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# A Creative Indirect Spectrophotometric Determination of Naproxen

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## ABSTRACT

A New, sensitive spectrophotometric method for determination of Naproxen (Nap) has been proposed. The method is based on a modification of Naproxen into a hydroxy analog (mNap). The modified compound is coupled with the diazotized p-aminobenzoic acid (PABA) in alkaline medium, the resulting orange azo dye exhibit a maximum absorption at 500 nm. Beer's law is obeyed over the concentration range from 10 to 650 µg/20 ml, (i.e. 0.5-32.5 µg/ ml) with a good sensitivity (molar absorptivity $2.14 \times 10^4$ l.mol$^{-1}$.cm$^{-1}$), good precision (RSD% better than ±1.93%) and high accuracy (relative error % better than 0.43%), Sandell's sensitivity index is 0.0107µg.cm$^{-2}$ and the limit of detection (LOD) is 0.024 µg/ml and the limit of quantitation (LOQ) is 0.082 µg/ml. The method has been applied successfully for determination of Naproxen in dosage forms after extraction of the active ingredient.

**Keywords**: Naproxen, spectrophotometric, modification reaction, diazotized p-aminobenzoic acid, extraction, Creative.

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# طريقة طيفية مستحدثة غير مباشرة لتقدير النابروكسين

## الملخص

تم اقتراح طريقة طيفية جديدة وحساسة لتقدير النابروكسين في مستحضراته الصيدلانية بعد تحوير النابروكسين الى مماثله الذي يحتوي على مجموعة هيدروكسيل ومن ثم اقترانه في المحيط القاعدي مع الكاشف حامض بارا امينو البنزويك المؤزوت لتكوين ناتج ذو لون برتقالي يعطي اعلى امتصاص له عند الطول الموجي 500 نانوميتر. تتبع الطريقة قانون بيير لحدود تقديرية 10-650 مايكروغرام/20 مل (0.5-32.5 مايكروغرام/مل) وبحساسية (معامل الامتصاص المولاري $10^4$ x 2.14 لتر.مول$^{-1}$ . سم$^{-1}$ ) ومضبوطية (RSD% افضل من±1.93 %) ودقة عالية (الخطأ النسبي % افضل من ±0.43 %). كانت قيمة معامل ساندل للحساسية 0.0107 مايكروغرام.سم$^{-2}$ وحد الكشف (LOD) 0.024 مايكروغرام.مل$^{-1}$وحد التقدير(LOQ) 0.082 مايكروغرام.مل$^{-1}$. تم تطبيق الطريقة بنجاح في تقدير النابروكسين في مستحضراته الصيدلانية بعد استخلاص المادة الفعالة.

**الكلمات الدالة**: نابروكسين، طريقة طيفية، تفاعل تحوير، حامض بارا امينو البنزويك المؤزوت، استخلاص، مستحدثة.

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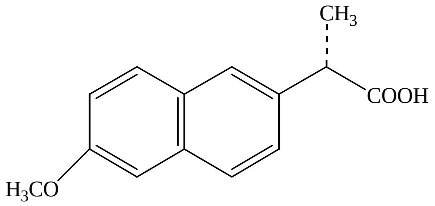
## INTRODUCTION

Naproxen (Nap) is an analgesic, anti-inflammatory drug with antipyretic activities largely related to inhibition of prostaglandin synthesis (Karch, 2010), this drug is used more and more frequently because it blocks RNA-binding groove of nucleoprotein of virus and may have antiviral activity against influenza (Lejal *et al.*,2013).

Naproxen is (S)-2-(6-methoxynaphthalen-2-yl)-(+) propanoic acid $C_{14}H_{14}O_3$ (230.259 g/mol) with the chemical structure as below (Acomoffat *et al.*,2005).



