

Conductometric Titration of Metformin Hydrochloride: Simulation and Experimentation

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Abstract: In order to teach students, the importance of conductometric titrations in this work, we present a laboratory experiment to quantify the amount of metformin hydrochloride in a tablet. The quantification was carried out through the evaluation of the chloride by silver nitrate. The titration and the end point were followed by conductometric titration, as well as by potentiometric and visually by the Volhard method. In addition, the theoretical conductivities of the metformin hydrochloride solution were calculated when known volumes of titrant are added, using the limit conductivity data for each of the ions present in the literature. To simulate the conductometric titration, the calculated conductivity values were plotted based on the volume of silver nitrate added. A comparison between techniques is made in order to determine the best monitoring method, being this one conductimetry to detect the equivalence point for metformin hydrochloride with 0.99 ± 0.03 , according to relative standard deviation (% RSD). Simulated titration curves adequately describe obtained results in an experimental way. The conductometric titration is the best method for quantification since it shows less dispersion between obtained results and has the highest concordance among results. Their application is shown through the analysis and conductometric titration.

Key words: Conductometric titration, metformin hydrochloride, simulation.

1. Introduction

Metformin hydrochloride (MetHCl) is a biguanide, named IUPAC, of 3-(diaminomethylidene)-1, 1-dimethylguanidine hydrochloride. MetHCl is an antihyperglycemic agent, used for the treatment of type II diabetes. Currently, metformin is the first drug of choice for the treatment of type II diabetes and is prescribed to at least 120 million people worldwide. Metformin is considered an antihyperglycemic drug because it reduces blood glucose concentrations in type II diabetes without causing hypoglycemia [1].

There are simpler methods to be carried out in an experimental teaching laboratory for quantification such as potentiometric and conductimetric techniques. There are methods to detect the equivalence point in a titration, which is substantial to quantitatively determine an analyte. This point corresponds to the quantity of substance being titrated. Detecting the equivalent point is error prone, therefore it is crucial to select the method that possesses the lesser error. For this, several instrumental and classic methods are available [2].

Among the classic methods, visual indicators that allow the endpoint to be recognized by an abrupt change in color are found. Likewise, instrumental methods determine a physicochemical property associated to a species of our interest. The technique's election will depend on the nature of the titration reaction. Potentiometric techniques can be used when the property measured is a difference in potential and in conductometric techniques, the solution's conductivity is measured according to the quantity of titrant added.

Svante Arrhenius in 1880, published his doctoral thesis about solutions and electrolyte conductivity [3], defining the latter as the measurement of a current flow that results from applying a given electric force. In Arrhenius' first contributions to electrolyte theories,

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| Structure | $H_2N \xrightarrow{NH} NH HCI H_2N \xrightarrow{H_2N} H_1 HCI H_3$ |
|------------------|--|
| pK _a | 12.4 |
| Water solubility | 0,285 mg/mL (20 C) |
| molecular weight | 165,63 g/mol |
| | |

 Table 1
 Properties of metformin hydrochloride.

the relationship between degree of dissociation for a weak electrolyte is found, which is the quotient of the molar conductivity by the molarlimiting conductivity [4]; Kohlrauch took advantage of this contribution and continued studying electrolyte solutions' conductivity, until in 1884 published his theory "Independent migration of Ions", in which he stipulates that molar conductivity of an electrolyte is due to the contribution of each ion present in the solution [5]. Kohlrauch's theory is applicable to strong and weak electrolytes [6, 7] in which he deduced equations that describe, predict and explain the behavior of electrolytic solutions [8]. Such theory is the basis for conductometry, since Kohlrausch established that conductometry is proportional to ion concentration in a solution. This allows monitoring the progress of the reactions.

The main advantage of conductometric titration is that very diluted solutions can be analyzed in a concentration interval from 10⁻⁴ M to 10⁻³ M. In the case of higher concentrations, activity coefficients need to be corrected [9]. Acid-base reactions can be typically monitored through conductivity, since redox usually require a highly acidic medium in order to be quantifiable. Given that the protons concentration is too high, the change in conductivity from the other ions would not be detected. Therefore, monitoring of conductometric titrations of redox reactions is not feasible [10].

