ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
20 (1999) 19–26

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

The non-aqueous titrimetric assay of the selected anti-inflammatory agents using tetra-*n*-butylammonium hydroxide as titrant

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Received 12 September 1997; received in revised form 28 December 1997; accepted 17 January 1998

Abstract

A potentiometric titration method in non-aqueous media is proposed for the determination of some commonly used anti-inflammatory agents. The direct potentiometric titration of three anti-inflammatory agents, namely mefenamic acid, fenbufen and ibuprofen; and the indirect potentiometric titration of diclofenac sodium was carried out in acetonitrile solvent using tetra-*n*-butylammonium hydroxide as titrant, at 25°C and under a nitrogen atmosphere. The method was found to be highly accurate and precise, having a relative standard deviation of $< 1.0\%$ for all anti-inflammatory agents studied. Also, it was shown that the method could be successfully applied to the assay of commercial pharmaceuticals containing the above-mentioned anti-inflammatory agents. The validity of the method was tested by the recovery studies of standard addition to pharmaceuticals and the results were found to be satisfactory. The proposed method is simple, rapid and sufficiently precise for quality control purposes.

Keywords: Mefenamic acid; Fenbufen; Ibuprofen; Diclofenac sodium; Anti-inflammatory agent; Potentiometric titration; Tetra-*n*-butylammonium hydroxide; Acetonitrile solvent; Titrimetric assay.

1. Introduction

Many of the active components of pharmaceutical preparations are of organic origin and contain acidic and/or basic groups. Some of these substances are not soluble in water or decompose in aqueous media. As a continuing part of our studies on the titration of compounds in non-aqueous media, this study was carried out to investigate the possibility of titrating commonly used anti-inflammatory agents such as mefenamic acid (I), fenbufen (II), ibuprofen (III), and diclofenac sodium (IV), in acetonitrile solution using a potentiometric method [1–3]. These compounds are widely used clinically as non-steroidal anti-inflammatory agents, and contain a carboxylic acid group. The structural formulae of these anti-inflammatory agents are given in Scheme 1.

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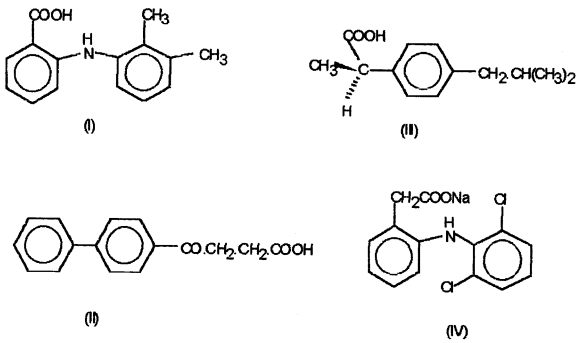
0731-7085/99/$ - see front matter
PII: S0731-7085(98)00044-2



Scheme 1. Structural formulae of anti-inflammatory agents (I)–(IV).

When the literature on the determination of these compounds is examined, it can be seen that potentiometric titrations in acetonitrile has not been investigated. Various available methods in the literature for the determination of these compounds in pure form or pharmaceutical formulations include chromatographic [9,23] and spectrophotometric methods [20,21] for mefenamic acid; chromatographic method [26] for fenbufen; chromatographic [11,16,18,23,25] and spectrophotometric methods [20] for ibuprofen; chromatographic [10–13,15,19,24], spectrophotometric [14,17,20,21], and titrimetric [22] methods for diclofenac sodium.

In the United States Pharmacopoeia (USP) [4,5], British Pharmacopoeia (BP) [6,7] and European Pharmacopoeia [8] various methods are described for the routine determination of the above-mentioned anti-inflammatory agents in pure form or pharmaceutical preparations. These methods are summarized in Table 1.

The methods employed in the pharmacopoeia for the assays of anti-inflammatory agents, especially mefenamic acid, fenbufen, ibuprofen and diclofenac sodium have some disadvantages such as, the using of an chemical indicator to indicate the end-point of the titrations in the presence of coloring or insoluble excipients in drug formulations, the separation of the excipient or the isolation of the analytes prior to assays, to be highly time-consuming and tedious, the causing of the used titrant an alkaline error.

It is obvious that a quick and reliable procedure is required for the determination of anti-inflammatory agents, especially mefenamic acid, fenbufen, ibuprofen and diclofenac sodium. The purpose of the present investigation was to develop a simple non-aqueous titrimetric assay for the anti-inflammatory agents mentioned above. The methods were designed to be rapid, capable of being semi-automated and giving commercially acceptable accuracy for quality control purposes.

