

Conductometric Titration of Metformin in Pure Form and in Pharmaceutical Preparations Using Sodium Tetrphenylborate and Cetylpyridinium Bromide

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A sensitive and accurate conductometric method for the determination of 0.4–8.5 mg of metformin hydrochloride (MetHCl) using sodium tetrphenylborate (TPB) and cetylpyridinium bromide (CPB) in aqueous solution is described. The effect of the solvent, reagent concentration, temperature and time on the shape of the titration curve was studied. Statistical treatment of the experimental results indicates that the method is precise and accurate. The accuracy of the method is indicated by the excellent recovery (99.5–100.9%) and the precision is supported by the low standard deviation < 0.06 . A comparative study between the suggested procedure and the pharmacopoeial method for this compound in its pharmaceutical preparations showed no significant difference between the two methods.

INTRODUCTION

Metformin is a biguanide hypoglycemic agent used in the treatment of noninsulin diabetes mellitus. Metformin was determined in pharmaceuticals by differential spectrophotometry based on dissolution in 0.1 N HCl solution and measurement of absorbance at 234 nm.¹ Conductometric titration based on the Cu-biguanide reaction, which gives a pink solution complex, was applied to determine metformin². Metformin titration with HClO_4 in AcOH medium was carried out in order to test several recommended indicators³. Metformin hydrochloride was determined by atomic absorption spectrophotometry of its copper complex⁴, gas-liquid chromatography⁵, nuclear magnetic resonance spectrometry⁶ and gas chromatography⁷. A method for the analysis of metformin was developed by use of HPLC with fluorometric detection⁸. A spectroscopic method is described for the determination of metformin based on its formation of a molecular complex with iodine in dichloroethane⁹. Potentiometric titration using a new metformin ion-selective plastic membrane electrode based on metformin tetrphenylborate¹⁰, phosphotungstate¹¹ or phosphomolybdate ion pair^{12,13} was applied to determine metformin in pure solutions and in pharmaceutical preparations.

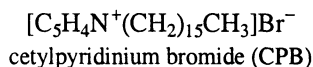
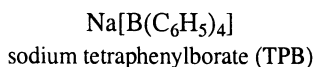
The aim of this work was to report new conductometric methods that are simple, time-saving and accurate for the determination of metformin

hydrochloride as a raw material and in some pharmaceutical preparations with no interference of other constituents in their formulations.

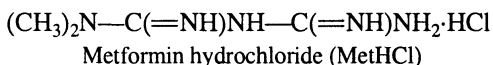
EXPERIMENTAL

A conductometer model C 525 (Crison Instrument Co., Spain), equipped with thermoprobe was used. The measurement ranges were 0–20, 0–200, 0–2000 $\mu\text{s cm}^{-1}$ and 0–20, 0–200 ms cm^{-1} with a precision ± 0.01 , ± 0.1 , $\pm 1.0 \mu\text{s cm}^{-1}$ and ± 0.01 , $\pm 0.1 \text{ms cm}^{-1}$ respectively. The diptype cell (Ingold Co., Swiss) was used with a cell constant, K_{cell} , of 0.95. The desired temperature was maintained with circulating water-bath thermostat model U10 (MLW Instrument Co., Germany) connected to a jacket around the analysis vessel.

Solutions of 0.01 M sodium tetraphenylborate (Aldrich) and cetylpyridinium bromide (BDH) were prepared by dissolving appropriate weights in bidistilled water. The solutions were standardized and kept in light-resistant, well-closed containers.



0.1 M metformin hydrochloride (Dolder) stock solution was prepared by dissolving appropriate weight of solid in bidistilled water. Working solutions of lower concentrations were freshly prepared by appropriate dilution.



General Procedure: A volume containing 0.4–8.5 mg of drug was transferred to a 25 mL volumetric flask and made up to the mark with water. The contents of the volumetric flask were transferred to a beaker and the conductivity cell was immersed in the sample solution. 0.01 M TPB or CPB solution was then added from a microburette with precision ± 0.005 mL and the conductance was measured subsequently to each addition of reagent solution and after thorough stirring and reaching the desire temperature. The conductance reading was taken after each addition of the reagent. A graph of conductivity (corrected values for dilution) vs. volume of titrant added was constructed and the end-point was determined from the computerizing calculated intersecting point.

Procedure for Tablets: Twenty tablets containing MetHCl were weighed and finely powdered. An accurately weighed portion of the powder equivalent to 100 mg of MetHCl was dissolved in 100 mL of methanol and mixed for about 15 min and then filtered. The methanol was evaporated to about dryness. The remaining portion of solution was diluted in a 100 mL volumetric flask to volume with bidistilled water. The general procedure was then followed in the concentration ranges mentioned above.

