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Research Article

A novel approach for spectrophotometric determination of naproxen

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ABSTRACT
In the present pandemic , Naproxen is one of the important drugs in which it blocks the binding groove of RNA nucleoprotein of influenza virus, in this paper (S)-2-(6-methooxynaphthalen-2-yl)-(+) propionic acid (Naproxen) has been refluxed with hydrobromic acid and acetic acid to form (S)-2-(6-hydroxynaphthalen-2-yl)-(+) propoinic acid (the hydroxyl analog of Naproxen , HAN). HAN has been oxidized with iron (III) ion followed by complex-formation reaction with 2,2-bipyridyl at 35°C in acidic medium to form an orange-red, complex that is soluble in water with good stability and exhibits maximum absorption at 523 nm. Concentration linearity range was from 0.25 to10 µg/ml of HAN. The calculated molar absorptivity is 6.0×10^4 l/mol.cm, Sandell's index for sensitivity is 0.0260 µg/cm^2, relative error % is from -0.1 to 0.15,and the rang of relative standard deviation % is from ± 0.10 to ± 0.35 % depending on the concentration level. 0.0132µg/ml is the limit of detection (LOD) and 0.0442 µg/ml is the limit of quantitation (LOQ). Nap has been determined in pure form. The application to the Naproxen Tablets requires an extraction by ethyl acetate in acidic medium.

Keywords: Naproxen, influenza, spectrophotometric, reflux, 2,2-bipyridyl, extraction

INTRODUCTION

Naproxen (Nap) [1] and Nap analogues exhibit broad antiviral activity against influenza [2]. The novel properties of antiviral structure of Nap against the nucleoprotein of influenza A virus has been discovered from 2013[3], followed by the evaluation of the antiviral properties of Nap against SARS-CoV-2 and show that Nap binding to the nucleoprotein of SARS-CoV2 inhibits viral replication and protected the bronchial epithelia against SARS-CoV-2 induced damage [4].

Nap is already an analgesic, anti-inflammatory drug with antipyretic activities and commonly used in the treatment of acute gout, dysmenorrhea and arthritis [5], chemically, it acts as a weak acid with a pK_a value of 4.2 classified as a low-solubility high-permeability drug [6].

My first manuscript for the determination of Nap in tablet include a coupling with the diazotized p-aminobenzoic acid in alkaline medium after a modification to the hydroxy analog to produce an orange azo dye measured at 500 nm. Beer's law was then followed over the range from 0.5 to 32.5µg/ml, this coloring method require many analytical reagents with many addition steps [7]. In the later manuscript Potassium permanganate was used for oxidation of the synthesized hydroxy analog of Nap by two procedures, in the first, the oxidation has occurred in acidic medium, the excess of permanganate was followed at 545 nm as a decrease with the increase in the modulate Nap. Beer's law is followed from 1 to 8µg/ml. In the second, potassium permanganate was used to oxidize the hydroxy analog of Nap in basic medium; the manganate produced was followed at 610 nm. The linearity range is followed from 2 to 7 µg/ml [8].

Other reported methods for quantitative determination of Nap include electrochemical method [9], Ion selective electrode [10], chemiluminescence [11], Conductometric [12], and chromatographic methods; HPLC- uv detection [13 - 16], LC-MS [17].

The large hydrophobic aromatic region present in the Nap molecule disfavors interactions with water molecules [18], hydrogen-bonding possibilities *via* the COOH group have been used for crystal structure of Nap by the interaction with π-stacking from the aromatic region nicotinamide and isonicotinamide [19] ,picolinamide [20], bipyridine and piperazine [21].

A spectrophotometric assay of Nap at uv region was reported by Sloka, et al [22], Nijhu, et al[23] ,Maheshwari, et al [24] and Jain, et al [25].

The correlation of molecular structure with observed physicochemical properties is a fundamental activity in the chemical sciences [26]. The problem in this drug is its chemically inert structure toward development reagents, in this

work Nap is converted into a chemically active compound by modification to hydroxyl analog, then develop a color reaction by an oxidation (with ferric ion)– the reduced iron undergoes a complex formation reaction with 2,2-bipyridyl reagent.

EXPERIMENTAL

Apparatus

BEL balance was used for weight measurements, reflux was utilized by electrothermal heater and stirring was utilized by Wisd stirrer and water bath type KARL KOLB Scientific Technical Supplies, West Germany. pH measurements were performed using HANNA 301 pH meter, 1.0 cm quartz cells and double-beam Jasco V-630 spectrophotometer were used.

