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Conductometric determination of naproxen in bulk and pharmaceutical dosage form

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ABSTRACT

This study aimed at the development of simple and cheap conductometric method that can be used for the determination of naproxen in bulk and dosage forms. During the study, naproxen was titrated with sodium hydroxide (Method A) and potassium hydroxide (Method B) and the end points were determined with conductivity cell. Variables affecting the end point determination were also studied in the range of 1-10 mg/mL of naproxen. The proposed methods were validated by precision and recovery studies. The percentage recoveries ranged from 99.15±0.659 and 101.13±0.543 with % RSD of 0.897 and 0.749 with sodium hydroxide and potassium hydroxide, respectively. The methods were effectively applied for the determination of naproxen in tablet dosage form. The methods proposed in this study can be used as substitute for more composite and classy methods used for the determination of naproxen and are highly reproducible as compared to other reported methods.

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1. Introduction

Naproxen ((2*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid, Figure 1), a nonsteroidal anti-inflammatory drug (NSAID), is an arylalkylpropanoic acid derivative and is used for the treatment of rheumatoid arthritis and other rheumatic disease, dysmenorrhea, and acute gout [1,2]. It is a potent cyclooxygenase inhibitor thereby decreasing the formation of prostaglandins and thromboxanes [3]. It also inhibits the enzyme thromboxane synthase causing inhibition of the platelet aggregation process [4].

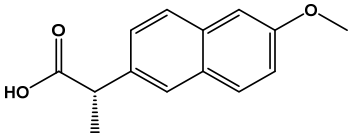

Figure 1. Chemical structure of naproxen.

Naproxen is determined in bulk and pharmaceutical dosage forms by UV spectrophotometric techniques [5,6], TLC [7], HPLC with UV detection methods [8], GC-MS [9], ion-selective methods [10], phosphorescence and chemiluminescence methods [11], spectrofluorimetric techniques [12-14] and capillary electrophoresis with mass detectors [15-17]. Bio-analytical methods for detection of naproxen and its metabolites have also been reported [8]. Most of the aforementioned techniques are time-consuming, involve costly and complicated instruments and therefore are not suitable for routine analysis.

For quality control purposes, conductometric titrations serve as an extremely useful method and can be widely used for determination of pharmaceuticals [18-20]. Measurements of conductivity of the solutions can be used to estimate total number of ions present in a solution. Conductometric methods have proved to be cost effective for the assay of pharmaceuticals in bulk and dosage forms because these offer the advantages of reasonable selectivity, fast response time, applicability to coloured and turbid solutions. However, no direct method utilising the concept of conductometric end point detection of naproxen has been reported in the literature. Therefore, the present work is aimed at finding and elaborating conditions for conductometric determination of naproxen. Earlier also the authors have described the accurate and precise determination of losartan potassium, pantoprazole sodium, sumatriptan succinate, rabeprazole sodium and lomefloxacin hydrochloride (by using precipitating agents) [21], diphenhydramine hydrochloride (by using silver nitrate) [22] and pioglitazone hydrochloride (by acid-base titrations) [23]

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in bulk and pharmaceutical dosage forms by conductometric titrations. Therefore, in continuation, the present study was undertaken to hold a good future for routine analysis of naproxen in poor resource settings.

2. Experimental

2.1. Chemicals and reagents

All chemicals used were of analytical reagent grade from Sigma-Aldrich. For preparing solutions, double distilled conductivity water was used. Sodium hydroxide, potassium hydroxide, phenolphthalein, oxalic acid and methanol were obtained from Merck, Germany. The authentic naproxen sample was obtained as a gift from Exela Pharmsci. Pvt. Ltd., Egypt. 2×10^{-4} M NaOH and 2×10^{-3} M KOH solutions were freshly prepared with bi-distilled water and standardized against oxalic acid.

2.2. Pharmaceutical formulations

Tablets of Riaproxen® (500 mg), Proxen® (500 mg) and Naprox DS® (250 mg) were procured from the local market (Jazan, Kingdom of Saudi Arabia).

2.3. Instrumentation

Jenway 470 model portable conductivity/TDS meter was used for all conductometric determinations.

