume of added NaOH was constructed and the equivalence point was determined. The concentration of drug under study was found according to the equation (1) as mentioned under the visual titration procedure.

2.4.4. Procedure for formulations

Ten tablets of Actos 30[®] were weighed and ground into a fine powder. An equivalent amount to 200 mg of PGZH was taken into 100 mL flask and then 50 mL of neutralized ethanol was added. The contents of the flask were shaken for 15 minutes. After that the volume was completed to 100 mL with neutralized ethanol and well mixed [22]. And then contents were filtered and the first portion of filtrate was discarded. A suitable aliquot was analyzed according to the three procedures.

3. RESULTS AND DISCUSSION

3.1. Method development

Several experiments were done to select the most suitable conditions for titration.

3.1.1. Medium of titration

Several solvents were investigated for dilution such as H₂O, methanol, ethanol and acetone. The procedure in H₂O was

found to be the most suitable for successful results and sharpest endpoint was detected.

3.1.2. Effect of temperature

To test the effect of temperature on the endpoint of the potentiometric and conductometric titrations, titrations were carried out at 25 – 40 °C. The results showed that the increase in temperature did not result in clear change in pH and conductance. This is why 25 °C (room temperature) was selected for carrying out the titrations.

3.1.3. Reagent's concentration

Constant and stable pH and conductance readings after 30 seconds mixing were obtained using 0.01 M as optimum concentrations of NaOH. Lower concentrations resulted in unstable readings.

3.2. Validation of the proposed methods

The validity of the proposed methods for PGZH determination in bulk form and formulation was examined by analyzing the samples using the proposed procedures.

$$\text{Recovery \%} = (\text{Found concentration} / \text{Taken concentration}) \times 100 \quad (3)$$

Results (Tables 1- 4) showed that the proposed methods are satisfactorily accurate, precise and reproducible. To test the precision and accuracy of the methods 5 replicates were analyzed

(Tables 1 and 2).

Figs. 1 and 2 represent the potentiometric and conductometric titration curves of 17.5 mg PGZH, respectively. Student's t- and F-test were applied for statistical comparison between the proposed methods result and those of reported method [4]. It is obvious that

there was no significant difference (Table 3).

Analysis of the PGZH (Table 4) in the tablet formulation applying standard addition technique resulted in good recovery for all the three methods at three different concentrations.

