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Original Article

QUANTITATIVE DETERMINATION OF SOME NON-STEROIDAL ANTI-INFLAMMATORY DRUGSAND THEIR ACID DISSOCIATION CONSTANTS BY DIRECT POTENTIOMETRY

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ABSTRACT

Objective: A potentiometric titration method was applied to determine non-steroidal anti-inflammatory drugs. The quantitative analysis and the treatment of the primary data are based on a nonlinear regression procedure using commercial software. A general formula valid for every type of acid-base titration, derived before is used as a direct input.

Methods: Potentiometric titration of ibuprofen, flurbiprofen, and ketoprofen with sodium hydroxide solution (0.1 mol/l). The solutions of ibuprofen, flurbiprofen, and ketoprofen were prepared in solvent CH_3OH: H_2O (40:60%). The determination was carried out using a 713 Metrohm pH meter, equipped with Metrohm combined electrode ref. 6.0228.000 Pt1000 with temperature sensor and auto burette. The analysis was performed at ionic strength (I=0.2 mol/l KCl) and t = 25±0.2 °C.

Results: The discussed substances were analyzed using potentiometric titration with a standard sodium hydroxide solution (0.1 mol/l). The experimental data V, ml/E, mV and the conditions of these titrations were used as input in the Data Fit program fixing the following parameters Vo =100.0 ml; Ct (NaOH) = 0.1000 mol/l; S = 59.16 mV (corresponding to 25 °C theoretical value) and Kw = 1.2 10^{-14} (ionic strength 0.2 mol/l). The analytical results for ibuprofen, flurbiprofen and ketoprofen were determined with good accuracy (error+0.4 % foribuprofen+0.2 % for flurbiprofen and+0.2 % for ketoprofen) and precision (1 % for the three). The quantity and acid-base constants of ibuprofen, flurbiprofen, and ketoprofen were determined alone and in tablets. The validation of the method showed very good accuracy and precision.

Conclusion: The present approach can be successfully used in routine analysis of the study drugs in quality control laboratories.

Keywords: Chemometrics, Potentiometry, Acid-base constants, Flurbiprofen, Ibuprofen, Ketoprofen, Non-steroidal anti-inflammatory drugs

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic, anti-inflammatory, and antipyretic properties. NSAIDs are used in musculoskeletal, postoperative affliction, joint disorders, osteoarthritis, rheumatoid arthritis, soft-tissue disorders, and in mild to appropriate pain including migraine. Ibuprofen, flurbiprofen, and ketoprofen belong to non-steroidal anti-inflammatory drugs [1-3]. Ibuprofen (chemically known as 2-(4-isobutylphenyl) propionic acid (fig. 1),molecular formula: $C_{13}H_{18}O_2$, molecular weight: 206.3, is describedas a white, crystalline powder, or colourless crystals, solubility: practically insoluble in water, freely soluble in acetone, methanol. Flurbiprofen, chemically known as (±)-2-fluoro-α-methyl-4-bi-phenylacetic acid, molecular formula: $C_{15}H_{13}FO_2$, molecular weight: 244.26, is described as a white or slightly yellow crystalline powder, solubility: slightly soluble in water, readily soluble in most polar solvents is of the structure (fig. 2) and is an important NSAIDs which belong to the 2-arylpropionic acid class known as profens [4-7]. Ketoprofen (chemically known as (rs)-2-(3-benzoylphenyl) propionic acid, molecular formula: $C_{16}H_{14}O_3$, molecular weight: 254.29, is described as a white, crystalline powder, odourless or almost odourless, solubility practically insoluble in water, freely soluble in acetone, alcohol, and methylene chloride) is of the structure (fig. 3) and is a non-steroidal anti-inflammatory drug (NSAIDs) with analgesic and antipyretic properties [8-11]. The chemical structures of flurbiprofen, ibuprofen, and ketoprofen are shown in fig. 1, 2, and 3.