Due to the fact that certain pharmaceutical formulations contain as active ingredients a hydrochloride, it is possible to titrate chlorides with a standardized silver nitrate solution and monitor the reaction through the ions conductimetric measures. Moreover, standardizing and quantifying acid-base solutions is possible in order to determine the equivalence point.

Metformin hydrochloride quantification is presented through a chloride titration using visual, potentiometric and conductometric monitoring. Methods are being compared and conductimetry highlights are demonstrated by using the molar conductivity values reported in literature. In order to promote conductimetry application, the simulated graphs comparison from experimentation is presented.

2. Experimentation

2.1 Reagents and Methods

Analytical grade reagents were used: silver nitrate (J.T. Baker), Iron (III) nitrate (J. T. Baker), sodium hydroxide (Merck), potassium thiocyanate (J. T. Baker), sulfuric acid (Sigma Aldrich), conductivity deionized water (Sigma Aldrich) < 4 μ S/cm, anhydrous sodium carbonate (J. T. Baker), potassium chloride calibrating solution 15 μ S/cm (Merck). Potentiometric titrations were carried out with a potentiometer Thermo Scientific Thermo Orion using a silver indicator electrode and calomel-saturated as reference electrode. Conductivity measurements were made with a conductivity meter Oakton with a cell in conductivity CON510.

Titrating solutions standardization. Sodium hydroxide solution standardization was made with anhydrous potassium hydrogen phthalate, using phenolphthalein as an indicator. Silver nitrate solution was standardized by titrating it with potassium thiocyanate according to Volhard's method.

Drug problem solution. Grind 3 tablets that contain metformin hydrochloride. From the tablet powder, weigh 30 mg, dissolve with deionized water, filter excipients and gauge to 50 mL. From this solution, take an aliquot of 20 mL and gauge to 100 mL.

2.2 Conductometric and Potentiometric Titration

For the conductometric and the potentiometric

monitoring, titrate by triplicate 10 mL of the problem solution with the standard silver nitrate solution 1.8867×10^{-3} M until completing a titrant volume of 10 mL In the potentiometric titration of the problem solution, use a silver electrode indicator, and the saturated calomel electrode as reference.

2.3 Volhard Method

Drug problem solution titration. For the visual technique, take an aliquot of 10 mL from the problem solution and add 10 mL of the silver nitrate standard solution 1.8867×10^{-3} M. Add three drops of Iron (III) nitrate 5% and backward titration with the potassium thiocyanate standard solution 2.2640×10^{-3} M until the first red tone in the system persists. Triplicate the procedure.

2.4 Simulation of Conductometric Titration Curves for Quantifying Metformin Hydrochloride Tablets

Specific conductivity, κ , is directly proportional to an ion concentration, according to equation 1.

$$\kappa = \lambda_i^o C_i \tag{1}$$

Proportionality constant, λ° , is the molar limiting conductivity for the ion, which is reported in literature (Table 2).

Kohlrauch established in his theory "independent ion migration" that the measured conductivity is the sum of each ion conductivity. Therefore, in a system that contains different ions, its conductivity will be given by adding each ion's conductivity [11], calculated with Eq. (2) for any given ion mixture:

$$\kappa = \sum_{i}^{n} \lambda_{i}^{o} C_{i}$$
⁽²⁾

Table 2Molar limiting conductivities of ions in thevaluation of hydrochloride with silver nitrate.

| Ion | Molar limiting conductivity λ° (Scm ² /mol) |
|------------------------------|---|
| H^+ | 349.81 |
| Cl | 76.35 |
| Ag^+ | 61.90 |
| NO ₃ ⁻ | 71.46 |

Using Eq. (2) enables the theoretical study and simulation of conductometric titration curves. Each curve has four regions to be analyzed:

- Start
- (1) Before the equivalent point
- (2) In the equivalent point
- (3) After the equivalent point

(4) It is necessary to use the equation for every region of the curve. The conductometric curve simulations carried out are shown below.