**Naproxen structure**

A few methods for quantitative determination of Naproxen have been reported, these including HPLC (Wahbi *et al.*,2009) (Tashtoush and Al-Taani, 2003) (Muneer *et al.,* 2017), RP-HPLC (Pansara *et al.*, 2013), LC-MS (Veeragoni *et al.*, 2016), electrochemical method (Soltani *et al.,* 2018), Ion selective electrode (Lenik *et al.,* 2002), chemiluminescence (Yinhuan and Jiuru, 2006), Conductometric (Alhazmiand and Al Bratty, 2017), While other papers report a spectrophotometric assay of Naproxen at uv region (Nijhu *et al.*,2011) (Maheshwari *et al.,* 2010) (Sloka *et al.*,2011) (Jain *et al.*,2011). A colorimetric assay of naproxen tablets based on chemical derivatization with the chromogenic reagent 4-carboxyl-2,6-dinitrobenzene diazonium ion was developed. The optimal reaction time was found to be 5 min at 30 $^{o}$C after vortex mixing of the drug/reagent mixture for 10 s. The optimal analytical wavelength was found to be 470 nm (Idowu *et al.*, 2009).

Naproxen was determined by formation of ion-pair complex with bromophenol blue,the colored product was measured at 432 nm (Keyhanian *et al.*,2014), another ion-pair procedure based on reaction between Naproxen with two sulfophthalein acid dyes, namely bromocresol green and bromothymol blue (Alizadeh and Keyhanian, 2015).

The aim of this work is determination of naproxen by indirect spectrophotometric method after modification of Nap to hydroxyl analog, then coupling with diazotized p-aminobenzoic acid (PABA).

## EXPERIMENTAL

### Apparatus

All spectral and absorbance measurement were performed on double-beam Jasco V-630 spectrophotometer with 1.0 cm matched quartz cells. pH measurements were performed using HANNA 301 pH meter, BEL balance was used for weight measurements, reflux was utilized by electrothermal heater and stirring was utilized by Wisd stirrer.

### Reagents

All chemicals used were of analytical grade.

**-Modification reaction of Naproxen:** 0.04 ml 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, dryed and finally was recrystallized using ethanol to produce a pink solid crystal with melting point (190-191 C°) (Al-Hamdany, 2009).

**-Modified Naproxen (mNap) (100 µg / ml)**: It was prepared by dissolving 0.0100 g of mNap in 2 ml ethanol and the volume was completed to 100 ml with distilled water in a volumetric flask. The solution was then transferred to a dark bottle and it is stable for at least one month.

**-Sodium Nitrite ($NaNO_2$) 1%:** This solution was prepared by dissolving 1.0 g of $NaNO_2$ in distilled water and the volume was completed to 100 ml in a volumetric flask.

**-Sulphamic acid 3%:** This solution was prepared by dissolving 3.0 g of sulphamic acid in distilled water and the volume was completed to 100 ml in a volumetric flask.

- **p-Aminobenzoic acid ($2x10^{-3}$ M)**: It was prepared by dissolving 0.0548 g of PABA in 200 ml distilled water in a volumetric flask.

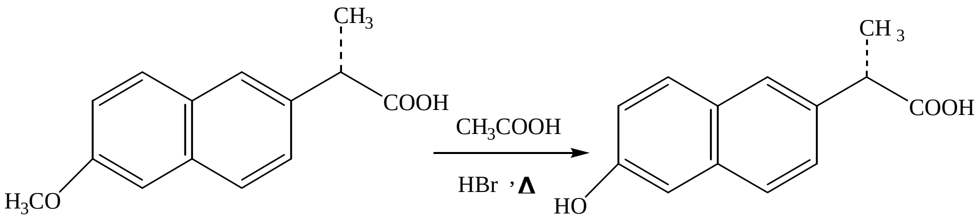
- **Phosphoric acid $H_3PO_4$ (1M):** This solution was prepared by dilution of 6.84 ml of the concentrated phosphoric acid (14.6 M) solution to 100 ml with distilled water in a volumetric flask.

- **Sodium hydroxide solution (1M):** This solution was prepared by appropriate dilution of the concentrated solution (Fluka) with distilled water to 1000 ml in a volumetric flask and then transferred to a plastic bottle.

-**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, the melting of dried product improve the formation of Nap hydroxy analog and proceed as mentioned above in modification of Nap. **(**Ka Le; project).