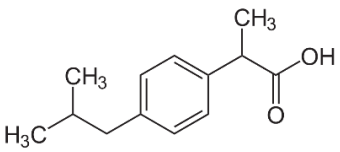

Fig. 1: Chemical structure of ibuprofen

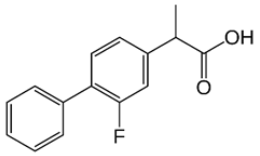

Fig. 2: Chemical structure of flurbiprofen

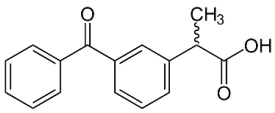

Fig. 3: Chemical structure of ketoprofen

All of the substances included in the present study can be regarded as monovalent weak acids, and belong to the arylpropionic acid group. They show a considerable number of uses and are relatively safe. Although they do not pose a risk to the health of consumers, the pharmaceutical industry must carry out strict quality control and production policies to ensure compliance with the dosage, by the national standards of each country. For this reason, the manufacture and use of drugs require reliable methods of quality control of bulk substances and pharmaceutical formulations. Various methods such as titrimetry, spectrophotometry, and spectrofluorimetry have been reported for the determination of these drugs [12-15]. Analysis based on capillary zone electrophoresis, HPLC, and GC-MS methods [16-20] are also available. However, recently the use of electrochemical techniques has been proposed, such as voltammetry, where boron-doped diamond electrodes have been used to study and evaluate the different ibuprofen redox processes [21, 22]. Determination of ibuprofen electroactivity by forming a radical cation followed by decarboxylation [21].

Despite the variety of techniques, potentiometry remains has been the most explored technique for quantifying ibuprofen and ketoprofen, due to its good sensitivity, high selectivity, better precision and accuracy, the simplest method in terms of materials used, equipment availability, and labour intensity. In many works, the electrodes are reduced, easily constructed experiments and low cost without destroying the sample [22, 23]. A few potentiometric sensors for drug detection and quantification have been reported. Membrane-based sensors containing ion exchangers [24], cyclodextrins [25], ion-pair complexes [26] and ionophores [27] have been reported for the quantification of ibuprofen with good results, although the construction of the selective membranes is complex, expensive, and sometimes responses are obtained after a long time. The other part of potentiometry, the use of second-type electrodes is noticeable because they serve as indicating electrodes of their cations and anions. The indicator electrode potential is reversible concerning measured ion concentration. These electrodes are constructed of metal on which a precipitate or complex compound is attached and so the response of the electrode depends on the Nernst equation [28]. Santini *et al.*, proposed a simple second type electrode for ibuprofen analysis, based on the Hg/HgIbu pair with very good results [29]. Another paper has presented the development of a new second-type electrode proposal, based on the pair silver/silver ibuprofenate, (Ag/AgIbu), which in agreement with the Nernst equation, allows the quantification of ibuprofenate ions [30]. Potentiometric methods based on ion-selective electrodes [31] proposed by various scientists, require strict pH control for accurate and precise results. Various experimental methods are often used to determine the values of acid dissociation constants, and these are shown of good accuracy and reproducibility [31-38].

The other disadvantage of these methods is contained in the developed programs–huge descriptions and the put programming languages are obstacles to their use. Touse a program, it must be rewritten and compiled, which can only be done by qualified specialists (the mathematics of non-linear regression methods is quite complex). These papers focus on the development and improvement of regression algorithms and programs, rather than solving analytical problems [32-38].

In the present work, the primary data mV/ml are transferred into pH/ml data using a self-calibration procedure, hence no preliminary pH-calibration of the glass electrode cell is necessary. The purpose of the present study is purely analytical. The regression methods used for data processing are based on ready-to-use software products rather than "home"-written programs. Thus, data processing is limited by the formulation of a single (individual) case of acid-base titration.

Acid-base dissociation constant provides some useful information about the molecular structure of drug molecules, various chemical, biochemical, distribution, absorption, pharmaceutical properties (protein binding, permeability, and solubility) of drugs, chromatographic retention behaviour, acid-base titration, toxicity, solvent extraction and complex formation, and ion transport [39]. The acid dissociation constant is an important physicochemical parameter [40]. The physicochemical parameters of drugs are important in pharmaceutical formulations and in preparing dosage forms [41, 42]. The wide application of titrimetric analysis is due to its undeniable advantages such as good accuracy and reproducibility, simplicity and speed of implementation, low cost, and availability.

