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# Development of Derivative Spectrophotometric with Zero Crossing Method For determination of Paracetamol and Ibuprofen in Tablet

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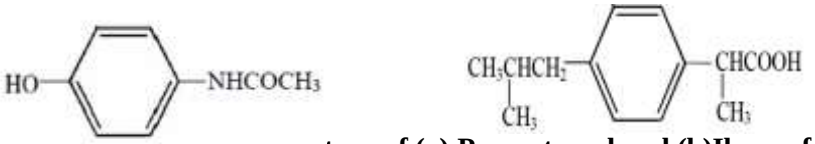
**Abstract :** The purpose of this study is to determine paracetamol and ibuprofen in tablet by derivative spectrophotometry with zero crossing method in methanol and distilled water. The results determined analysis wavelength of paracetamol and ibuprofen on the second derivative with $\Delta\lambda$= 8 nm at the wavelength of 253.4 nmand 228.6 nmrespectively.The paracetamol levels in NR® tabletand OS® tablet were100.03% ± 1.28% and 100.11% ± 1.55% respectively and ibuprofen were 101.15% ± 1.00% and 100.89% ± 0.57% respectively.The percent recovery for paracetamol and ibuprofen were 101.11% and 100.40% respectively and relative standrad deviation were 2.00% and 1.67% respectively. The proposed method is simple as there is no need for seperation, rapid and low cost.

**Keywords** : *Paracetamol,Ibuprofen,Tablet, Derivative Spectrophotometric, Zero-Crossing, Second Derivative.*

## 1. Introduction

Many drug that use a variety of active subtances, such as analgesics, this combination aims to enhance the therapeutic effect. One of the preparations that are popular today are combinations paracetamol and ibuprofen which is an analgesic drugs. Paracetamol (PAR) efficatious as analgesic and antipyretic agent, but not anti-imflammatory, anti-pain agents are the safets and also for self medication. Ibuprofen (IBU) a was the first member of the propionic acid class of the non-steroidal anti-imflammatory drugs ($NSAID_S$)[1]. Analgesics are subtance that reduce pain without losing consciounces by combaining PAR and IBU in does remain on the tablet is better than a single drug treatment alone for the treatment of acute pain about this showed that the combinations can anhance the analgesic improvement[2]. Chemical structure of PAR and IBU can be seen in Figure 1.

(a) (b)




**ture of (a) Paracetamol and (b)Ibuprofen**

According to Farmakope Indonesia V Edition for PAR and IBU contains is not less than 90.0% and not more than 110.0% of the amount listed on the label[3].

Some recearchers had previously conducted as determination mixture of PAR and IBU can be determined by High Performance Liquid Chromatography (HPLC) used mobile phase simultaneously with acetonitril and phosphate buffer[4], RP-HPLC[5-9], ultraviolet spectrophotometry[10-15], zero crossing method[16-17]and by ratio spectra using methanol as solvent[18]. Now it spectrophotometry ultraviolet-visible evolve in line with developments in science, so that it can be used to set the levels of the mix, namely through the applications of derivative spectrophotometric method,with the result that good accuracy and precision. The most common used is zero crossing methodwith directly without separation[19-20].The aims of this work to developed a spectrophotometric with zero-crossing method for determination of PAR and IBU mixture in tablet using methanol and distilled water solvent.

## 2. Experiment

### 2.1 Apparatus

UV- Visible Spectrophotometer(Shimadzu 1800) with a computer equipped with UV Probe 2.34 software (UV-1800 Shimadzu), analytical balance (Mettler Toledo),sonicator (Branson 1510), pH meter (Hanna), glass tools, mortar and pestle, and other tools required in sample preparation.

### 2.2 Materials

Material used were methanol (E. Merck), distilled water,Paracetamol BPFI, IbuprofenBPFI, NR®Tablets and OS®Tablets (each tablet contains350 mg PAR and 250mg IBU).

### 2.3Preparation of Paracetamol and Ibuprofen Stock Solution

An accurately weighed 50 mg of PAR BPFI and IBU BPFI raw material respectively was dissolvedin 10 ml of methanol and diluted with a distilled water in a 100 mL flask until the line mark, then shaken until to obtain homogeneous solution with a concentration of500 µg/mL stock solution I (SS I). From this solutions pipette5.0 mL was put into a 50 mL flask, diluted with distilled water shaken in order to obtain a solution with a concentration of 50µg/mL (SS II).

### 2.4Preparationof Maximum Absorption Spectrum Paracetamol and Ibuprofen

Taken as much as 3.3mL and 4 ml from SS II (concentration 50 µg/ml) for PAR and IBU respectively. Each solution was then inserted into 25 mL and then dilutted with distilled water until the line mark, then shaken until to obtain a homogeneous concentration 6.6µg/mL and 8.0µg/mL forPAR and IBU respectively. Absorbance was measured at a wavelength of 200-400 nm.