The drug being analyzed is a hydrochloride which dissociates in water according to the scheme 1

 $MetHCl \rightarrow Met + H^+ + Cl^-$ (Scheme 1) Where MetHCl is the drug in its hydrochloride form, that when dissociates produces metformin in its neutral form (Met), protons and chloride ions. Chloride ions are then titrated with silver nitrate (Scheme 2) and given by their stoichiometric relation, the active ingredient can be calculated. The titration of the chloride ions, including all the ions present in the solution, are shown in scheme 2. Where the H⁺ and NO₃⁻ ions are spectator ions since they do not react but their concentration does contribute to the total value of the conductivity.

 $H^++Cl^+Ag^++NO_3^- \rightarrow AgCl_{(s)}+H^++NO_3^-$ (Scheme 2) It is then necessary to establish a material balance for each of the curve's region, being *Co* the initial chloride concentration and *Vo* the aliquot's volume being titrated: *C* is the titrant (silver nitrate) concentration, and *V* the volume added with the burette. In this case, the spectator ions are the protons (chloride's contra-ions) and nitrate ions (silver contra-ions). Matter balance is described in Table 3.

In the beginning of titration, only chlorides and protons exist. Thus, conductivity can be expressed as:

$$\kappa = \lambda_{Cl^{-}}^{o} Co + \lambda_{H^{+}}^{o} Co \tag{4}$$

Before the equivalence point, existing ions are chloride, protons and nitrate. Conductivity is given by:

$$\kappa = \lambda_{Cl^{-}}^{o} C_{Cl^{-}} + \lambda_{H^{+}}^{o} C_{H^{+}} + \lambda_{NO_{3}^{-}}^{o} C_{NO_{3}^{-}}$$
(5)

| Design of the summer | Main reaction | | | | | Spectator ions | |
|------------------------------|----------------------------|---|----------------------------|--|---------------------|--------------------------------------|--|
| Region of the curve | Cl | + | Ag^+ | | AgCl _(s) | $\mathrm{H}^{+},\mathrm{NO}_{3}^{-}$ | |
| Start | Со | | _ | | | | |
| Before the equivalence point | $\frac{CoVo - CV}{Vo + V}$ | | ε | | | CV | |
| In the equivalence point | ε | | ε | | | $\overline{Vo+V}$ | |
| After the equivalence point | ε | | $\frac{CV - CoVo}{Vo + V}$ | | | | |

 Table 3
 Material balance for chloride titration with silver nitrate (MetHCl).

Table 4 Equation summary to simulate the chloride conductometric titration with silver nitrate (Metformin).

| Region of the curve | Ions present in the solution | Equation that allows conductivity calculations |
|------------------------------|---|---|
| Start | Cl ⁻ , H ⁺ | $\kappa = \lambda_{Cl^-}^o Co + \lambda_{H^+}^o Co$ |
| Before the equivalence point | $Cl^{-}, H^{+}, NO_{3}^{-}$ | $\kappa = \lambda_{C\Gamma^-}^o \frac{CoVo - CV}{Vo + V} + \lambda_{H^+}^o \frac{CV}{Vo + V} + \lambda_{NO_3^-}^o \frac{CV}{Vo + V}$ |
| In the equivalence point | H ⁺ , NO ₃ ⁻ | $\kappa = \lambda_{H^+}^o \frac{CV}{Vo + V} + \lambda_{NO_3}^o \frac{CV}{Vo + V}$ |
| After the equivalence point | Ag^+ , H^+ , NO_3^- | $\kappa = \lambda_{Ag^{+}}^{o} \frac{CV - CoVo}{Vo + V} + \lambda_{H^{+}}^{o} \frac{CV}{Vo + V} + \lambda_{NO_{3}}^{o} \frac{CV}{Vo + V}$ |

Substituting Eq. (5) with the expressions given in Tablet 4:

$$\kappa = \lambda_{CI^-}^o \frac{CoVo - CV}{Vo + V} + \lambda_{H^+}^o \frac{CV}{Vo + V} + \lambda_{NO_3^-}^o \frac{CV}{Vo + V}$$
(6)

Eq. (6) allows conductivity to be calculated for the solution before the equivalent point.