Reagents

Analytical grade chemicals were used.

-Hydroxy analog of Naproxen (HAN) (100 µg / ml): dissolve 0.0100 g of HAN in 2 ml ethanol, then dilute to the make of 100 ml volumetric flask. Keep the solution into a dark bottle to gate stable solution for at least one month.

-Ferric Chloride ($FeCl_3$) ($5x10^{-3}$): dissolve 0.0811g of $FeCl_3$ in 5 ml acetic acid (1 M) and dilute to 100 ml.

-2,2-Bipyridyl ($1x10^{-2}$ M): dissolve 0.1561 g in 4 ml ethanol and dilute to 100 ml.

*-Pharmaceutical preparation (Naproxen Tablet(500 mg)):*10 tablets of Nap was grinded to a fine particles and a weight equivalent to one tablet ,was dissolved in 3 ml ethyl acetate and 1 ml HCl(3M), two layer was separated , the organic layer was transferred to another tube and extraction was repeated 3 times , 1 ml of saturated solution of NaCl was added to organic layer and sufficient amount of sodium sulphate was added after separation, The layer was left on air for drying [27].

The pure dried extract of Naproxen was modified to the hydroxyl analog which produce pink solid crystals with melting point of 190-191°C.

Chemical reactions

1-Modification reaction of Naproxen: This step involves a conversion of Nap into a hydroxy analog (HAN) using hydrobromic acid in presence of acetic acid at a certain amount.

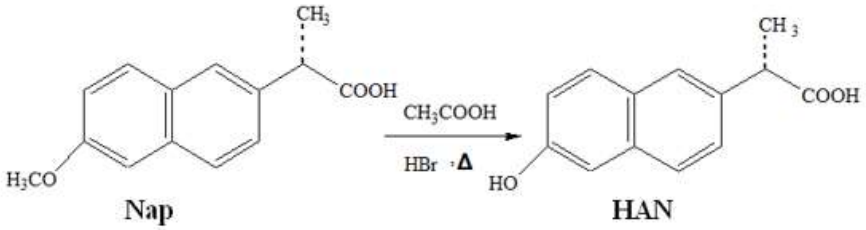

Fig.1: Modification reaction of Naproxen to the hydroxy analog

Modification reaction of Naproxen-Formation of HAN: 0.04 mol of pure Naproxen (9.2 g) was mixed with 25 ml hydrobromic acid (48%) and 25 ml acetic acid, the mixture was refluxed for 1.5 hour and then was cooled, diluted with 25 ml distilled water, filtrated, dried and finally was recrystallized using ethanol [28].

2- Oxidation of HAN by ferric chloride.

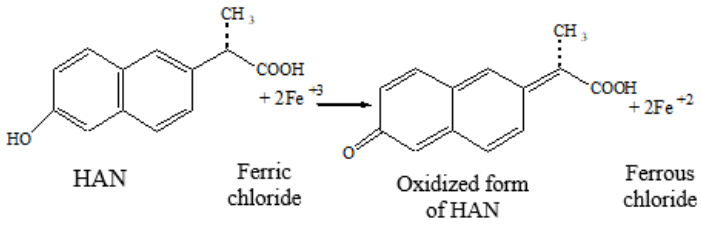

Fig.2: Oxidation reaction of HAN

Complex-formation reaction between ferrous chloride and 2,2'-bipyridyl

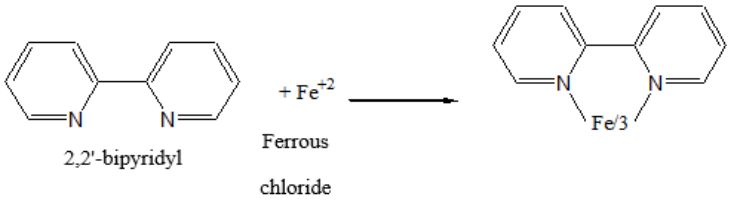

Fig.3: Complex-formation reaction between ferrous with 2,2'-bipyridyl

Study of the optimum reaction conditions

Selection of acid and its amount

Effect of different amount of many acids on absorption intensity has been studied (Table1).

Table 1: Selection of acid and its amount.