Table 1
The routine determinations of the four anti-inflammatory agents in Pharmacopoeia

Name of substance	Pure form/type of formulation	Pharmacopoeia	Method	Ref.
Mefenamic acid	Pure form/capsule	USP	Chromatographic	[5]
Mefenamic acid	Pure form/capsule	BP	Titrimetric with sodium hydroxide in ethanol using chemical indicator	[6]
Ibuprofen	Pure form/tablet	USP	Chromatographic	[4]
Ibuprofen	Pure form	BP	Titrimetric with sodium hydroxide in ethanol using chemical indicator	[6]
Ibuprofen	Tablet	BP	Potentiometric titration with sodium hydroxide in ethanol after separation and neutralization	[6]
Ibuprofen	Pure form	Ph. Eur.	Titrimetric with sodium hydroxide in methanol using chemical indicator	[8]
Fenbufen	Pure form	BP	Titrimetric with sodium hydroxide in acetone-water using chemical indicator	[7]
Diclofenac sodium	Pure form	Ph. Eur.	Potentiometric titration with perchloric acid in glacial acetic acid	[8]

2. Experimental

2.1. Apparatus

A Jenway 3040 digital pH-ionmeter equipped with a combined pH-electrode (Ingold) was used throughout the study. All titrations were carried out manually, under a nitrogen atmosphere, at 25 ± 1°C, in a specially designed cell as described previously [1].

2.2. Materials

Mefenamic acid, fenbufen, ibuprofen and diclofenac sodium obtained from Refik Saydam hygiene centre (Turkey), were of chemically pure laboratory working standards having purity's of 100.0, 99.3, 99.6, and 99.7%, respectively.

Ponstan (Eczacıbaşı) was labeled as containing 500 mg mefenamic acid, and yellow iron oxide-titanium dioxide as pigment, per tablet.

Cinopal (Faco) was labelled as containing 300 mg fenbufen, and crystalline sugar, titanium dioxide-indigotin as pigment, per tablet.

Artril (Eczacıbaşı) was labelled as containing 400 mg ibuprofen, and titanium dioxide -tartrazine (F.D. and C Yellow No:5) as pigment, per tablet.

Dikloron (Deva) was labelled as containing 25 mg diclofenac sodium per tablet.

Tetra-*n*-butylammonium hydroxide (TBAH) was purchased from Merck (Darmstadt, Germany) as a 0.100 M solution in 2-propanol/methanol and was diluted with 2-propanol to give an approximately 0.020 M solution. This solution was standardized against sublimed benzoic acid (Merck) and kept in a dark-coloured ground glass-stoppered flask in a refrigerator.

Perchloric acid was purchased from Merck (70%) and a 0.020 M solution in glacial acetic acid was prepared as follows. 0.80 ml of perchloric acid was added dropwise into 5.0 ml of ice-cooled acetic anhydride and left overnight and then diluted with glacial acetic acid to obtain a solution at roughly the required concentration. The solution was standardized potentiometricaly against tris base (THAM) in acetic acid.

Acetonitrile, 2-propanol and glacial acetic acid were purchased from Merck and used after purification [27].

The solutions of anti-inflammatory agents: Accurately weighed quantities (2.0–4.0 mg) of three anti-inflammatory agents (mefenamic acid, fenbufen and ibuprofen) were dissolved directly in 15 ml of acetonitrile, depending upon their molar weights. All the assay solutions were prepared prior to titrations directly in a titration cell, and titrated with standard tetrabutylammonium hydroxide with stirring, at 25°C, under a nitrogen atmosphere. However, diclofenac sodium is insoluble in acetonitrile. Therefore, an accurately weighed quantity (3.0–4.0 mg) of diclofenac sodium was dissolved in a measured and excess of 0.020 M perchloric acid solution (diclofenac sodium/perchloric acid in 1/2 mole ratio); and diluted to 15 ml with acetonitrile. After the reaction is judged complete, the excess perchloric acid is back-titrated with TBAH under the same conditions.

The solutions of the pharmaceutical preparations: Capsules: Twelve cinopal capsules were weighed, and their average contents were calculated. The contents were pooled and finely powdered, and the required amount of this powder was weighed accurately, dissolved in 15 ml of acetonitrile solvent. Tablets: Twenty ponstan, 10 artril or 25 dikloron tablets were weighed, and their average weights were calculated. All the tablets were finely powdered, pooled and the required amounts of these powders were dissolved in 15 ml of acetonitrile solvent.