In the equivalence point, only spectator ions are present, calculating conductivity as follows:

$$\kappa = \lambda_{H^+}^o C_{H^+} + \lambda_{NO_3^-}^o C_{NO_3^-}$$

When substituting this with what was established in Table 4, the equation to calculate conductivity in the equivalence point can be established

$$\kappa = \lambda_{H^+}^o \frac{CV}{Vo+V} + \lambda_{NO_3^-}^o \frac{CV}{Vo+V}$$
(7)

Lastly, for the region after the equivalence point, the ions that contribute to conductivity are silver, protons and nitrates. The following equation expresses the way to calculate conductivity in such a case:

$$\kappa = \lambda_{Ag^+}^o \frac{CV - CoVo}{Vo + V} + \lambda_{H^+}^o \frac{CV}{Vo + V} + \lambda_{NO_3^-}^o \frac{CV}{Vo + V}$$
(8)

Table 4 sums up all the equations to simulate the conductometric curve.

To titrate chloride with silver nitrate 0.0071 M, it

was determined that the chloride concentration in the titrated aliquot 0.0009 M, finding that the equivalence point is that of 4.79 mL. Molar limiting conductivity values for the ions are 0.0349 for the proton, 0.0076 for the chloride, 0.062 for silver and 0.0072 for nitrate [8]. The units for molar limiting conductivity are Sm^2/mol . With this data, the conductometric curve can be simulated as shown in Fig. 3.

3. Results and Discussion

3.1 Conductometric Monitoring

Fig. 1 shows the conductometric titration for chlorides in metformin.

The equivalence point was determined by regression of the data, matching the linear trends of the areas before and after the equivalence point (Fig. 2).

By equating the equations of the straight line, we obtain the volume value of the equivalence point, which is 4.78 mL. Obtaining 493.15 mg of metformin hydrochloride per tablet, the percentage of relative standard deviation being 1.09%

As shown in Table 5, relative standard deviation coefficients for the conductometric method are lower



Fig. 1 Chloride conductimetric titration in metformin hydrochloride with AgNO₃.



Fig. 2 Determination of the equivalence point by linear regression of the data.

than that of the visual detection and the potentiometric technique. Hence, conductimetry is reliable and replicable. To compare the quantification result for each technique with that the product's table reports in its specifications, the confidence interval is calculated by using the Eq. (1).

$$CI = \overline{X} \pm t_{n-1} \frac{S}{\sqrt{n}} \tag{9}$$

Confidence intervals are shown in Table 6. It is reported each tablet contains 500 mg of metformin hydrochloride active ingredient. As shown in Table 2, confidence intervals include what was reported by the manufacturer. Likewise, the three methods are feasible to carry out the quantification.

To establish a comparative point between the methods, the recovery percentage is calculated in each monitoring, and the relative standard coefficient is calculated. According to Table 7, conductometric monitoring has the highest recovery percentage. Thus, this technique is exact and since it has the lowest variation coefficient, it can be considered as the best technique to carry out the quantification.