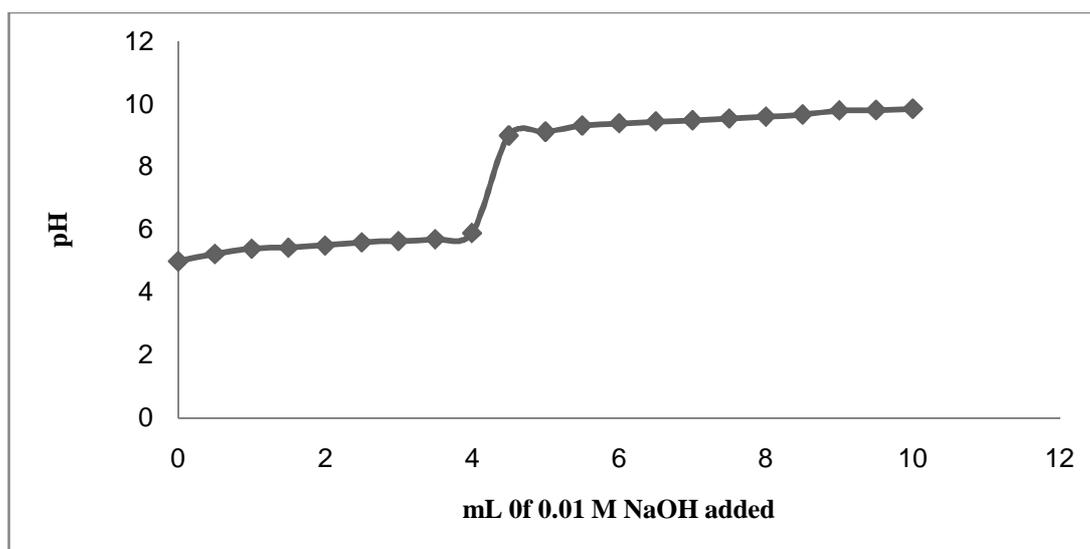


Fig. 1: Potentiometric titration curve of 17.5 mg with 0.01 M NaOH

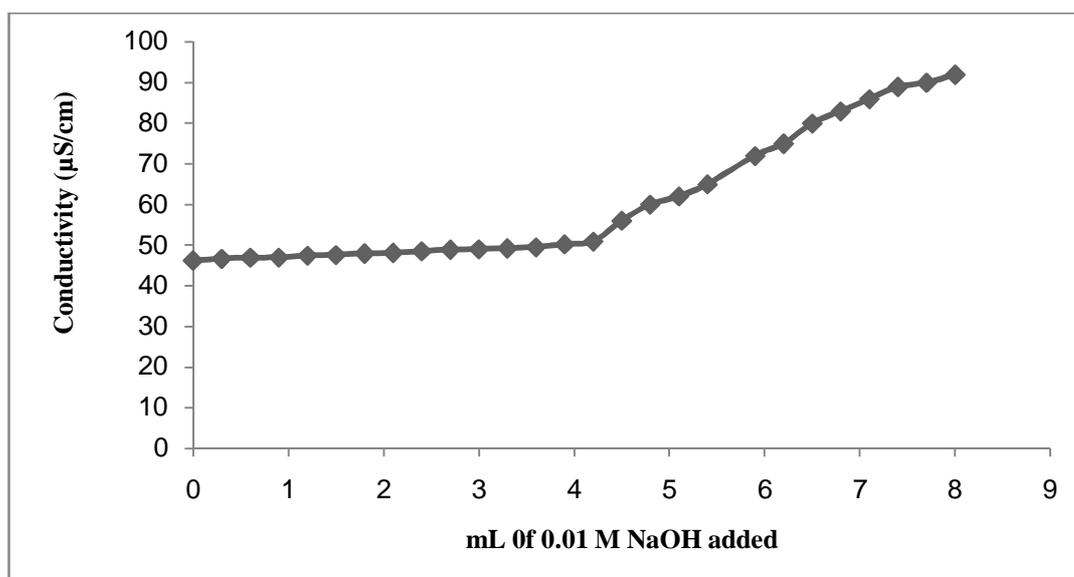


Fig. 2: Conductometric titration curve of 17.5 mg with 0.01 M NaOH

Table 1: Intra-day precision data

Procedure	Taken (mg)	Found (mg)	Recovery%	RSD%
Visual titrimetry (n=5)	4	3.90	97.50	0.13
	12	12.11	100.92	0.64
	20	19.96	99.80	0.33
Potentiometric titrimetry (n=5)	4	3.92	98.00	0.25
	12	12.2	101.67	0.96
	20	19.92	99.60	0.54
Conductometric titrimetry (n=5)	4	3.85	96.25	0.78
	12	11.90	99.17	0.93
	20	20.30	101.50	1.04

Table 2: Inter-day precision data

Procedure	Taken (mg)	Found (mg)	Recovery%	RSD%
Visual titrimetry(n=5)	4	4.12	103.00	1.09
	12	12.31	102.58	2.04
	20	20.33	101.65	0.93
Potentiometric titrimetry(n=5)	4	4.13	103.25	0.69
	12	12.40	103.33	0.55
	20	20.40	102.00	1.33
Conductometric titrimetry (n=5)	4	3.98	99.50	2.18
	12	11.83	98.58	1.97
	20	19.70	98.50	0.96

Table 3: Statistical comparison of results of the proposed procedures applied on Actos 30[®] tablets compared with those of reported method.

	Visual procedure	Potentiometric procedure	Conductometric procedure	Reportedmethod [4]
N	5	5	5	8
Mean Recovery	99.77	101.74	99.36	100.72
Variance	1.19	1.77	3.17	0.45
±S.D.	1.09	1.33	1.78	0.67
±R.S.D.	1.09	1.31	1.79	0.67
Student-t	1.96 (2.20) ^a	1.86 (2.20) ^a	1.99 (2.20) ^a	
F-test	2.64 (4.12) ^b	1.93 (4.12) ^b	1.36 (4.12) ^b	

a and b are the Theoretical Student t-values and F-ratios at p=0.05.

Table 4: Accuracy of the proposed methods applying standard addition technique

	PGZH in tablet extract, mg	PGZH added in mg (pure)	Total PGZH found mg	Pure PGZH recovered (%) ± RSD
Visual procedure	8.1	4	12.00	97.50 ± 1.32
	8.1	8	15.70	95.00 ± 0.89
	8.1	12	20.20	100.83 ± 1.73
Potentiometric procedure	7.9	4	11.80	97.50 ± 2.10
	7.9	8	15.60	96.25 ± 1.99
	7.9	12	20.40	104.17 ± 2.09
Conductometric procedure	7.9	4	12.00	102.50 ± 0.38
	7.9	8	15.50	95.00 ± 0.07
	7.9	12	20.30	103.33 ± 1.15

4. CONCLUSION

The proposed methods represent, for the first time, conductometric and potentiometric acid-base titrations of pioglitazone-HCl. In addition, a new visual acid-base titration was established. The three proposed methods are simple, precise, low expensive and accurate. The statistical comparison between the results of the proposed methods and those of the reported method reflected no significance difference. The proposed methods enabled determination of pioglitazone-HCl in tablet formulation.

CONFLICT OF INTEREST

The authors ensure that there is no conflict of interest.

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