The titrations were repeated for different amounts of each anti-inflammatory agents and pharmaceutical preparation.

3. Results and discussion

3.1. Determination of standard active components

Mefenamic acid, fenbufen and ibuprofen were titrated direct potentiometrically in acetonitrile with tetrabutylammonium hydroxide as titrant. However, the diclofenac sodium was back-titrated after addition of the measured excess of standard

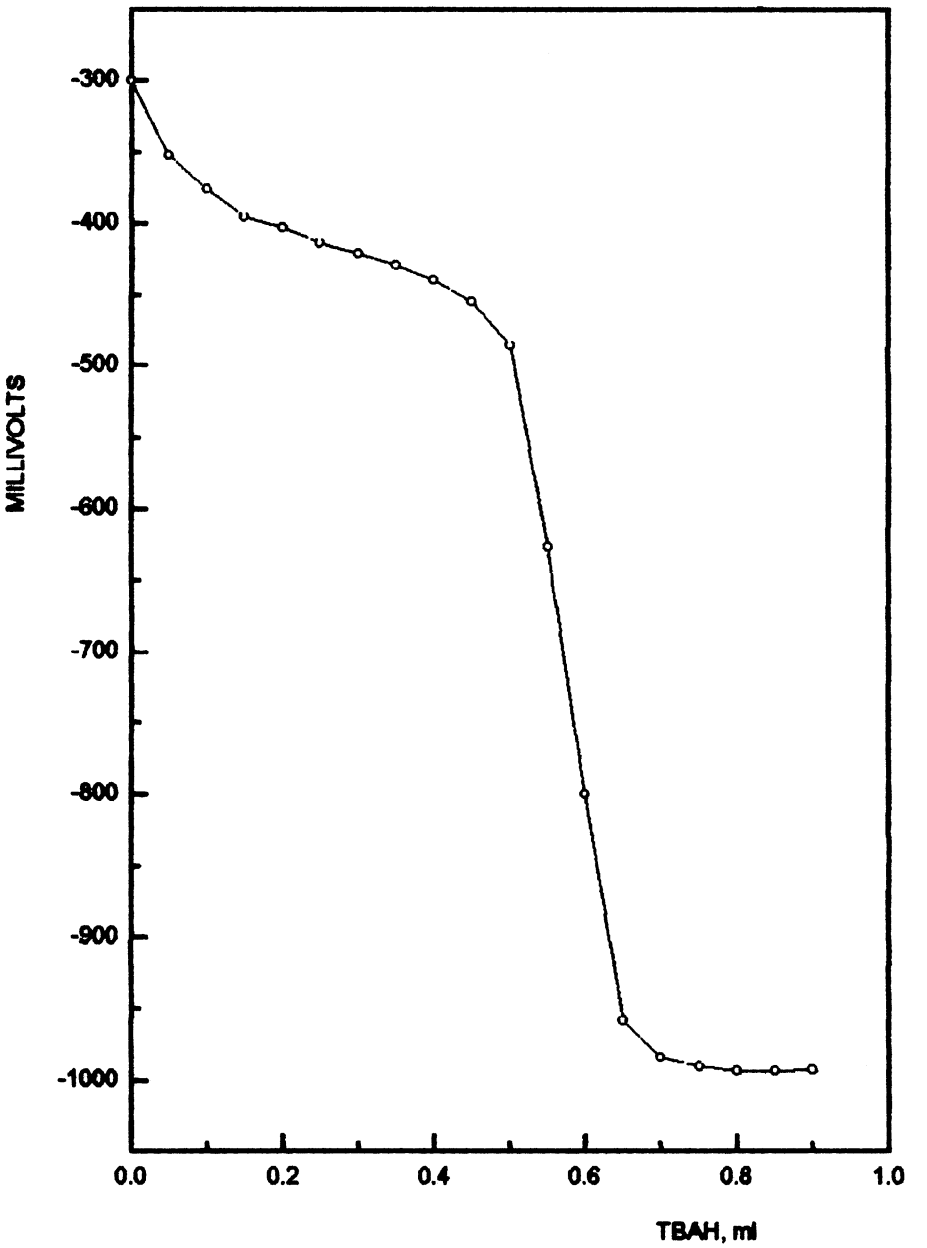


Fig. 1. Potentiometric titration curve for mefenamic acid titrated with tetrabutylammonium hidroxide in acetonitrile solution.

perchloric acid under the same conditions; and then performed a blank determination, and made the necessary correction. The titration curve of the anti-inflammatory agents showed one well-defined S-shaped stoichiometric end-point (see Figs. 1–3).