The present study is related to the hard-modelling approach [43-46]. Based on the mass balance concept, acid-base equilibrium constants and constancy of activity factors a single equation V = f (h), derived in an earlier paper [47], is valid for the determination of every combination of acids and bases (monoprotic, polyprotic substances, their mixtures, drugs with acid-base properties etc.) covering thus the whole spectrum of acid-base titration analyses. The method is also verified for the case of close or overlapping pK-values. As a result, the proton stability acid-basic constants βn (resp. pK), autoprtolysis constant (Kw) of the water, and the concentration of the analyzed substance (Bo) are obtained. The most important parameter is the concentration (Bo), which is the analytical result. This study presents the development and validation of an alternative method for the routine analysis of ibuprofen, flurbiprofen, and ketoprofen in pharmaceutical preparations using direct potentiometry.

MATERIALS AND METHODS

Apparatus

The potentiometric analysis was developed and used procedure previously by our research team [47], with some steps modified and adapted to suit the present analysis. The potentiometric titrations were carried in a thermostated vessel at 25±0.2 °C and an ionic strength of 0.2 mol/l. The ionic strength was supported with KCl. The determination was carried out using a 713 Metrohm pH meter, equipped with Metrohm combined electrode ref. 6.0228.000 Pt1000 with temperature sensor and auto burette.

Materials

Sodium hydroxide–p. a. and potassium chloride–p. a. (Merck, Darmstadt, Germany) was used without purification. Ibuprofen, flurbiprofen, and ketoprofen standards were obtained from Sigma Aldrich. Tablet formulations containing ibuprofen 200 mg, flurbiprofen 100 mg, and ketoprofen 25 mg were obtained commercially. All chemicals investigated corresponded to p. a. purity and were used without purification. Sodium hydroxide (0. 1 mol/l) in water was prepared by dilution of certified volumetric solutions with carbon-dioxide-free redistilled water. The solution of sodium hydroxide was standardized with a standard solution of hydrochloric acid.

Preparation of the standard solution

Solutions with concentrations 0.1 mol/l of ibuprofen, flurbiprofen, and ketoprofen were prepared. The titrant used was a standard sodium hydroxide solution (0. 1 mol/l).

Sample preparation

Procedure for the determination of ibuprofen, flurbiprofen, and ketoprofen

A solution of the analyzed substances at a concentration of 0.1 mol/l and with ionic strength of 0.2 mol/l was prepared. Aliquot samples of 10.0 ml and 90.0 ml 0.2 mol/l KCl were titrated in a thermo-stated glass cell (25.0±0.1) °C with a standard sodium hydroxide solution at a concentration of 0. 1 mol/l.

Procedure for the determination of ibuprofen, flurbiprofen, and ketoprofen in tablets

Twenty tablets of any drug were weighed accurately and ground into a fine powder. A portion of the powder equivalent to 200 mg ibuprofen, 100 mg flurbiprofen, and 25 mg ketoprofen (0.1 mol/l) was accurately weighed into 100 ml volumetric flasks. Extractions were done by shaking for 20 min with 40 ml of methanol, then the volume was diluted to the mark with distilled water: methanol (60:40 %), mixed well and filtered using a filter paper. Aliquot samples of 10.0 ml were taken from the filtrates, mixed with 90.0 ml 0.2 mol/l KCl, and titrated according to the above-described scheme.

RESULTS AND DISCUSSION

This work is based on a developed approach for data processing of potentiometric titration of substances with acid-base properties. The proposed approach is based on a system of equations for a material balance of the components involved in acid-base titration. The general formula (1), valid for any acid-base titration, is quickly solved using the computer program Data Fit.

$$V = V_o * \left(h - K_w/h + \sum_{m=1}^{M}\sum_{n=1}^{N} B_{o,m} * \bar{n}_{H,m}\right)/(C_t - h + K_w/h) \quad (1)$$

where, V -is the volume of the added titrant, ml; V_o -is the initial volume of the titrated solution, ml; h-concentration of protons, mol/l; K_w–is the autoprotolysis constant of water; M-number of components; N-is the maximum number of protons that a protolite can accept or release; B_o-concentration of the analyzed base (resp. A_o for acid), mol/l; C_t-total concentration of the titrant, mol/l. $\bar{n}_H$ is the average number of coordinated protons (2), β-proton stability constants for determined substance, Nm indicates the maximum number of protons that the m^{th} protolith can accept or donate.