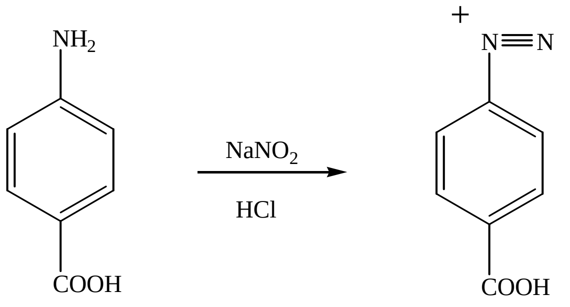
**Chemical reactions**

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



**Nap** **mNap**

2-Diazotization reaction of PABA: In this step PABA is treated with an excess amount of nitrite in acidic medium to form the corresponding diazonium salt.

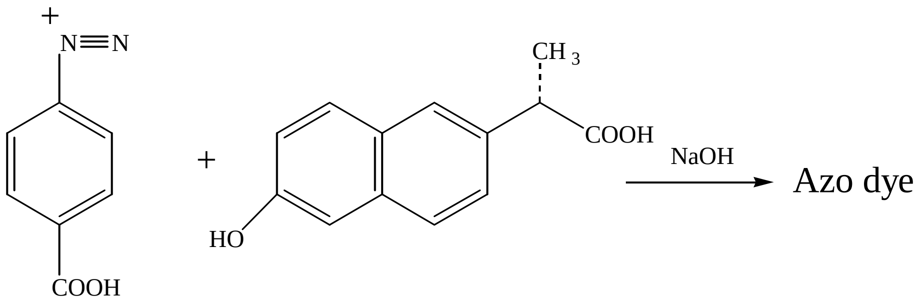


**PABA** **Diazotized PABA**

3- Excess of nitrite can be removed by sulphamic acid

$$\underset{\text{Excess}}{HNO_2} + \underset{\text{Salphamic acid}}{NH_2SO_3H} \longrightarrow N_2\uparrow + H_2O + H_2SO_4$$

4- Coupling reaction: The corresponding diazonium salt coupled with the modified Nap in alkaline medium to produce the colored azo dye.



**Diazotized PABA** **mNap**

## Procedure and calibration graph

The following reagents has been added in the following order: 2ml of (2 x $10^{-3}$ M) p-aminobenzoic acid, 2 ml of ($H_3PO_4$), 1 ml of 1% $NaNO_2$ , 0.5 ml of 3% sulphamic acid, increasing volumes (0.1-6.5) ml of 100 µg.$ml^{-1}$ standard mNap solution and finally 2 ml of NaOH (1M), the volumes were completed to 20 ml in a volumetric flasks with distilled water, the absorbances have been measured at 500 nm against blank solution. Fig. (1)