The determination of the end points from the potentiometric data was carried out using the Gran's method [28]. The end points for the three anti-inflammatory agents, namely mefenamic acid, fenbufen and ibuprofen corresponded to one equivalent of base and related to the neutralization of the –COOH group.

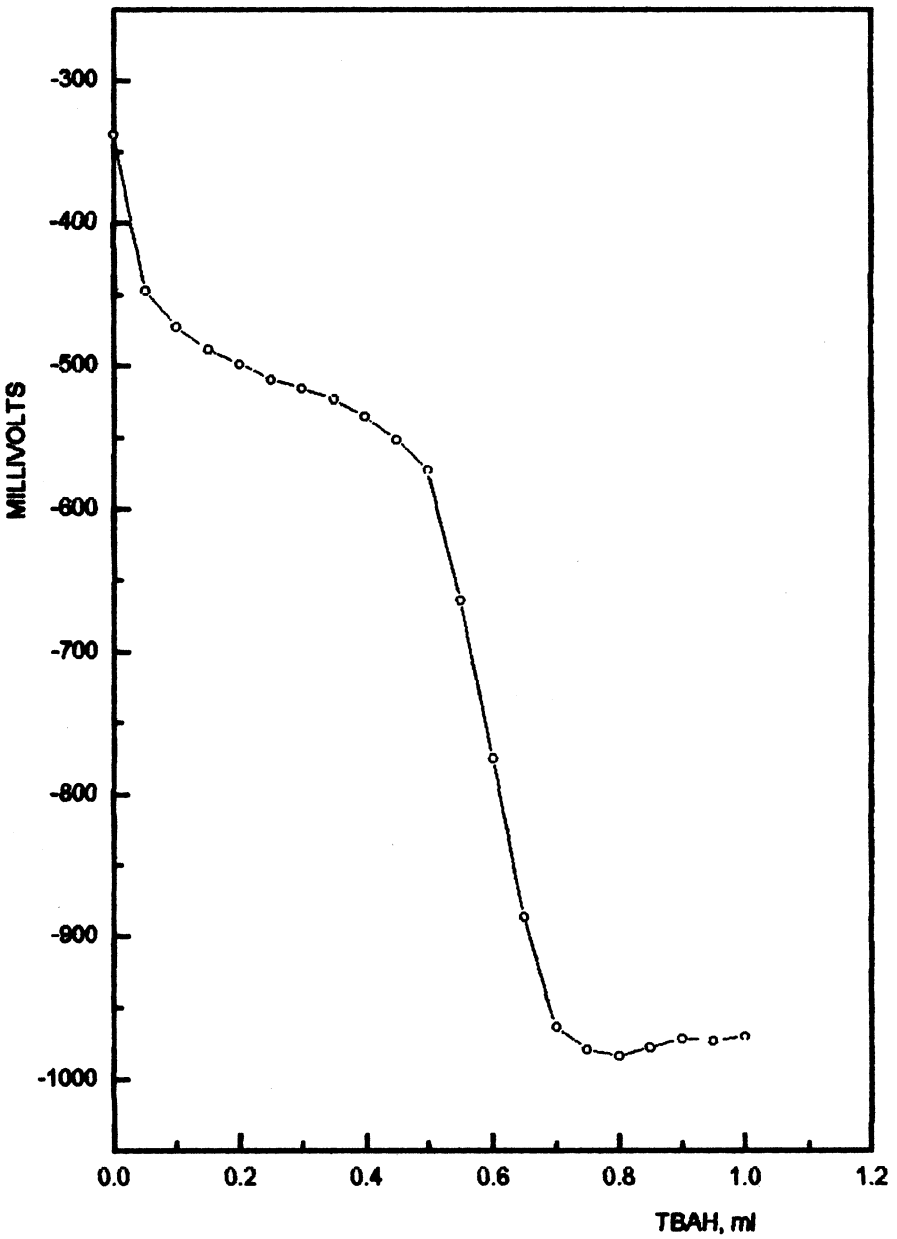


Fig. 2. Potentiometric titration curve for fenbufen titrated with tetrabutylammonium hidroxide in acetonitrile solution.