2.4. Standard solution

The stock solution of 1 mg/mL was prepared by dissolving 100 mg of standard naproxen in 75 mL of methanol (previously neutralised with phenolphthalein). The final volume was made to 100 mL with bi-distilled water.

2.5. General procedures

2.5.1. Conductometric titration

Into a 100 mL calibrated flask, aliquots of standard drug solution containing 1-10 mg of naproxen were transferred and final volume made to 100 mL with a mixture of methanol: bi-distilled water (3:1, *v*:*v*) and continued as per the procedure mentioned in method A and method B.

2.5.1.1. Method A

In method A, the contents as obtained from above were transferred to a conductivity cell and titrated with 2×10^{-4} M NaOH solution. The conductance was measured after each 0.1 mL addition of titrant with stirring for 30 seconds. The corrected conductance values for each dilution were calculated as per the standard reported procedure [23,24].

2.5.1.2. Method B

In method B, the contents as obtained from above were transferred to a conductivity cell and titrated with 2×10^{-3} M KOH solutions. The conductance was measured after each 0.1 mL addition of titrant with stirring for 30 seconds. The corrected conductance values for each dilution were calculated as per the standard reported procedure [23,24].

Equation (1) was used for correction of conductance for dilution [25].

$$\Omega^{-1}_{Correct} = \Omega^{-1}_{Obs}\,[v1+v2/v1] \quad (1)$$

where, $\Omega^{-1}_{Correct}$ and Ω^{-1}_{Obs} are the corrected electrolytic conductivity and the observed electrolytic conductivity, respecttively, $v1$ represents the initial volume and $v2$ represents the volume of NaOH and KOH added [26]. The equivalence point was determined by plotting a graph between corrected conductivity and volume of NaOH and KOH added for Method A and Method B, respectively.

A plot of corrected conductivity versus the volume of added NaOH and KOH was constructed and the equivalence point was determined. The percentage drug content was determined by the formula given in Equation (2),

$$\text{Amount (mg)} = V\times M\times R/N \quad (2)$$

where, V is the volume of titrant, M is molecular weight of the drug, R is molar concentration of NaOH and KOH, respectively, and N is number of moles of titrant consumed by one mole of the drug.

2.5.2. Procedure for formulations

An equivalent amount 100 mg of powder of twenty tablets each of Riaproxen® 500 mg, Proxen® 500 mg and Naprox DS® 250 mg were taken in 100 calibrated flasks. To each flask 75 mL of methanol was added (previously neutralised with phenolphthalein solution) and stirred for 10 minutes. The final volume was made up to 100 mL with bi-distilled water. All solutions were filtered through 0.45 µm filter. The suitable aliquots were then analysed for their percentage purity by following the procedure given in conductometric titrations.

2.5.3. Reference method

The procedure given in USP-31 is used as a reference method and used is for comparison of results [27].

3. Results and discussion

Various ionic solutions wherein there is a significant change in the conductance values during the end point, conductometric measurements can be used for their quantitative analysis. Conductometric titrations depend mainly on all the ionic species that will be present during the titration. Secondary factors affecting the process include ion-ion association, ion-solvent interactions, temperature, viscosity, dielectric constant and proton transfer species etc. [24,25]. Conductivity of a solution can be defined as ability of a solution to pass an electric current and depends on a number of factors such as concentration, mobility of ions, valence of ions and temperature. The conductivity can be calculated by the Equation (3):

$$\kappa = G \bullet K \quad (3)$$

where, κ = Conductivity (S/cm); G = Conductance (S), where G = 1/R; and K = Cell constant (cm^{-1}).

Generally conductivity of solutions is measured in aqueous solutions because water by the process of solvation can stabilise the ions formed. Pharmaceutical substances can behave as electrolytes and include acids, bases and salts and can be either strong or weak. Strong electrolytes are substances that are fully ionised in solution. Solutions of strong electrolytes conduct electricity because the positive and negative ions can migrate largely independently under the influence of an electric field. Weak electrolytes are substances that are not fully ionised in solution. A solution of a weak electrolyte can conduct electricity, but usually not as well as a strong electrolyte because there are fewer ions to carry the charge from one electrode to the other.

