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Utility of Nickel for Atomic Absorption Spectrophotometric Determination of Selected Acidic Drugs

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Abstract

A simple and accurate method is described for the quantitative determination of flufenamic acid, mefenamic acid, tranexamic acid, furosemide, diclofenac sodium and thiaprofenic acid by precipitation reactions with nickel(II) followed by direct determination of the ions in the precipitate or indirect determination of the ions in the filtrate by atomic absorption spectroscopy. Statistical analysis of the results compared to assays used in pharmacopeas and the $A_{max.}$ methods revealed equal precision and accuracy. Furthermore the assays were also applied for the determination of these drugs in pharmaceutical preparations.

Key Words: Nickel; Flufenamic acid; Mefenamic acid; Tranexamic acid; Furosemide; Diclofenac sodium; Thiaprofenic acid; Atomic Absorption spectrophotomerty.

Introduction

Flufenamic acid [N-(ααα-Trifluoro-m-tolyl) anthranilic acid] is a non steroidal anti-inflammatory, antipyretic drug with analgesic properties.. Several techniques were used for determination of flufenamic acid such as fluorometric[1], chromatographic[2] and spectrophotometric[3,4] ones.

Mefenamic acid is an anti-inflammatory, antipyretic drug with analgesic properties. Its chemical structure is N-(2,3 Xylyl) anthranilic acid. Several techniques were used for the determination of this drug such as polarographic[5] ,fluorometric[6], chromatographic[7]and spectrophotometric[8] methods.

Tranexamic acid [4-(amino methyl) cyclohexane carboxylic acid] is an anti-fibrinolytic agent used mainly in the treatment and prophylaxis of hemorrhage associated with excessive fibrinolysis. Several techniques were used for the determination of this drug, including fluorometric[10] , chromatographic[11] and spectrophotometric[12] assays.

Furosemide is the most potent diuretic available. It is therapeutically used in cases of pulmonary edema, renal failure and

hypercalcemia. Its chemical structure is 4-chl-oro-N-furfuryl-5-sulf-amoylanthranilic acid. Potentiometric[13], chromatographic[14,15] and spectrophotometric[16,17] methods have been reported for the assay of furosemide.

Diclofenac sodium [2-(2,6-dichloroanilino) phenyl] sodium acetate is widely used as an anti-inflammatory agent. Several techniques have been used for the determination of this drug including chromatographic [18,19] and spectrophotometric[7,20,21] methods.

Thiaprofenic acid is anti-inflammatory, antipyretic drug with analgesic properties. Its chemical structure is 2-(5-Be-nzoyl-2-Thienyl) propionic acid. Several techniques were used for the determination of this drug such as spectrophotometry[2,23], polarography[4] , and high pressure liquid chromatography[5,26].

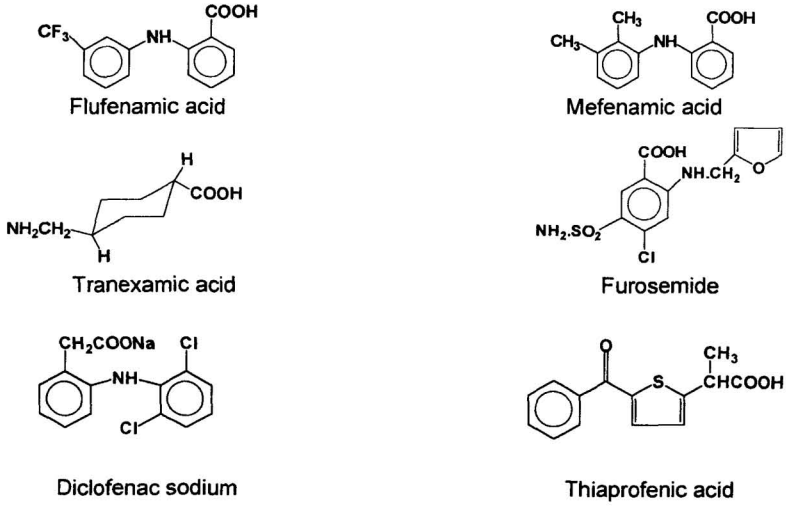

Figure 1: Structures of the studied drugs

The present work demonstrates the utilization of nickel as a reagent for the determination of free drugs by direct and indirect A.A.S. measurements .The methods were also sensitive and accurate for the determination of these compounds in pharmaceutical preparations.