The percentage of each anti-inflammatory agent (chemically pure laboratory working standard) was calculated from the potentiometric titration data. The accuracy and precision (reproducibility) of the proposed method were tested by five successive determinations carried out on mefenamic acid, fenbufen, ibuprofen and diclofenac sodium. The results are tabulated in Table 2.

As seen from the data in Table 2, the mean values obtained by the proposed method are in

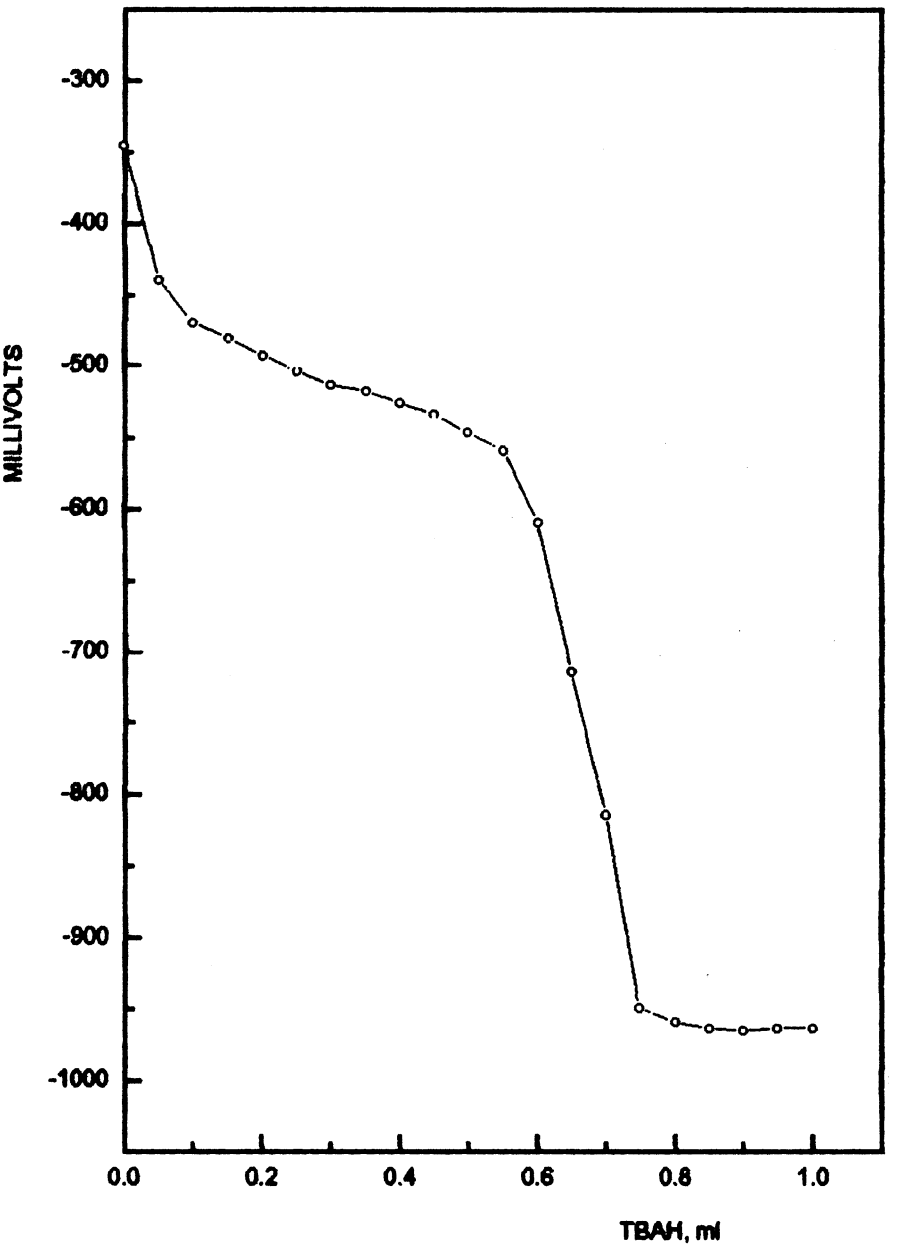


Fig. 3. Potentiometric titration curve for ibuprofen titrated with tetrabutylammonium hydroxide in acetonitrile solution.

good agreement with the nominal value given for each anti-inflammatory agent and furthermore the relative standard deviations are $< \pm 1\%$. This indicates that the accuracy and precision of this method is quite satisfactory.