Organic acids having a p*K*a ranging from 4.0 to 5.5 can be titrated with inorganic bases such as sodium hydroxide (at low concentrations), lithium hydroxide (in presence of ammonia) [28], as well as organic bases such as potassium methoxide in

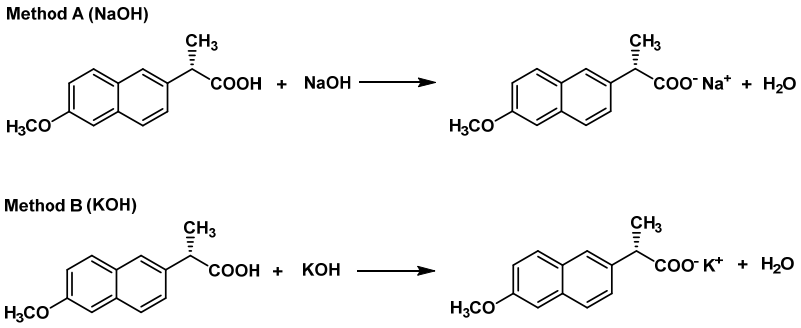

Figure 2. Simple chemical reactions between naproxen and two bases, sodium hydroxide (Method A) and potassium hydroxide (Method B)

pyridine-benzene or tetramethylammonium hydroxide in benzene, with intersection angles as satisfactory as those given by strong acids [29]. Naproxen having one carboxylic acid group with p*K*a value of 4.15 [2] serves as a suitable candidate for conductometric titration.

Conductance measurements were used successfully in our studies in the quantitative titration of naproxen as the conductance of naproxen solution varies significantly before and after the equivalence point. The point of intersection of two lines was taken as the end point.

The molecular structure of naproxen and its possible chemical reaction with sodium hydroxide and potassium hydroxide has been depicted in Figure 2.

Different conductometric titration curves obtained during the studies of pure naproxen in bulk and tablet dosage form have been depicted in Figure 3-6. The trends obtained could be compared with the representative curves of weak acid and strong base titrations.

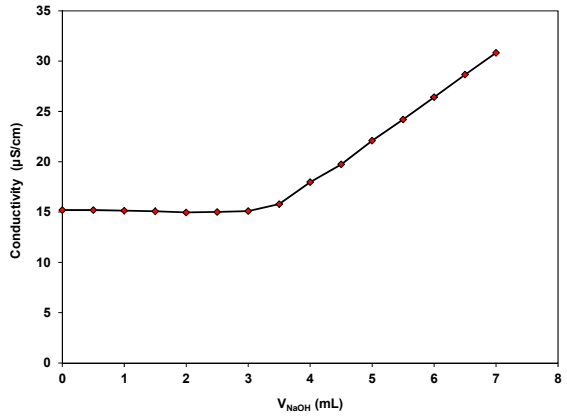

Figure 3. Conductometric titration curve of naproxen with 2×10^{-4} M NaOH.

Initially, the high conductance values of naproxen solution could be attributed to the high conductivity of its H^+ ions (349.82). However, during the titration high conductivity H^+ ions (349.82) of naproxen were replaced by low conductivity Na^+ ions (50.11) of sodium hydroxide and K^+ ions (73.52) of potassium hydroxide indicating the slight decrease in the conductivity of the solution. This result in little change in conductivity with respect to the volume of base added. During the titration of naproxen with sodium or potassium hydroxide, the salt (sodium or potassium salt of naproxen with Method A and Method B, respectively) tends to limit ionisation of naproxen still present so that its conductance decreases. The rising salt concentration however will tends to produce an increase in conductance. As a result of these opposing influences the titration curves show a minima depending upon the concentration and strength of naproxen. The conductance values near the equivalence point are high because of the hydrolysis of the respective salts. The initial change in conductivity values can also be attributed to weakly basic of nature of naproxen. This could be further justified as very dilute solutions of bases were used for the titrations. No significant differences in the shape of curves were observed when naproxen was titrated with sodium hydroxide or potassium hydroxide; however potassium hydroxide was used in comparatively higher concentrations than the sodium hydroxide. After the end point, a sudden increase in conductance was observed. This may be due to increase of ions of high conductivity such as OH^- during the end point.