Experimental

Instruments:

1-Shimadzu Atomic Absorption, Flame Spectrophotometer.

2- Shimadzu UV 1601, UV-Visible spectrophotometer (Tokyo, Japan).

Materials and Reagents:

Flufenamic acid from Alex.Co., Egypt, mefenamic acid from Parke-Davis Co.,USA, tranexamic acid from Pharmacia AB, Stockholm, Sweden, furosemide from Hoechst Co., Egypt, diclofenac sodium from Pharco Co., Egypt and thiaprofenic acid from Roussel uclaf Co.,France were used. Pinox® capsules (100 mg flufenamic acid) were obtained from Alex. Co., Egypt. Ponstan® capsules and syrup were obtained from Nile Co., Egypt (250 mg and 50 mg mefenamic acid per each capsule or 5 ml syrup, respectively). Cyklokapron® tablets and ampoules were obtained from Pharmacia AB, Stockholm Sweden (500 mg and 100 mg tranexamic acid per each tablet or 1 ml ampoule, respectively). Lasix® tablets and ampoules were obtained from Hoechst Co., Egypt (40 mg and 20 mg furosemide per tablet or ampoule, respectively). Declophen® tablets and ampoules, Pharco Co., Egypt (25 mg and 75 mg diclofenac sodium per tablet or ampoule, respectively). Surgam® tablets, Roussel Co., Egypt (300 mg thiaprofenic acid). Stocks flufenamic acid, mefenamic acid, tranexamic acid, furosemide, diclofenac sodium and thiaprofenic acid solutions were prepared by dissolving 100 mg, 80 mg,100 mg, 50 mg, 50 mg, 50 mg in 50 ml alcohol, respectively. The solutions were rendered neutral or slightly alkaline (pH 7.3-8.2) with 0.1N sodium hydroxide and then complete to 100 ml with redistilled deionized water. For the studied drugs 0.01M of the working solutions were used for Job's method of continuous variation[27].

Procedures for Authentic Drugs:

Atomic absorption spectrophotometry utilizing nickel:

To aliquots of stock solutions (equivalent to 1.2-48.0 mg flufenamic acid, 3.5-70.6 mg mefenamic acid, 2.4-36.0 mg tranexamic acid, 1-25 mg furosemide, 3-80 mg diclofenac sodium and 4-80 mg thiaprofenic acid), five ml of nickel sulphate solution was added. Solutions were well shaken, filtered (Whatman No.44) and the precipitates were washed with redistilled deionized water till free of nickel

Direct method

The precipitates obtained above were dissolved in a minimum amount of dilute ammonia solution and completed to 25

ml with redistilled deionized water. Two ml of the resulting solutions were diluted to 25 ml with redistilled deionized water.

Indirect method

The filtrates and washings were collected in 100 ml volumetric flasks and completed to volume with redistilled deionized water. Ten ml of the resulting solution were diluted to 100 ml with redistilled deionized water.

A blank (omitting addition of drugs) was prepared and the absorbance was measured at the suitable flaming conditions. Nickel concentration was calculated from a calibration curve.

Procedures for assay of pharmaceutical preparations:

For tablets:

Twenty tablets of either Cyclokapron® or Lasix® or Declophen® or Surgam® were weighed and finely powdered. An accurate weight portion of the powders equivalent to 100 mg tranexamic acid, 80 mg furosemide, 25 mg of diclofenac sodium and 100 mg of thiaprofenic acid were added to 10 ml of water and shaken for 10 minutes in a 100 ml volumetric flask. Exactly 50 ml of alcohol were added, mixed and filtered if necessary. The solutions were rendered neutral or slightly alkaline (pH 7.3-8.2) with 0.1N NaOH and completed to volume with redistilled deionized water. To 5 ml aliquots of the resulting solutions the specified amount of nickel solution was added and samples were processed as described for authentic drugs.