3.2. Determination of the active components in pharmaceuticals

In order to evaluate the applicability of the method to pharmaceutical preparations, mefe-

Table 2
Titrimetric determinations of the anti-inflammatory agents which are chemically pure laboratory working standards

Anti-inflammatory agents	No. tests	Proposed method		Nominal value (%)
		Mean (%)	RSD	
Mefenamic acid	5	99.93	0.44	100.0
Fenbufen	5	99.25	0.33	99.3
Ibuprofen	5	99.42	0.69	99.6
Diclofenac sodium	5	100.55	0.61	99.7

namic acid, fenbufen, ibuprofen and diclofenac sodium were determined in ponstan, cinopal, artril and dikloron, respectively, under the same conditions as employed for the pure anti-inflammatory agents. The fact that the mV values before the end-points in the titration curves of pure anti-inflammatory agents and their corresponding pharmaceuticals are almost identical, provides evidence that the titration curves which are not due to other excipients that might be present in the pharmaceutical preparations do not effect the ti-tration curves. The excipients in the above-mentioned pharmaceutical preparation does not include acidic substances.

Table 3 summarizes the results obtained for each anti-inflammatory agent in the corresponding

Table 3
Titrimetric determinations of the anti-inflammatory agents in some pharmaceutical preparations

Pharmaceuticals	Anti-inflammatory agents	No. tests	Recovery[a] (% ± RSD)
Ponstan	Mefenamic acid	5	100.63 ± 0.78
Cinopal	Fenbufen	5	100.52 ± 0.76
Artril	Ibuprofen	5	100.47 ± 0.58
Dikloron	Diclofenac sodium	5	101.28 ± 0.62

[a] Recovery relative to nominal content.

Table 4
Recovery studies of standard additions to some pharmaceutical preparations

Pharmaceuticals	Anti-inflammatory agents	Added (mg)	Found (mg)	Recovery (%)	Mean ± RSD (%)
Ponstan	Mefenamic acid	1.60	1.61	100.38	101.15 ± 0.59
		1.60	1.62	101.25	
		1.10	1.12	101.82	
Cinopal	Fenbufen	1.50	1.51	100.66	99.92 ± 0.64
		1.10	1.09	99.10	
		1.30	1.30	100.00	
Artril	Ibuprofen	1.50	1.50	100.00	99.49 ± 0.37
		1.20	1.19	99.17	
		1.40	1.39	99.29	
Dikloron	Diclofenac sodium	2.00	2.03	101.50	102.07 ± 0.42
		1.80	1.84	102.22	
		2.40	2.46	102.50	

pharmaceuticals, expressed as percentages of the nominal contents. The recoveries are in good agreement with the nominal contents and the RSD values are $< \pm 1\%$. Thus, the reproducibility and accuracy is very satisfactory for the analysis of pharmaceutical preparations as well as bulk drugs. These results indicate that the content of each anti-inflammatory agent in the pharmaceuticals can be safely determined using this method without interference from other substances in the preparations.

The recovery studies of standard additions to commercial pharmaceuticals were also carried out in order to determinate linearity, sensitivity and selectivity of the method. In these titrations, as the amount of pure standard added to commercial pharmaceuticals increases, the volume of titrant used increases linearly. The analytical sensitivity of the method is not linearly related to the amount of standard added to the pharmaceuticals. Thus the recoveries values (%) are found to be constant approximately. The results related to these studies are presented in Table 4. It can be seen from this table that the mean recoveries and RSD values are good evidence of the validity of the method.

As a result of this work, mefenamic acid, fenbufen, ibuprofen and diclofenac sodium can now be determined potentiometrically in acetonitrile by the proposed method. This non-aqueous titrimetric assay was successfully applied to the determination of pure authentic samples and some of their pharmaceutical preparations. The acetonitrile solvent has a high potential range. In the proposed method, the titrations of all anti-inflammatory agents in acetonitrile have shown rather well-shaped end-points with high potential jumps. In conclusion, the proposed potentiometric method could be utilized readily for routine analysis of pharmaceuticals since it offers a simple system and with short analytical time coupled with good reproducibility and accuracy.

Acknowledgements

The authors would like to thank Refik Saydam Hygiene Centre for providing pure anti-inflammatory agents.

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