Acid used (1M)	Absorbance/ ml of acid					
	0	0.25	0.5	1.0	1.5	2.0
CH_3COOH	0.330 at pH= 3.61	0.281	0.262	0.195	0.137	0.108
pH		3.35	3.14	3.04	2.98	2.92
H_2SO_4		0.004	0.0041	0.0042	0.0040	0.0042
pH		2.14	2.03	1.81	1.66	1.52
H_3PO_4		0.0075	0.0041	0.0038	0.0031	0.0025
pH		2.79	2.24	2.08	1.95	1.88
HCl		0.0028	0.0021	0.0021	0.0020	0.0021
pH		1.89	1.88	1.77	1.54	1.38

From Table (1), exhibits the maximum absorptions intensity of the colored product produced when no acid used.

Effect of ferric chloride amount: Effect of (0.25-2.0) ml of (5×10^{-3}) M ferric chloride has been studied against 30-200 μg of HAN /20 ml and the determination coefficient of a measured absorbance has been evaluated. Table (2) shows that 1.5 ml of oxidant agent solution gave the best result.

Table 2: Effect of oxidize agent amount.

ml of $FeCl_3$ (5×10^{-3}) M	Absorbance/μg of HAN					B	R^2
	30	50	100	150	200		
0.25	0.095	0.121	0.223	0.235	0.280	0.019	0.9965
0.5	0.096	0.137	0.254	0.349	0.438	0.022	0.9969
1.0	0.105	0.170	0.285	0.386	0.485	0.043	0.9952
1.5	0.110	0.174	0.307	0.418	0.533	0.061	0.9969
2.0	0.105	0.172	0.299	0.399	0.512	0.070	0.9953

Selection of reagent and its amount

Effect of (0.25-2.5) ml of (1×10^{-2}) M 2,2'-bipyridyl has been studied against 30-200 μg of HAN /20 ml and the determination coefficient of a measured absorbance has been evaluated. Table (3) shows that 1.5 ml of reagent solution gave the best result.

Table 3: Effect of 2,2'-bipyridylamount.

ml of 2,2'-bipyridyl (1×10^{-2}) M	Absorbance/μg of HAN					B	R^2
	30	50	100	150	200		
0.25	0.058	0.07	0.092	0.114	0.133	0.046	0.9970
0.5	0.109	0.139	0.206	0.261	0.333	0.050	0.9982
1.0	0.115	0.176	0.306	0.421	0.514	0.058	0.9985
1.5	0.119	0.180	0.316	0.457	0.574	0.061	0.9986
2.0	0.106	0.163	0.302	0.443	0.554	0.070	0.9979
2.5	0.103	0.160	0.301	0.441	0.548	0.078	0.9971

Study the order of addition

Different arrangements of Drug (D), Oxidant (OX), Reagent (R), addition has been checked for prediction the best absorbance value. Table (4) shows that the final order D+OX+R gives the best results.

Table 4: Study the order of addition.

Order of addition	Absorbance
D+OX+R	0.315
D+R+OX	0.303
OX+D+R	0.309

Study the presence of surfactant

In order to study the effect of surfactants on absorption intensity, 1ml of the anionic surfactant [sodium dodecyl sulphate (SDS)], the cationic surfactant [cetylpyridinium chloride (CPC)], [cetyltrimethylammonium bromide (CTAB)] surfactants with the following order of (I. HAN (D)+ surfactant (S) + $FeCl_3$(OX)+ 2,2'-bipyridyl (R), II. D + OX +S + R, and III. D + OX + R + S). Table (5) show the result.

Table 5: Effect of surfactants.

Surfactant solution (1×10^{-3}M)	Absorbance/order of addition		
	I	II	III
SDS	Turbid	Turbid	Turbid
CTAB	0.307	0.303	0.308
CPC	0.292	0.287	0.291

From Table (5), there is no enhancement in absorbance value in which the absorbance without surfactant is 0.316), therefore the reaction is followed without addition of surfactant.

Effect of temperature

Table 6: Effect of temp.

Temp.	R.T(19°C)	25	35	40	45	50
Absorbance	0.134	0.210	0.319	**0.360**	0.362	0.364

Time of heating

Table 7: Effect of time of oxidation.

Temp.	1	3	5	10	12	15
Absorbance	0.156	0.240	0.266	**0.362**	0.368	0.368

Stability of reaction

The Stability of the formed complex against time has been followed using 100 µg.ml^{-1} of HAN.

Table 8: Stability of reaction.