For ampoules:

Portion of Cyklokapron®, lasix® or Declophen® ampoules equivalent to 100 mg tranexamic acid, 40 mg furosemide and 75 mg diclofenac sodium were transferred into 100 ml volumetric flasks and mixed with 50 ml ethanol. The solutions were rendered neutral or slightly alkaline (pH 7.3-8.2) with 0.1N NaOH, then transferred into 100 ml volumetric flasks and completed to volume with redistilled deionized water. The specified amount of nickel solution was added to 5 ml aliquots of the resulting solutions and then the samples were processed as described for authentic drugs.

For capsules:

Twenty capsules of Ponstan® or Pinox® were weighed and finely powdered. The stock solution was prepared by dissolving an amount of powder equivalent to 80 mg mefenamic acid and 100 mg flufenamic, respectively, in 100 ml double-distilled deionized water. The stock solutions were prepared as described above (in materials and reagents) and completed as before.

For syrup:

An aliquot of Ponstan® syrup equivalent to 80 mg of mefenamic acid was pipetted into a 100 ml volumetric flask, 40 ml ethanol was added and shaked for 5 min. The solution was rendered neutral (pH 7.0-7.6) with 0.1N sodium hydroxide, then filtered in a 100 ml volumetric flask and completed to volume with redistilled deionized water. The specified amount of the metal solution was added to 5 ml aliquots of the resulting solution and then completed as before.

Results and Discussion

Neutral or slightly alkaline (pH 7.3-8.2) alcoholic solutions of mefenamic acid, flufenamic acid, tranexamic acid, furosemide, diclofenac sodium and thiaprofenic acid gave coagulated precipitates with nickel sulphate. These precipitates form the basis of the micro-quantitative determinations of the cited acidic drugs. The nickel ion content can be determined either directly in the precipitate or indirectly in the filtrate by atomic absorption spectrophotometry.

Addition of the recommended amount of alcohol is to enhance the solubilization of the drugs and coagulation of the precipitates. Larger volumes of alcohol must be avoided to prevent solubilization of the precipitates.

In order to study the effect of pH on precipitation, buffer solutions covering the acid to the alkaline range were tried. Acid media have a solubilizing effect on the precipitate leading to lower results for the direct technique and higher ones for the indirect technique while alkali media precipitate the metal as its oxide or hydroxide leading to higher results for the direct technique. The optimum pH was found to be neutral or slightly alkaline (pH 7.1-8.1).

Considering metal ion concentration effect on precipitation, 5 ml of the precipitating solutions were found to be sufficient for complete precipitation.

Regarding the temperature effect on precipitation, room temperature was found to be the most efficient. Higher temperatures showed solubilizing effect on the precipitate producing lower results for the direct technique and higher ones for the indirect technique.

Concerning the stoichiometric relationships, the Job's method of continuous variation[27] indicated molar ratios of 1:2 (drug to metal).

Statistical analysis of the results obtained by the proposed methods compared with those of the official methods[28,29] and $A_{max.}$ method[30] are given in tables (2-7) at 95%confidence level, the calculated t and F values do not exceed the tabulated ones, revealing equal precision and accuracy.

Table 1. Determination of flufenamic acid by the proposed A.A.S. (Ni^{2+} method) compared to an assay used in Pharmacopoeia[28]

	Nickel method		
	Direct	Indirect	Pharmacopoeia
$\bar{X} \pm$ S.D.	99.10 ± 0.44	99.19 ± 0.44	99.00 ± 0.45
N	8	8	8
V	0.19	0.19	0.20
t	0.46	0.86	
F	1.05	1.05	

(t=2.14, F=3.79 for P=0.05)

Table 2. Determination of mefenamic acid by the proposed A.A.S. (Ni^{2+} method) compared to an assay used in Pharmacopoeia[29].