$$\bar{n}_{H,m} = \frac{\sum_{n=0}^{Nm} n * \beta_{m,n} * h^n}{\sum_{n=0}^{Nm} \beta_{m,n} * h^n} \quad (2)$$

The developed method allows direct calculation of the analytical result and some important parameters of the system in the same experiment with the corresponding standard deviations, while the other methods achieve this through a series of experiments. The theoretical basis of the proposed method is based on the fact that the acid-base interaction is represented as a proton complexation process between (the base (B) or the acid (A)) and the ligand H (protons), i.e. the established equilibrium represents an interaction in a mononuclear system.

The discussed substances were analyzed using potentiometric titration with a standard solution of sodium hydroxide. The experimental data V, ml/E, mV and the conditions of these titrations were used as input in the DataFit program fixing the following parameters V_o =100.0 ml; Ct (NaOH) = 0.1000 mol/l; S = 59.16 mV (corresponding to 25 °C theoretical value) and Kw = 1.2.10E-14 (ionic strength 0.2 mol/l). The output of the computer calculations is shown in table 1.

Table 1: Output from computer treatment (Program DataFit)

Equation ID: monofuncacids MV			
Solver type: Nonlinear			
Residual Sum of Squares (Absolute) = 1.50E-02			
Adjusted coefficient of multiple determination (R^2) = 0.99999			
Regression Variable Results			
	Ibuprofen	Flurbiprofen	Ketoprofen
A1	0.01002±0.00011	0.01006±0.00014	0.009947±0.00019
B1	$0.043651.10^6$±0.03(pKa=4.64)	$0.017782.10^6$±0.02 (pKa=4.25)	$0.024547.10^6$±0.05(pKa=4.39)
Accuracy Error, %	+0.4 %	+0.2 %	+0.2 %

A1-concentration of the analyzed acid, B1-proton stability constants, values represent mean±SD (n=3)

As seen in table 1, the analytical results for ibuprofen, flurbiprofen and ketoprofen are determined with good accuracy (error+0.4 % for ibuprofen+0.2 % for flurbiprofen and+0.2 % for ketoprofen) and precision (1 % for the three). The adjusted coefficient of multiple determination R^2, which is a measure for the response of the regression model described with equations (1) and (2), shows a highly good correlation between the model and experiment (R^2) = 0.99999. The acid-base constants of both protolytes are found with good accuracy and precision: pKa=4.64±0.03 ibuprofen, pKa=4.25±0.02 flurbiprofen and pKa=4.39±0.05 ketoprofen.

The proposed procedure was applied to the analysis of ibuprofen, flurbiprofen, and ketoprofen substances. After processing the experimental data with the help of a developed approach, the equilibrium constants and quantitative content were determined. The results of these tests are presented in table 2.

Once determined pKa-values can be set as constants in the INPUT at which the calculation time of the analytical results is reduced. Further, to validate the method, the procedure was applied for the analysis of synthetic mixtures of the pharmaceutical forms of ibuprofen, flurbiprofen, and ketoprofen as well as a placebo sample.

Table 2: Results of the quantitative determination and dissociation constants values of studied arylpropionic acids obtained by the pharmacopoeial method and with the help of the proposed approach

Substance	pK_{a1}	Found, %	Ph. Eur.10
Ibuprofen	4.64	99.53	99.80
Flurbiprofen	4.25	99.39	99.75
Ketoprofen	4.39	99.48	99.85

All of the analytical validation parameters for this proposed method were determined according to ICH guidelines [48]

Selectivity

The proposed method was tested for selectivity by placebo blank and synthetic mixture. A placebo blank containing povidone, lactose monohydrate, potato starch, talc, silicon dioxide, colloidal anhydrous, and magnesium stearate was prepared, extracted, and solution made as described under "procedure for tablets". An aliquot of solution was subjected to analysis by titrimetry according to the recommended procedure. It was found that there was no interference between the analyte and placebo.