Time(min)	Absorbance 100 μg of HAN/20 ml at 40°C
Immediately	0.368
5	0.368
10	0.368
15	0.369
20	0.370
25	0.371
30	0.372
35	0.373
40	0.374
50	0.375
60	0.376
80	0.379
90	0.380
1 day	0.442
5 days	0.530

Table (8) indicates that the colored product is stable at least for 90 minutes in 40°C.

Absorption Spectrum

Under the optimum reaction conditions, the absorption spectrum of the formed colored product vs.blank (Fig.4) shows that wavelength of maximum absorption intensity is 523 nm.this wavelength has been used in subsequent investigations.

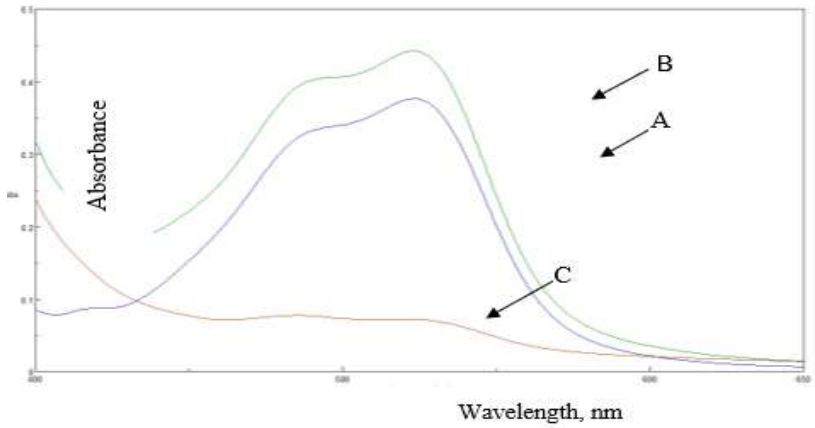

Fig.4: Absorption spectrum of 100µg/20 ml of HAN measured (A) sample vs. blank (B) sample vs. distilled water and (C) blank vs. distilled water

Procedure followed in calibration graph:
The following reagents has been added in the following order:(0.05-2) ml of (100 ppm) HAN, 1 ml of ($5x10^{-3}$ M) ferric Chloride, 1 ml of ($1x10^{-2}$M)2,2'-bipyridyle, heat at 40°C and the volumes were completed to 20 ml finally measured at 523 nm. (Fig.5)

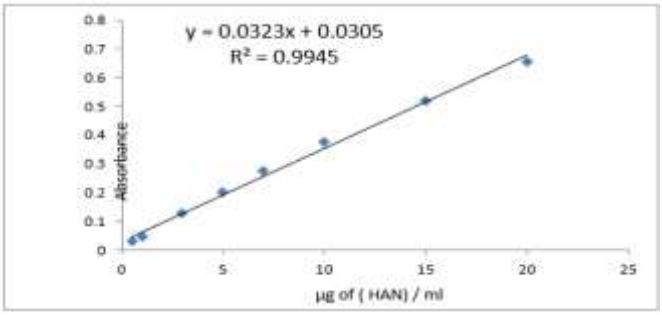

Fig.5: Calibration graph of Naproxen

A linear calibration graph is obtained over the range 0.25-10 μg of Nap / ml (0.05-20 μg/20 ml) with a molar absorptivity 6.976 x 10^4l.mol^{-1}.cm^{-1} and Sandell's index for sensitivity is 0.0309 μg.cm^{-2}.

Accuracy and precision: To check the accuracy and precision of the calibration graph, Nap is determined at three different concentrations; the results are shown in Table (7), which indicates good accuracy and precision.

Table 7: Accuracy and precision.

Amount Nap taken µg/20 ml	Relative standard deviation %*	Relative error %*
50	±0.35	0.15
100	±0.12	0.13
150	±0.10	-0.1

*Average of five determinations.

Reaction ratio between naproxen and iron (III) ion
The composition of the intense orange dye has been established using Job's method and mole – ratio method [29] fig. 6. The results show that both methods confirm the presence of 2 iron to1 naproxen with the expected structure as in fig. 2.