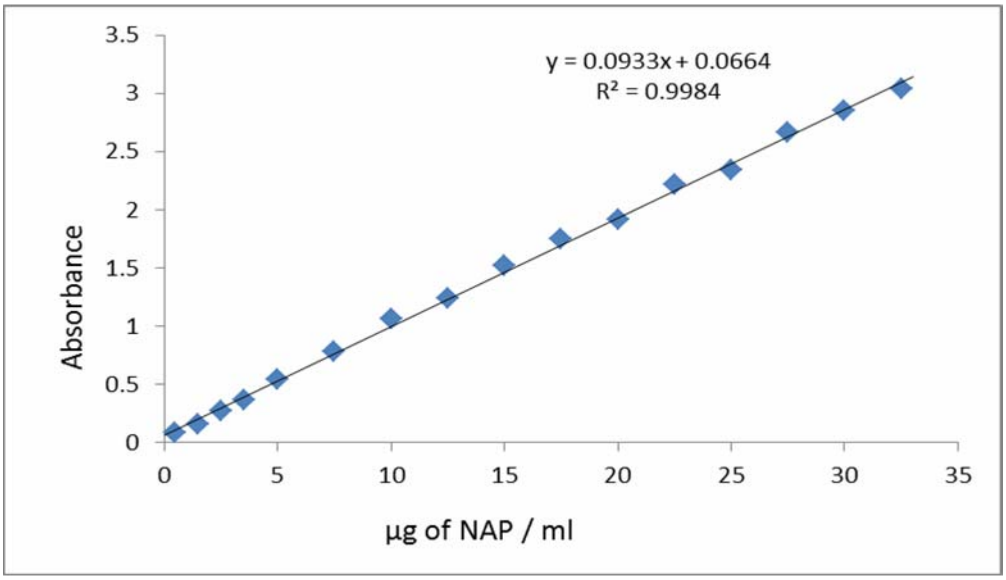


**Fig. 1: Calibration graph of Naproxen**

A linear calibration graph is obtained over the range 0.5-32.5 µg of mNap / ml (10-650 µg/20 ml) with a molar absorptivity 2.14 x $10^4$ $l.mol^{-1}.cm^{-1}$ and Sandell's sensitivity index 0.0107 µg.$cm^{-2}$.

## Study of the optimum reaction conditions

## Selection of acid and its amount

Diazotization of PABA undergoes in acidic medium, therefore, effect of different amount of many acids on absorption intensity has been studied (Table 1).

**Table 1: Selection of acid and its amount**

| **Acid used (1M)** | **Absorbance/ ml of acid** | | | | |
|---|---|---|---|---|---|
| | **0.5** | **1.0** | **1.5** | **2.0** | **2.5** |
| **HCl** | 0.259 | 0.225 | 0.184 | 0.137 | 0.073 |
| **$H_2SO_4$** | 0.236 | 0.226 | 0.220 | 0.218 | 0.212 |
| **$HNO_3$** | 0.285 | 0.278 | 0.278 | 0.271 | 0.270 |
| **$H_3PO_4$** | 0.205 | 0.255 | 0.390 | 0.537 | 0.360 |
| **$CH_3COOH$** | 0.201 | 0.274 | 0.480 | 0.089 | 0.040 |

From (Table 1), 2 ml of $H_3PO_4$ gives the maximum absorptions intensity of the colored product; therefore it is used for the following experiments.

### Effect of nitrite amount with time

Between 0.1 ml to 1.2 ml of $NaNO_2$ (1%) has been checked with a standing time from 0 to 5 min, the results are listed in (Table 2).

**Table 2: Effect of nitrite amount with time**

| ml of (1% ) $NaNO_2$ solution | Absorbance / minute standing time | | | | |
|---|---|---|---|---|---|
| | **Immediatly** | **1** | **2** | **3** | **5** |
| **0.1** | 0.476 | 0.499 | 0.480 | 0.480 | 0.480 |
| **0.3** | 0.504 | 0.520 | 0.509 | 0.504 | 0.504 |
| **0.5** | 0.520 | 0.536 | 0.523 | 0.524 | 0.519 |
| **0.7** | 0.529 | 0.539 | 0.530 | 0.526 | 0.508 |
| **1.0** | 0.520 | 0.545 | 0.528 | 0.528 | 0.523 |
| **1.2** | 0.338 | 0.377 | 0.250 | 0.154 | 0.241 |

From (Table 2), 1ml of 1% $NaNO_2$ has been selected with one minute as a reaction time.

### Effect of sulphamic acid amount with time

Between 0.3-1.5 ml of 3% of sulphamic acid solution was added, and absorbance of the solutions was followed at different standing time.

**Table 3: Effect of sulphamic acid amount with time**

| ml of sulphamic acid ( 3% ) solution | Absorbance/minute standing time with shaking | | | | |
|---|---|---|---|---|---|
| | **1** | **2** | **3** | **5** | **7** |
| **0.3** | 0.041 | 0.129 | 0.115 | 0.112 | 0.102 |
| **0.5** | 0.526 | 0.544 | 0.495 | 0.413 | 0.339 |
| **0.7** | 0.472 | 0.514 | 0.493 | 0.413 | 0.335 |
| **1.0** | 0.420 | 0.453 | 0.455 | 0.405 | 0.330 |
| **1.2** | 0.395 | 0.445 | 0.406 | 0.368 | 0.327 |
| **1.5** | 0.361 | 0.392 | 0.353 | 0.352 | 0.343 |

From (Table 3) 0.5 ml of 3% of sulphamic acid solution was selected with standing time two minute.