### 2.5 Preparation Derivative Absorption Spectrum of Paracetamol and Ibuprofen

Taken as much as2.5 mL; 3.5 mL; 4.5 mL; 5.5 mL; and 6.5 mL of stock solutionPAR with concentration 50 µg/mL and taken as much as2.0 mL; 3.0 mL; 4.0 mL; 5.0 mL; and 6.0 mL of stock solutionIBU with concentration 50 µg/mL. Then each put in a 25 ml flask to be diluted with the solvent distilled water. Make absorption spectrum from PAR solution with concentration 5-13 µg/mL and from IBU solution with concentration 4-12 µg/mL at a wavelength of 200-400 nm. Then the spectrum is transformed into first and second derivative absorption spectra with $\Delta\lambda = 8$ nm.

### 2.6 Determination of Zero Crossing

Determination the zero crossing is conductided by operlapping the absorption spectra each derivative in range of the solution concentration. The zero crossing of each subtance shown by the wavelength that has zero absortion at various concentrations.

### 2.7 Determination of Wavelength Analysis

Created PAR solution (concentration of 7 µg/ml), IBU solution (concentration of 4 µg/mL)and a mixed solution of PAR 7 µg/mL and IBU 4 µg/mL respectively. Each solution is then measured absorbance at a wavelength of 200-400 nm. Then absorption spectrum istransformed into the first and second derivatives of each single substance from a mixture of PAR and IBU. The second derivative absorption spectrum from a

single substance solution and a mixture ofboth overlay. Were chosen to be the wavelength analysis is that at a particular wavelength, the absorptionsingle one of the compounds zero while single absorption partner compound and a mixture of both is almost thesame or exactly the same. Because at these wavelength can selectively measure the uptake of one of thecompounds without being bothered by the uptake of compounds partner.

### 2.8 Determination Linearity Calibration Curves Paracetamol and Ibuprofen

Created PAR stock solution with a concentration of 5-13 µg/mL and IBU stock solution with a concentration 4-12 µg/mL, then the second derivative absorption measured with $\Delta\lambda$ = 8 nm in wavelength analysishas been determined. Then do the analysis of the relationship between concentration and absorbance values thisobtained linear regression equation y=ax+b, and the calculation of Limit of Detection (LOD) and Limit of Quantification (LOQ)[21].

### 2.9 Determination of Paracetamol and Ibuprofen Levels in Tablets

Twenty tablets are weighed and crushed homogeneous,the powder equivalent to 50 mg of PAR and equality of IBU contained in there is calculated it should be weight up to a six repitision. Subsequently incoporated into the flask 100 ml, dilluted with 10 ml methanol (homogeneous with a sonicator for 15 minutes) and distilled water until the line mark.The solutions is then filtrateand 0.35 ml filtrate put into the flask 25 ml, added with distilled water until the line mark in order to obtained a solutions in which there are PAR and IBU concentrations of 7 µg/mL and 4 µg/mL respectively. Measured absorptions at a wavelength of 200-400 nm, further uptake curve is transformed into a second derivative absorption spectrum with $\Delta\lambda$ 8 nm.

### 2.10Accuracy Test

Accuracy test was conducted by the addition of raw materials, is to make three samples with analyte concentration of a specific range of 80%, 100%, 120%.Where in each specific rangeis used 70% and 30% of raw samples to be added and then mix the sample and standard absorbance was measured at a wavelength of 200-400 nm, then the absorption spectrum is transformed into a second derivative absorption spectrum with $\Delta\lambda$ 8 nm.

## 3 Results and Discussion

### 3.1 Results Determination of the Maximum Absorption Curves

Based on the research results, obtained the maximum wavelength at 253.40 nm and 228.60 nm for PAR and IBU respectively.