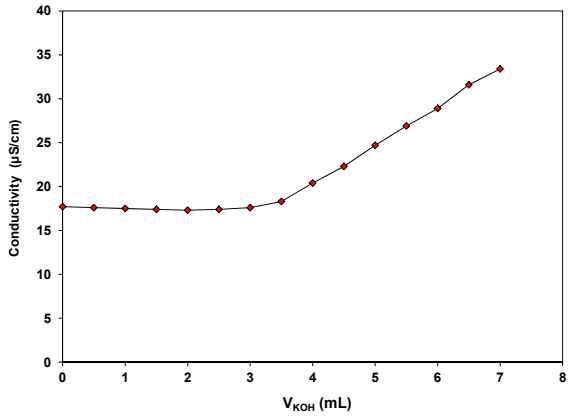

Figure 4. Conductometric titration curve of naproxen with 2×10^{-3} M KOH.

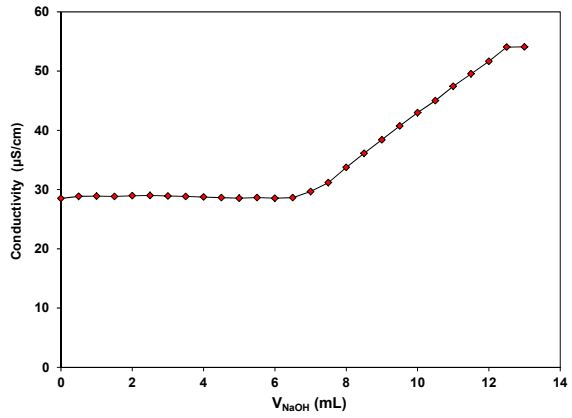

Figure 5. Conductometric titration curve of Riaproxen® with 2×10^{-4} M NaOH.

Table 1. Linear regression parameters for naproxen determination using conductometric titrations.

Parameters	NaOH (Method A)	KOH (Method B)	Reference method USP-31 [27]
Optimum concentration range of naproxen	1-10 mg/mL	1-10 mg/mL	1-10 mg/mL
Intercept of the regression line	1.227	1.231	1.216
Slope of regression line	0.993	0.993	0.994
Student t-test (2.310)	1.837	1.859	2.106
Range of error (%)	±0.74	±0.74	±0.79

Table 2. Accuracy studies (% Recovery).

Method	Amount taken (mg/mL)	Amount added (mg/mL)	% Recovery	RSD%
NaOH	10	8	99.5143±0.6163	0.4074
(Method A)	10	10	99.1356±0.7033	0.4102
	10	12	99.2416±0.6995	0.3628
KOH	10	8	99.4513±0.7019	0.3052
(Method B)	10	10	98.9916±0.8896	0.4136
	10	12	99.3096±0.7012	0.4151
Reference method	10	8	98.8396±0.8016	0.3052
USP-31 [27]	10	10	98.9316±0.7896	0.4136
	10	12	98.9011±0.8013	0.4151

Table 3. Determination of naproxen in different tablet formulations.

Drug Formulation	Amount of drug (mg/mL)	% Drug content [a]				Reference method	Mean RSD%
		NaOH	RSD%	KOH	RSD%		
Riaproxen®	6	99.9580±0.7874	0.4822	99.7590±0.8173	0.4723	99.7910±0.6969	0.4699
(500 mg)	8	99.9280±0.1014		99.8990±0.1103		99.9240±0.1090	
	10	99.2970±1.1140		99.1980±1.1160		99.2920±1.1100	
Proxen®	6	99.3231±0.7026	0.4662	99.2991±0.6926	0.4665	99.2991±0.6926	0.4672
(500mg)	8	99.2241±0.7027		99.2264±0.7022		99.2264±0.7022	
	10	99.1641±0.7019		99.1642±0.7197		99.1642±0.7197	
Naprox DS®	6	99.3231±0.7026	0.4662	99.3235±0.7029	0.4669	99.3235±0.7029	0.4677
(250 mg)	8	99.2241±0.7027		99.2245±0.7030		99.2245±0.7030	
	10	99.1641±0.7019		99.1646±0.7022		99.1646±0.7022	

[a] Five independent analyses At 95% confidence level t-value is 2.776 and F-value is 6.26 (n = 5, $p < 0.05$, t = 2.677 and F-value = 6.37).