### Effect of diazotized agent amount

Effect of (1-5) ml of ($2\times10^{-3}$) M PABA has been studied against 50-200 µg of mNap /20 ml and the determination coefficient of a measured absorbance has been evaluated. (Table 4) shows that 2 ml of diazotized agent solution gave the best result.

**Table 4: Effect of diazotized agent amount**

| ml of PABA ( $2\times10^{-3}$) M | Absorbance/µg of mNap | | | | | $R^2$ |
|---|---|---|---|---|---|---|
| | **50** | **70** | **100** | **150** | **200** | |
| **1** | 0.252 | 0.358 | 0.521 | 0.746 | 1.016 | 0.9989 |
| **2** | 0.275 | 0.368 | 0.542 | 0.781 | 1.06 | 0.9991 |
| **3** | 0.243 | 0.351 | 0.498 | 0.744 | 1.03 | 0.9990 |
| **4** | 0.237 | 0.349 | 0.478 | 0.738 | 1.01 | 0.9989 |
| **5** | 0.229 | 0.321 | 0.452 | 0.731 | 0.998 | 0.9982 |

### Selection of base and its amount

Four types of bases or basic salts at different volumes (1-5) ml of each have been tasted for their effect on the absorption intensity of the dye formed. The results are listed in (Table 5).

**Table 5: Selection of base and its amount**

| Base used (1M) | ml of base used | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| **NaOH** | 0.091 | 0.544 | 0.280 | 0.237 | 0.189 |
| **KOH** | 0.109 | 0.323 | 0.104 | 0.051 | 0.027 |
| **$Na_2CO_3$** | 0.206 | 0.540 | 0.432 | 0.108 | 0.078 |
| **$NaHCO_3$** | 0.078 | 0.158 | 0.548 | 0.537 | 0.124 |

From (Table 5) 2 ml of sodium hydroxide solution (1M) has been selected.

### Effect of surfactant

In order to study the effect of surfactants on absorption intensity, 2 ml of anionic [sodium dodecyl sulphate (SDS)], cationic [cetylpyridinium chloride (CPC)], [cetyltrimethylammonium bromide (CTAB)] surfactants with different order of additions were followed (Table 6).

**Table 6: Effect of surfactants**

| Surfactant solution ($1\times10^{-3}$M) | Absorbance/order* of addition | | | | | |
|---|---|---|---|---|---|---|
| | I | II | III | IV | V | VI |
| **SDS** | 0.500 | 0.508 | 0.519 | 0.518 | 0.520 | 0.519 |
| **CTAB** | 0.303 | 0.312 | 0.316 | 0.311 | 0.312 | 0.312 |
| **CPC** | 0.342 | 0.351 | 0.348 | 0.344 | 0.345 | 0.344 |

Not: Absorbance without surfactant = 0.542

* I. p-aminobenzoic acid (PABA) + surfactant (S) + $H_3PO_4$(H) + $NaNO_2$(N) + Sulphamic acid (F) + mNaproxen(D) + NaOH (B)

II. PABA +H+S+N+F+D+B
III. PABA +H+N+S+F+D+B
IV. PABA +H+N+F+S+D+B
V. PABA +H+N+F+D+S+B
VI. PABA +H+N+F+D+B+S

From (Table 6), there is no enhancement in absorbance value, therefor the reaction is followed without addition of surfactant.

### Stability of reaction

The Stability of the colored product against time has been followed using 100 µg.ml$^{-1}$ of mNap.

**Table 7: Stability of the colored product**

| µg of mNap/20 ml | Absorbance/min | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 45 | 50 | 60 |
| 100 | 0.522 | 0.542 | 0.545 | 0.545 | 0.543 | 0.541 | 0.539 | 0.537 | 0.534 | 0.528 | 0.524 | 0.511 |

(Table 7) indicate that the colored product is stable at least for 60 minute.