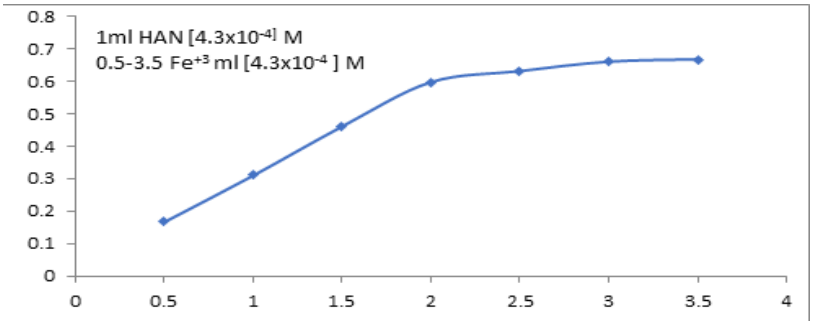

Fig.6: Mole ratio method of HAN - iron (III) ion reaction

Stability constant

The conditional stability constant of the formed dye in aqueous solution is estimated and found to be $7.3x10^{9}l^{2}.mol^{-2}$. The results of estimation are given in Table (8).

Table 8: Stability constant.

ml of HAN (2×10^{-3} M)	Absorbance			K $L^{3}.mol^{-3}$)(
	A_s^*	A_m^{**}	α***	
0.5	0.245	0.321	0.310	$2.21x10^{13}$
0.7	0.343	0.443	0.291	$4.06x10^{13}$
0.1	0.454	0.558	0.229	$8.08x10^{13}$

*Absorbance of the same amount of sample and reagent (1 sample:1 reagent)
**Absorbance of a maximum amount of reagent (1 sample:10 reagent)
*** Ratio of dissociation ($\alpha = A_m-A_s/A_s$)

Effect of organic solvents

The spectrophotometric characteristic of the colored product is more detectable using acetic acid but water is still being the choice because of its availability and low cost.

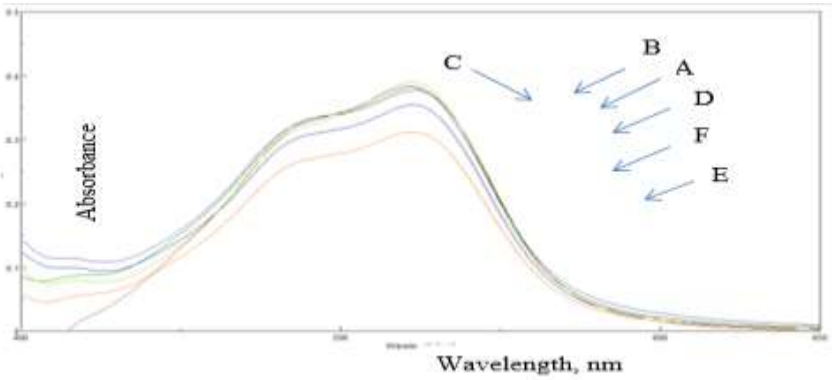

Fig.7: Effect of solvents A: Ethanol B: Methanol C: Acetone D: Water E: Acetone F: Propanol

Effect of interferences

In order to realize the analytical application of this method, effect of foreign compounds have been studied by carrying out the determination of 100 μg of HAN in the presence of 100 ,300, 500,1000 μg of foreign compounds using the recommended procedure. The result is shown in Table (9).

Table 9: Effect of interferences.

Interferences	Recovery /μg of Interferences			
	100	300	500	1000
Starch	99.2	99.3	100.1	99.2
Glucose	97.8	98.1	99.2	100.3
Lactose	96.4	96.8	96.9	97.0
Fructose	100.2	100.0	99.5	97.3

Application of the method

To test the applicability of the present method, it has been applied to the determination of Nap in pharmaceutical preparations. The results are listed in Table (11) indicating a good applicability of the method.

Table 10: application of the method.

Amount of Nap /20 ml	Recovery* (%) of Nap		
	Naproxen (tablet 500 mg) -Inaprolfort,Bilim, Turky	Naproxen (tablet 500 mg)-S.D.I, Iraq	Naprox (tablet 500mg) -Medical Bahri Company, Damascus -Syria
50	99.9	98.8	96.4
100	100.0	98.4	99.5
150	100.2	99.1	99.2

*Average of three determinations.

t-test

Both the present method and British Pharmacopeia method [30] has been applied at the same time to t-test calculation [31] and the value compared with statistical tables for four degree of freedom at 95% validation level. The result in Table (11) show that there is no a real difference between the two methods.

Table 11: T-test.

Drug	Recovery * %		t-exp
	Present method	British Pharmacopeia method	
Naproxen (tablet 500 mg)-Inaprolfort,Bilim,Turky	100.0	99.9	0.230
Naprox (tablet 500mg) -Medical Bahri Company, Damascus -Syria	98.3	97.4	0.838

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