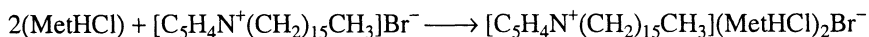
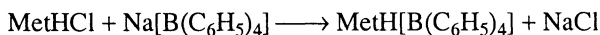
RESULTS AND DISCUSSION

Conductometric measurements can be used in quantitative titration of ionic solutions in which the conductance of the solution varies before and after the

equivalence point, so that two intersecting lines can be drawn to indicate the end-point.

The shape of the titration curve depends on all the species present during the titration process and other factors such as viscosity, dielectric constant, solvation, ion-pair association and proton transfer.

The results show an obvious inflection point in the conductance curve at drug-reagent molar ratios of 1 : 1 and 2 : 1 for TPB and CPB, respectively. the reactions may be represented by the equations:



The optimum conditions for performing the titration in a quantitative manner were elucidated as described below:

Three different titrations were described: (I) aqueous drug solution with aqueous reagent solution; (II) methanolic or ethanolic drug solution with methanolic or ethanolic reagent solution and (III) drug solution with reagent solution, both in methanol-water or in ethanol-water mixture with different ratios. Preliminary experiments showed that procedure (I) was the most suitable for successful results. The reagent concentration in each titration must be not less than ten times that of the drug solution in order to minimize the dilution effect on the conductivity throughout the titration.

The optimum concentration of TPB and CPB was 0.01 M to achieve a constant and highly stable conductance reading. Lower concentrations led to unstable readings and more time was needed to obtain constant conductance values.

On raising the temperature to 40°C, no significant change in the angle between the two intersecting straight lines at the titration curves was observed, whereas above 40°C the shape of the titration curve changed and so decreased the precision of the end-point. The suitable working temperature was $25 \pm 0.1^\circ\text{C}$.

The relationship between the conductance values and the concentration of MetHCl, TPB and CPB solutions were linear increasing in the range of 0.01–100 mM. The conductance value of MetHCl solution was greater than that for TPB or CPB solution at the same concentration with about one time or three times, respectively.

Representative titration curves are shown in Fig. 1. Two straight lines are obtained, intersecting at the end-point. If TPB was used as a reagent, the first branch slowly increasing and the second sharply ascending. The increase of conductance may be attributed to the formation of alkali halides in the solution as a result of the reaction, where $[\text{C}_5\text{H}_4\text{N}^+(\text{CH}_2)_{15}\text{CH}_3](\text{MetHCl})_2\text{Br}^-$ represents the very slightly soluble precipitate.

After the end-point, the titration curves indicate a sharp increase of conductance. This may be due to this dissociation of the reagent.

When CPB reagent was used the conductance values sharply ascended due to the formation of ion-associated in the solution as a result of the reaction. A slight increase of conductance was obtained after the equivalence point, despite the excess of the bromide ion-containing reagent.

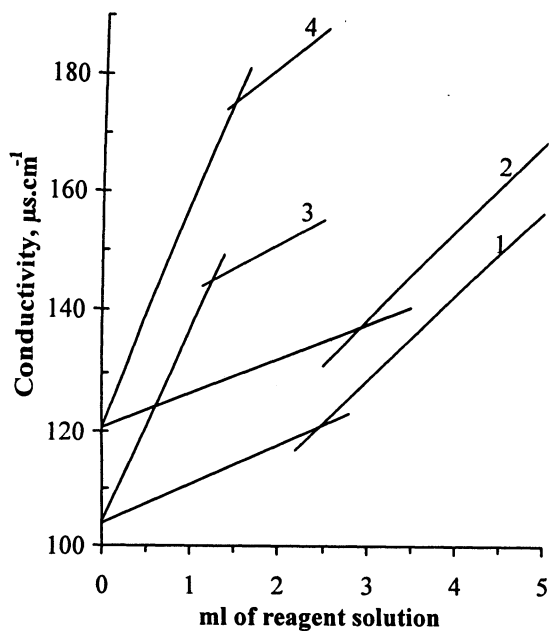


Fig. 1. Conductometric titration curves of 25 mL 1.0 and 1.2 mM MethHCl vs. 0.01 M TPB (1, 2) or CPB (3, 4).