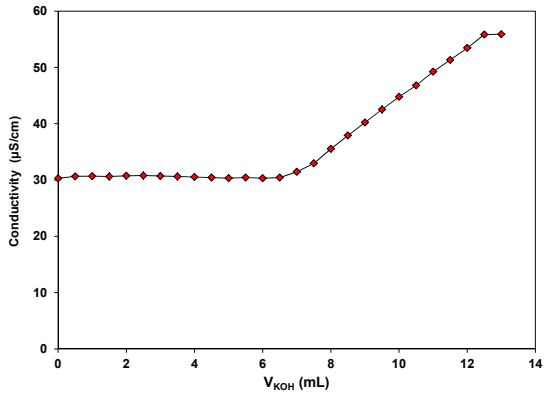

Figure 6. Conductometric titration curve of Riaproxen® with 2×10^{-3} M KOH.

3.1. Optimization of variables

During the studies different variables to obtain the optimum conditions for performing the titration in a quantitative manner were also performed and are as follows.

3.1.1. Effect of solvent used

Different solvents such as methanol, ethanol, water and acetone in different ratios with water were tried to obtain the acceptable results. Preliminary investigations suggested that methanol and water in the ratio of 3:1 provide the most suitable conductometric titration curve. Ethanol:water mixture resulted in distorted curve shape proving that ionic mobility was not proportional to the conductance and hence was not considered for the studies. When titration was continued with acetone:water in ratio 3:1, the solution became turbid after base addition and unstable conductance values were also observed for other ratios.

3.1.2. Reagent concentration

Titrant concentrations ranging from 2×10^{-2} to 4×10^{-4} M of sodium hydroxide and potassium hydroxide were studied. The optimum concentration of 2×10^{-4} M for sodium hydroxide and 2×10^{-3} M for potassium hydroxide was selected for further studies based on stable conductance values.

3.1.3. Effect of temperature

Preliminary investigations suggested that no significant change in conductance values were observed at 20-40 °C. Therefore, an optimum temperature of 25 °C was selected for further studies.

3.1.4. Method validation

The proposed procedures were applied and validated for the determination of naproxen in pure and tablet forms. The results are presented in Table 1 to 5. Linear regression parameters for determination of naproxen using the conductometric titration methods have been depicted in Table 1. The percentage recovery for accuracy and precision studies was determined on six replicates and the data is presented in Table 2. The low values of %RSD indicated that the method to be precise and reproducible. The data from percentage recoveries also confirmed the accuracy of the proposed methods. Further, it could be concluded that the excipients present in the tablets did not interfere with the determination of naproxen. The proposed methods when applied to the tablets of three brands also showed statistically significant results. The data is presented in Table 3. The suitability of the proposed methods could be further ascertained by intra-day precision studies, Table 4 and 5 on different days and different analysts. In all cases, the average results obtained by developed methods and official method were statistically identical, as the difference between the average values had no significance at 95% confidence level.

Table 4. Precision Studies (Intra-day precision).

Method	Concentration (mg/mL)	% Drug Content	RSD%
NaOH	6	99.958±0.7976	0.4833
(Method A)	8	99.928±0.1064	
	10	99.297±1.116	
KOH	6	99.4231±0.7028	0.4226
(Method B)	8	99.2941±0.7029	
	10	99.346±0.7019	

Table 5. Precision Studies (Intra-day precision).

Method	Analyst	Concentration (mg/mL)	% Drug Content	Mean RSD
NaOH (Method A)	Analyst 1	10	99.78	0.5286
KOH (Method B)	Analyst 2	10	99.88	0.5315

4. Conclusion

Electroanalytical methods utilising the conductometric titrations offer a distinctive and rather simple approach for quantitative analysis of drugs in bulk and dosage forms. The proposed methods have shorter running time and do not require expertise like HPLC, GC, MS or other methods. The methods utilise cheap and commonly available reagents and chemicals and do not require special methods for sample preparation. The results obtained confirmed the methods to be simple, sensitive, accurate, precise, and economical and can be used in the determination of naproxen in bulk and dosage forms in a routine manner.

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