As shown in Fig. 3, the simulated curve adequately describes the behavior of experimental conductivity. A pronounced chance can be observed in the slopes before and after the equivalence points, which allows this point to be easily detected. Before the equivalence point, conductivity descends slightly since the chloride ions are consumed, but nitrate ions that come from the titrating solution are added. Given that

Table 5 Amount obtained from metformin hydrochlorideby three quantification methods.

| Monitoring | Metformin hydrochloride amount | % Relative standard |
|----------------|-----------------------------------|---------------------|
| | in the drug (mg/tablet) | deviation (n=3) |
| Visual | 475±28 | 1.91 |
| Potentiometric | 481±25 | 2.03 |
| Conductometric | 493±15 | 1.09 |

| Table | 6 | Confidence | intervals | to | determine | metformin |
|--------|-------|-----------------|-----------|----|-----------|-----------|
| hydroe | chloi | ride in tablets | 5. | | | |

| • | |
|----------------|---------------------|
| Monitoring | Confidence interval |
| Visual | 500.86,449.13 |
| Potentiometric | 504.09,457.91 |
| Conductometric | 506.86,476.14 |

 Table 7
 Percentage recovery and relative standard deviation.

| | | Recovery percenta | ge | % RDS | | |
|--|------------|-------------------|----------------|--------|----------------|----------------|
| Compound | Monitoring | | | | | |
| | Visual | Potentiometric | Conductometric | Visual | Potentiometric | Conductometric |
| Metformin hydrochloride in tablets | 0.95±0.056 | 0.96±0.05 | 0.99±0.03 | 5.89 | 5.21 | 2.03 |



Fig. 3 Comparison of the simulated and experimental conductometric curve of chloride titration with silver nitrate.



Fig. 4 Potentiometric titration curve chloride titration in drugs with AgNO₃

nitrate ions molar conductivity is slightly low than that of the chloride ions, the conductivity of the solution decreases. After the equivalence point, silver ions, nitrate ions and protons are present, so the conductivity of the solution increases sharply. This allows the equivalence point to be adequately detected

3.2 Potentiometric Titration

Fig. 4 shows titration curves to determine chlorides in metformin hydrochloride. We obtained a sigmoid curve and a big potential change when it has added approximately 5 mL of silver nitrate, since has ended the precipitation of chloride, in the form of AgCl, corresponding to the content of the sample metformin hydrochloride from according to the scheme of reaction 1. Determining the equivalence point by the method of parallel slopes, and making the corresponding calculation. He was obtained. For the drug, 481 ± 25 mg metformin hydrochloride were obtained per tablet (RSD = 2.03%)

3.3 Visualtitration (Volhard Method)

For determining metformin hydrochloride contained in the drug for the visual monitoring, chlorides precipitate by adding a standard solution of silver nitrate, according to the following reaction

The remaining silver quantity is titrated with a potassium thiocyanate standard solution (Volhard method), detecting the endpoint of the reaction through the red tone in the system given by the Iron (III)-thiocyanate complex with the first titrant excess

 Ag^++SCN $AgSCN\downarrow$ (Scheme 3) In the quantification of metformin hydrochloride content occurs the precipitation of chlorides to add the 10 mL of the standard solution of silver 1.8867×10^{-3} M, then proceed to assess the remaining silver by titration with potassium thiocyanate, Volhard [2] method, stopping the addition of evaluation at the appearance of the first persistent red due to the formation of complex iron (III)-thiocyanate. Since the detection of the equivalence point is visual, this causes a greater d valuation by recoil of chlorides was 475 ± 28 mg of active ingredient per Tablet (RSD = 1.91%)

4. Conclusions

Metformin hydrochloride was quantified, obtaining 493±15 mg of active ingredient per drug tablet. Conductimetry presented the lowest percentage of relative standard deviation, having the smallest dispersion and a greater concordance degree within the obtained results. In such a way, this is the most reliable technique since the equivalence point can be easily detected through a Sharp change given by the ions increase in conductivity after the equivalence point. Confident intervals for the analyte content

include the quantity reported by the manufacturer, showing that quantification is precise. Conductometric titration curves were simulated, which accurately describe the data behavior experimentally obtained, being the conductimetric technique reproducible.

This type of experiment teaching proposal may be used in the teaching and learning [12] of qualifications conductivity through the strategy of cooperative group [13] in which the group can be divided into three sections, a section would work the visual titration, another section the potentiometric titration and another section conductometric titration. At the end the three sections discuss their results and establish general conclusions of the group on the experiment.

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