TABLE-1
ACCURACY AND PRECISION OF THE PROPOSED CONDUCTOMETRIC
TITRATION METHODS

Reagent	MethHCl ($\mu\text{g mL}^{-1}$)			Recovery (%)
	Taken	Found*	S.D.	
TPB	16.00	15.97	0.057	99.81
	50.00	49.97	0.014	99.94
	100.00	100.67	0.017	100.67
	150.00	150.75	0.021	100.50
	200.00	200.16	0.014	100.08
	250.00	250.25	0.019	100.10
	340.00	340.37	0.051	100.11
CPB	100.00	99.60	0.031	99.60
	130.00	131.20	0.024	100.92
	150.00	151.10	0.014	100.73
	165.00	164.30	0.013	99.57
	180.00	180.04	0.015	100.02
	200.00	199.52	0.016	99.72
	250.00	249.10	0.046	99.64

*Average of five determinations

TABLE-3
DETERMINATION OF MeHCl IN TABLETS BY THE PROPOSED AND NON-AQUEOUS TITRATION METHODS APPLYING THE STANDARD ADDITION TECHNIQUE

Tablet	Taken mg	Added mg	TPB		CPB		Non-aqueous	
			Found* mg	Recovery %	Found* mg	Recovery %	Found* mg	Recovery %
Glucostop	3	-	2.98	99.33 ± 0.65	2.97	99.66 ± 0.54	3.01	100.33 ± 0.58
	3	1	3.99	99.75 ± 0.21	4.01	100.25 ± 0.52	4.02	100.50 ± 0.31
	3	2	5.01	100.20 ± 0.43	4.98	99.60 ± 0.65	4.99	99.80 ± 0.46
	3	3	5.98	99.66 ± 0.32	6.08	101.33 ± 0.30	5.97	99.50 ± 0.60
	3	4	6.97	99.85 ± 0.39	-	-	7.05	100.71 ± 1.21
Glyciphage	3	5	8.02	100.25 ± 0.55	-	-	8.04	100.50 ± 1.32
	3	-	2.98	99.33 ± 0.66	2.99	99.66 ± 0.54	3.01	100.33 ± 0.58
	3	1	3.98	99.50 ± 0.55	3.97	99.25 ± 0.43	4.03	100.75 ± 0.70
	3	2	5.02	100.40 ± 0.26	5.03	100.60 ± 0.33	4.99	99.80 ± 0.63
	3	3	6.10	101.66 ± 0.38	6.07	101.16 ± 0.25	6.09	101.50 ± 1.02
	3	4	7.04	100.57 ± 0.64	-	-	7.05	100.85 ± 0.58
	3	5	8.05	101.00 ± 0.65	-	-	8.06	100.75 ± 1.04

*Average of six determinations

The results from the conductometric titration are summarized in Table-1 and show that good recoveries and standard deviations were obtained. The optimum concentration ranges for determining MetHCl using TPB and CPB were 16–340 and 100–250 $\mu\text{g mL}^{-1}$, respectively, at which well-defined inflections and stable conductance values were obtained.

In order to establish whether the proposed method exhibits any fixed or proportional bias, a simple linear regression¹⁴ of observed drug concentration against the theoretical values (7 points) was calculated. Student's t-test (at 95% confidence level) was applied to the slope of the regression lines (Table-2) and showed that it did not differ significantly from the ideal value of unity. Hence, it can be concluded that there are no systematic differences between the determined and true concentrations over the cited ranges. The standard deviations (S.D.) can be considered satisfactory, at least for the level of concentrations examined.

TABLE-2
LINEAR REGRESSION ANALYSIS FOR MetHCl USING TPB AND CPB

Parameters	TPB	CPB
Optimum concentration range (mg/25 mL)	0.4–8.5	2.50–6.25
Intercept of the regression line ^a	0.0011	0.0164
Slope of regression line	1.0014	0.9951
Student's t-test ^b (2.310) ^c	2.0650	2.0390
Range of error (%)	± 0.43	± 0.67

^aObserved vs. theoretical, ^bComparison with pharmacopoeial method¹⁵,

^cValue in parenthesis is the theoretical t-value for five degrees of freedom.

Analytical Applications

The validity of the proposed method was assessed by measuring drug concentration of a pharmaceutical dosage form, glucostop tablets (K&C Lab., Syria) and glyciophage tablets (MBC, Syria) containing 500 mg MetHCl (equivalent 390 mg Met-base) per tablet. The results obtained with the proposed method were compared with the official non-aqueous titration method for MetHCl¹⁵ and shown in Table-3. This comparison indicated that the proposed procedure is as accurate and precise as the official method. The proposed methods are simple, rapid, sensitive and use simple reagents and apparatus.

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