## Absorption Spectrum

Under the optimum reaction conditions, the absorption spectrum of the colored product against blank Fig. (2) shows that wavelength of maximum absorption intensity is 500 nm.this wavelength has been used in subsequent investigations.

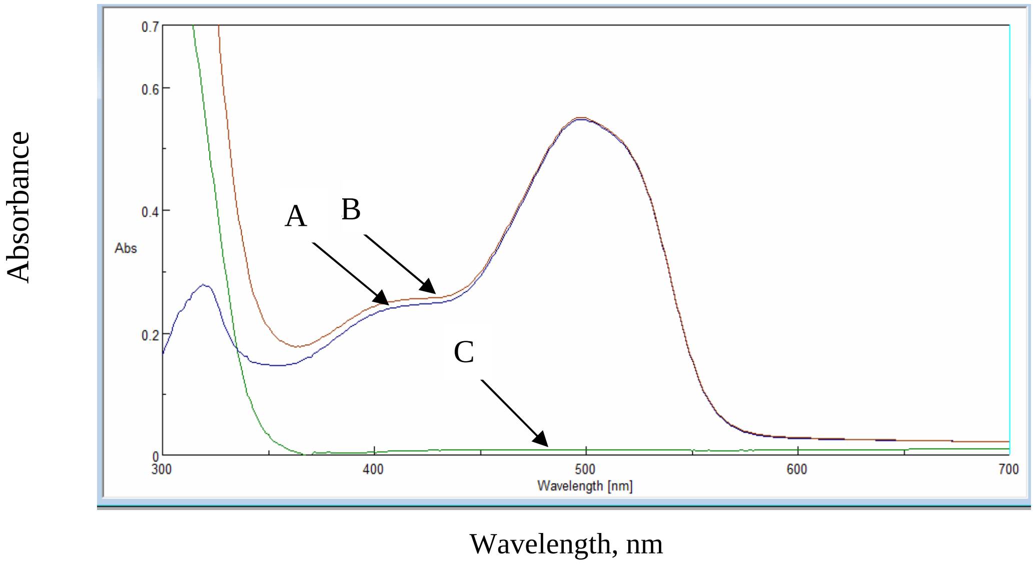


**Fig. 2: Absorption spectrum of 100µg/20 ml of mNap measured (A) sample against blank (B) sample against distilled water and (C) blank against distilled water**

## Accuracy and precision

To check the accuracy and precision of the calibration graph, mNap is determined at three different concentrations; the results are shown in (Table 8), which indicates good accuracy and precision.

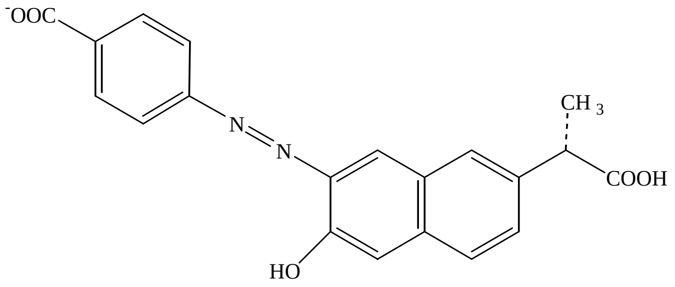
**Table 8: Accuracy and precision**

| Amount mNap taken µg/20 ml | Relative standard deviation %* | Relative error %* |
|---|---|---|
| 50 | ±2.65 | 1.74 |
| 100 | ±1.93 | 0.43 |
| 200 | ±0.66 | -0.10 |

*Average of five determinations.

## Nature of the Dye

The composition of the intense orange azo dye has been established using Job's method and mole –ratio method.The results show that both methods confirm the presence of 1:1 azo dye of probably the following structure:



**The suggested structure of the orange azo dye**

### Stability constant

The conditional stability constant of the formed azo dye in aqueous solution is estimated and found to be 1.1x10$^{4}$ l.mol$^{-1}$. The results of estimation are given in (Table 9).