	Nickel method		
	Direct	Indirect	Pharmacopoeia
$\bar{X} \pm$ S.D.	99.51 ± 0.30	99.50 ± 0.22	99.48 ± 0.25
N	8	8	8
V	0.09	0.05	0.06
t	0.21	0.17	
F	1.50	1.20	

(t=2.14, F=3.79 for P=0.05)

Table 3. Determination of tranexamic acid by the proposed A.A.S. (Ni^{2+} method) compared to an assay used in Pharmacopoeia[28]

	Nickel method		
	Direct	Indirect	Pharmacopoeia
$\bar{X} \pm$ S.D.	100.0 ± 0.99	99.98 ± 1.43	100.2 ± 1.37
N	8	8	8
V	0.98	2.04	1.88
t	0.33	0.31	
F	1.92	1.09	

(t=2.14, F=3.79 for P=0.05)

Table 4. Determination of furosemide by the proposed A.A.S. (Ni^{2+} method) compared to an assay used in Pharmacopoeia[29].

	Nickel method		
	Direct	Indirect	Pharmacopoeia
$\bar{X} \pm$ S.D.	99.39 ± 0.20	99.49 ± 0.30	99.48 ± 0.25
N	8	8	8
V	0.04	0.09	0.06
t	0.82	0.07	
F	1.50	1.50	

(t=2.14, F=3.79 for P=0.05)

Table 5. Determination of diclofenac sodium by the proposed A.A.S. (Ni^{2+} method) compared an assay used in Pharmacopoeia[29].

	Nickel method		
	Direct	Indirect	Pharmacopoeia
$\bar{X} \pm$ S.D.	99.72± 0.59	99.69 ± 0.64	99.78 ± 0.66
N	8	8	8
V	0.35	0.41	0.44
t	0.19	0.28	
F	1.26	1.07	

(t=2.14, F=3.79 for P=0.05)

Table 6. Determination of thiaprofenic acid by the proposed A.A.S. (Ni^{2+} method) compared to the $A_{max.}$ method[30].

	Nickel method		
	Direct	Indirect	$A_{max.}$ method
$\bar{X} \pm$ S.D.	99.61 ± 0.34	99.59 ± 0.40	99.56 ± 0.39
N	8	8	8
V	0.12	0.16	0.15
t	0.27	0.15	
F	1.25	1.07	

(t=2.14, F=3.79 for P=0.05)

In order to prove the validity and applicability of the proposed methods, Pinox® capsules containing flufenamic acid, Ponstan® capsules and syrup containing mefenamic acid, Cyklokapron® tablets and ampoules containing tranexamic acid, Lasix® tablets and ampoules containing furosemide, Declophen® tablets and ampoules containing diclofenac sodium and Surgam® tablets containing thiaprofenic acid were analyzed by the proposed methods.

The results obtained compared with the official methods[28,29] and $A_{max.}$ method[30] showed a high degree of accuracy and reproducibility (Tables 8-17).

Table7. Determination of flufenamic acid in Pinox® capsules by the proposed A.A.S.(Ni^{2+} method) compared to an assay used in Pharmacopoeia[28].

	Nickel method		
	Direct	Indirect	Pharmacopoeia
$\bar{X} \pm$ S.D.	99.01 ± 0.38	99.10 ± 0.47	99.00 ± 0.45
N	8	8	8
V	0.14	0.22	0.20
t	0.05	0.43	
F	1.43	1.10	

(t=2.14, F=3.79 for P=0.05)

Table 8. Determination of mefenamic acid in Ponstan® capsules by the proposed A.A.S.(Ni^{2+} method) compared to an assay used in Pharmacopoeia [29].

	Nickel method		
	Direct	Indirect	Pharmacopoeia
$\bar{X} \pm$ S.D.	99.41 ± 0.23	99.43 ± 0.19	99.48 ± 0.25
N	8	8	8
V	0.05	0.04	0.06
t	0.61	0.64	
F	1.20	1.50	

(t=2.14, F=3.79 for P=0.05)

Table 9. Determination of mefenamic acid in Ponstan® syrup by the proposed A.A.S.(Ni^{2+} method) compared to an assay used in Pharmacopoeia [29].