Accuracy

The accuracy of the proposed method was determined by performing replicate determinations. The intra-day and inter-day variation in the analysis of ibuprofen, flurbiprofen, and ketoprofen was measured at three different levels. The accuracy of the analytical method expresses the closeness between the reference value and the found value. Accuracy was evaluated as a percentage relative error between the measured and taken amounts/concentrations. The results of this study are compiled in table 3 and speak of the excellent accuracy of the results.

Table 3: Evaluation of intra-day and inter-day accuracy

Drug	Intra-day accuracy		Inter-day accuracy			Intra-day accuracy		Inter-day accuracy			Intra-day accuracy		Inter-day accuracy	
Ibuprofen, taken, mg	Ibuprofen, found, mg	%, RSD	Ibuprofen found, mg	%, RSD	Flurbiprofen, taken, mg	Flurbiprofen, found, mg	%, RSD	Flurbiprofen found, mg	%, RSD	Ketoprofen, taken, mg	Ketoprofen, found, mg	%, RSD	Ketoprofen, found, mg	%, RSD
100.0	100.21	0.684	100.12	1.135	50.0	49.67	1.213	49.58	1.112	12.50	12.37	1.118	12.24	1.233
200.0	190.78	0.345	200.03	0.432	100.0	99.87	0.569	99.73	0.423	25.00	25.06	0.238	24.90	0.876
300.0	290.93	0.231	290.56	0.324	150.0	149.58	0.459	149.25	0.532	37.50	37.34	0.457	37.20	0.486

±RSD–relative standard deviation, (n=6)

Table 4: Results of the precision analysis of Ibuprofen, flurbiprofen, and ketoprofen tablets

	Ibuprofen		Flurbiprofen		Ketoprofen	
№	Substance, %	Tablets, mg	Substance, %	Tablets, mg	Substance, %	Tablets, mg
1	99.95	200.13	99.67	100.53	99.59	25.18
2	100.05	190.89	99.21	99.79	99.28	25.05
3	99.87	200.34	98.97	99.17	98.99	24.89
4	99.29	200.16	99.59	100.03	99.89	24.68
5	99.86	200.11	100.32	99.94	100.12	24.78
6	100.5	190.56	99.89	98.99	99.84	24.91
Parameter						
Mean	99.92	197.03	99.61	99.74	99.62	24.92
SD	0.389	4.887	0.481	0.572	0.421	0.180
RSD,%	0.389	2.480	0.483	0.574	0.422	0.724
CI	0.408	5.125	0.504	0.600	0.441	0.189
% Error	0.408	2.601	0.506	0.602	0.443	0.759

±SD–standard deviation,±RSD–relative standard deviation, CI-confidence interval, values represent mean±SD (n=6)

Table 5: Results for dosage forms–Ibuprom max US PHARMACIA SP (ibuprofen 400 mg), Miprofen tablets NOBEL (flurbiprofen 100 mg), and Ketonal, Lek Pharmaceuticals (ketoprofen 50 mg)

No	Ibuprofen, mg	Flurbiprofen, mg	Ketoprofen, mg
1	398.95	99.83	50.23
2	400.13	98.89	49.29
3	399.96	100.32	48.75
4	400.31	100.57	50.79
5	399.12	99.71	49.63
6	400.27	98.92	48.95
Mean	399.79	99.71	49.61
SD	0.599	0.696	0.782
RSD, %	0.150	0.698	2.569
CI% Error	0.629	0.730	0.820
	0.157	0.732	1.653

±SD–standard deviation,±RSD–relative standard deviation, CI-confidence interval, values represent mean±SD (n=6)

Precision

The precision of the method was established by a six-time analysis of ibuprofen, flurbiprofen, and ketoprofen samples, in substance and tablets. The results obtained are presented in table 4.

Application in dosage form

The proposed method was applied to dosage forms. The results of the statistical processing by the obtained method are presented in table 5.

CONCLUSION

The developed and validated potentiometric method is rapid and economical. The statistical parameters and the recovery data reveal good accuracy and precision. We can say in conclusion that the proposed method is simple and selective for the determination of ibuprofen, flurbiprofen, and ketoprofen in drug substance and commercial dosage forms. The present approach can be successfully used in routine analysis of the drugs in quality control laboratories.

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Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

Declared none

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