**Table 9: Stability constant**

| ml of mNAP (2×10$^{-3}$ M) | Absorbance | | | K l.mol$^{-1}$)( |
|---|---|---|---|---|
| | $A_s$* | $A_m$** | α*** | |
| **0.5** | 0. 827 | 1.086 | 0.238 | 1.3×10$^{4}$ |
| **1.0** | 1.662 | 2.113 | 0.213 | 8.6×10$^{3}$ |

*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 .

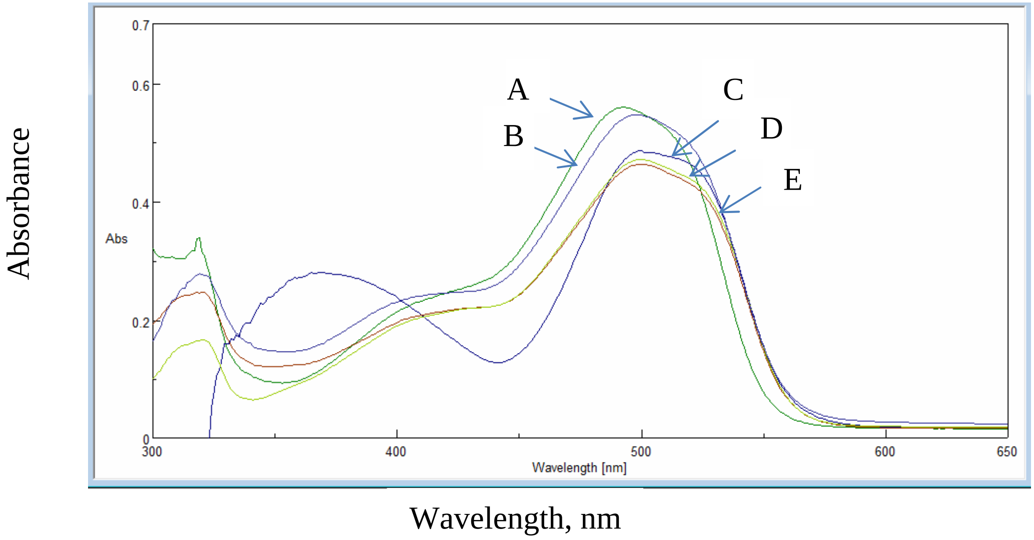


**Fig. 3: Effect of solvents**
**A: Acetic acid B: Acetone C: n-Propanol D: Ethanol E: Water**

### 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 mNap in the presence of 100, 300, 500,1000 µg of foreign compounds using the recommended procedure. The result are shown in **(**Table 10).

**Table 10: Effect of interferences**

| Interferences | Recovery /µg of Interferences | | | |
|---|---|---|---|---|
| | **100** | **300** | **500** | **1000** |
| **Starch** | 98.15 | 97.12 | 99.85 | 97.94 |
| **Glucose** | 98.76 | 96.06 | 96.71 | 96.71 |
| **Gum Arabic** | 94.66 | 93.63 | 91.99 | 93.02 |
| **Lactose** | 100.0 | 100.2 | 95.68 | 97.33 |

## 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 11: application of the method**

| Amount of mNap /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 | 97.8 | 95.9 | 96.7 |
| 100 | 98.2 | 96.3 | 99.5 |
| 200 | 100.0 | 96.9 | 102.0 |

*Average of three determinations.

## t-test

Both the present method and British Pharmacopeia method (British Pharmacopeia, 2013) has been applied at the same time to t-test calculation (Christian, 2004) and the value compared with statistical tables for four degree of freedom at 95% validation level. The result in Table (12) show that there is no a real difference between the two methods.

**Table 12:T-test**

| Drug | Recovery * % | | t-exp |
|---|---|---|---|
| | Present method | British Pharmacopeia method | |
| Naproxen (tablet 500 mg)-Inaprolfort,Bilim,Turky | 98.7 | 99.9 | 1.49 |
| Naprox (tablet 500mg) -Medical Bahri Company, Damascus -Syria | 99.4 | 97.4 | -1.03 |

- Average of three determinations.

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