	Nickel method		
	Direct	Indirect	Pharmacopoeia
$\bar{X} \pm$ S.D.	99.38 ± 0.24	99.47 ± 0.27	99.48 ± 0.25
N	8	8	8
V	0.06	0.07	0.06
t	0.08	0.16	
F	1.00	1.17	

(t=2.14, F=3.79 for P=0.05)

Table 10. Determination of tranexamic acid in Cyklokapron® tablets by the proposed A.A.S. (Ni^{2+} method) compared to an assay used in Pharmacopoeia [28].

	Nickel method		
	Direct	Indirect	Pharmacopoeia
$\bar{X} \pm$ S.D.	99.9 ± 1.31	100.0 ± 1.30	100.2 ± 1.37
N	8	8	8
V	1.72	1.69	1.88
t	0.45	0.30	
F	1.09	1.11	

(t=2.14, F=3.79 for P=0.05)

Table 11. Determination of tranexamic acid in Cyklokapron® ampoules by the proposed A.A.S. (Ni^{2+}method) compared to an assay used in Pharmacopoeia[28].

	Nickel method		
	Direct	Indirect	Pharmacopoeia
$\bar{X} \pm$ S.D.	100.3 ± 1.19	99.8 ± 1.26	100.2 ± 1.37
N	8	8	8
V	1.42	1.59	1.88
t	0.16	0.61	
F	1.32	1.18	

(t=2.14, F=3.79 for P=0.05)

Table 12. Determination of furosemide in Lasix® tablets by the proposed A.A.S. (Ni^{2+} method) compared to an assay used in Pharmacopoeia[29].

	Nickel method		
	Direct	Indirect	Pharmacopoeia
$\bar{X} \pm$ S.D.	99.49 ± 0.19	99.45 ± 0.24	99.48 ± 0.25
N	8	8	8
V	0.04	0.06	0.06
t	0.09	0.25	
F	1.50	1.00	

(t=2.14, F=3.79 for P=0.05)

Table 13. Determination of furosemide in Lasix® ampoules by the proposed A.A.S. (Ni^{2+} method) compared to an assay used in Pharmacopoeia[29].

	Nickel method		
	Direct	Indirect	Pharmacopoeia
$\bar{X} \pm$ S.D.	99.43 ± 0.29	99.40 ± 0.29	99.48 ± 0.25
N	8	8	8
V	0.08	0.08	0.06
t	0.38	0.62	
F	1.33	1.33	

(t=2.14, F=3.79 for P=0.05)

Table 14. Determination of diclofenac sodium in Declophen® tablets by the proposed A.A.S.(Ni^{2+}method)compared to an assay used in Pharmacopoeia[29]

	Nickel method		
	Direct	Indirect	Pharmacopoeia
$\bar{X} \pm$ S.D.	99.70± 0.67	99.71 ± 0.60	99.78 ± 0.66
N	8	8	8
V	0.45	0.36	0.44
t	0.24	0.22	
F	1.02	1.22	

(t=2.14, F=3.79 for P=0.05)

Table 15. Determination of diclofenac sodium in Declophen® ampoules by the proposed A.A.S. (Ni^{2+}method) compared to an assay used in Pharmacopoeia[29]

	Nickel method		
	Direct	Indirect	Pharmacopoeia
$\bar{X} \pm$ S.D.	99.81± 0.59	99.77 ± 0.67	99.78 ± 0.66
N	8	8	8
V	0.35	0.45	0.44
t	0.10	0.03	
F	1.26	1.02	

(t=2.14, F=3.79 for P=0.05)

Table 16. Determination of thiaprofenic acid in Surgam® tablets by the proposed A.A.S. (Ni^{2+} method) compared to the $A_{max.}$method[30].

	Nickel method		
	Direct	Indirect	$A_{max.}$method
$\bar{X} \pm$ S.D.	99.50 ± 0.35	99.60 ± 0.38	99.56 ± 0.39
N	8	8	8
V	0.12	0.14	0.15
t	0.32	0.21	
F	1.25	1.07	

(t=2.14, F=3.79 for P=0.05)

In view of the above results, the proposed methods can be considered to be sensitive and selective for routine analysis of flufenamic acid, mefenamic acid ,tranexamic acid, furosemide, diclofenac sodium and thiaprofenic acid either in raw materials or in dosage forms.

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