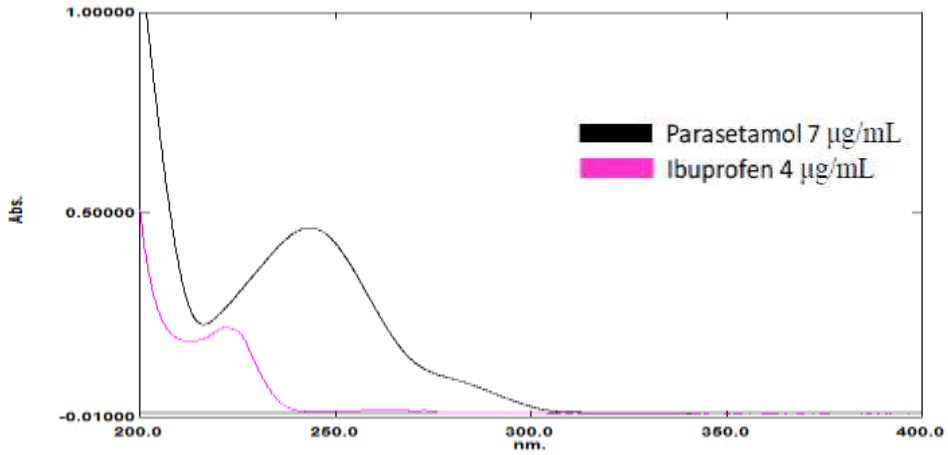



**Figure 1. The overlapping maximum absorption spectrum of PAR and IBU**

### 3.2Results Determination of Zero Crossing at Frist Derivative

Determination of the zero crossing first derivative by riding overlaid first derivtive absoprtion spectrum of each concentration of PAR and IBUwith $\Delta\lambda$ = 8 nm. Zero crossing in the first derivative of the absorption spectrum of PAR and IBU each wavelength indicated by the has zero absorption at various concentrations. The overlapping PAR and IBU at the second derivative can be seen in Figure 2, and absorption spectrum of PAR and IBU at second derivative different concentration can be seen Figure 3a and Figure 3b respectively.

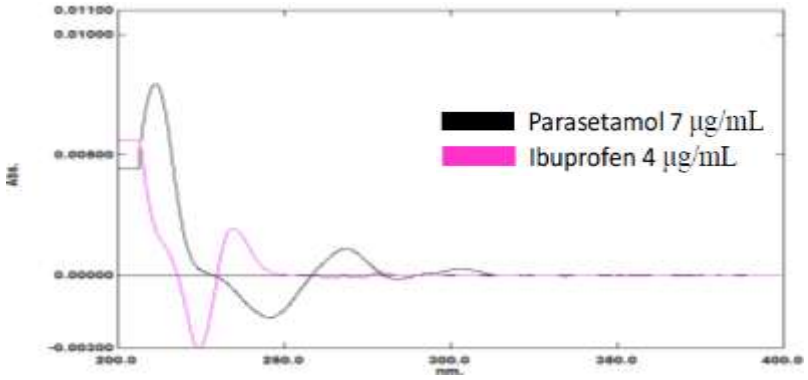



**Figure2. The overlapping absorption spectrum of PAR and IBU at second derivative**

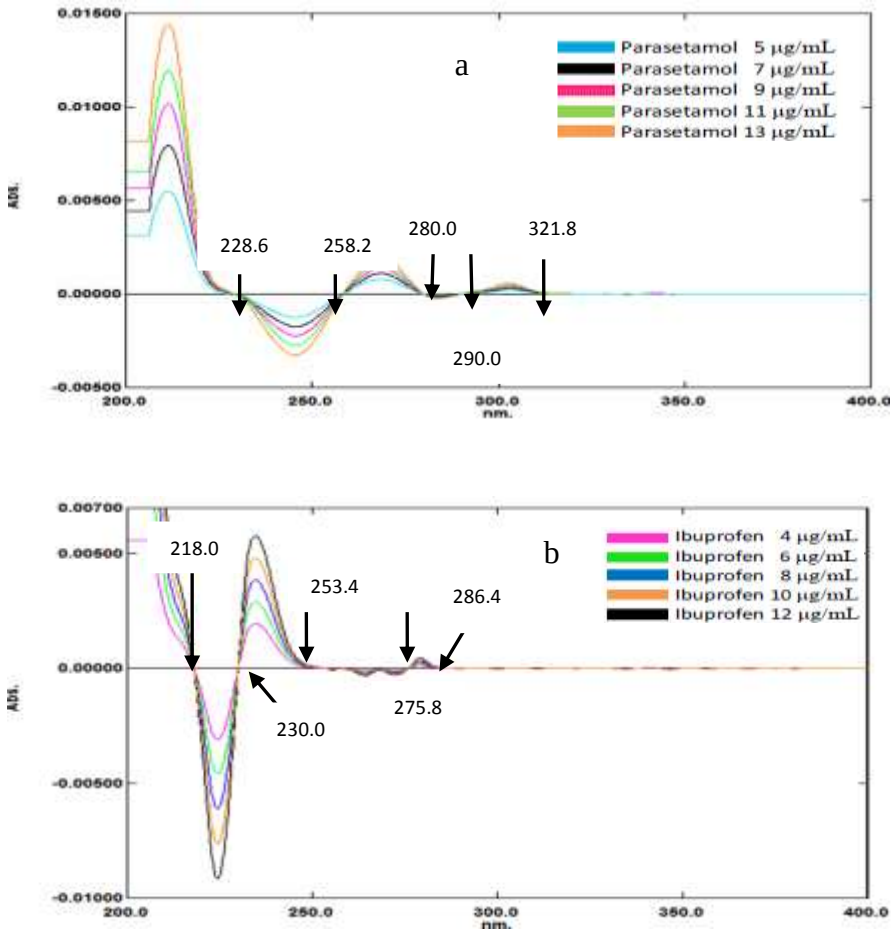



**Figure 3. Absortion spectrum of (a) PAR and (b) IBU at second derivative different concentration**

### 3.3 Result Determination of Wavelength Analysis

Determination of the wavelength of the analysis done by making a solution of PAR (7 µg/mL), IBU (7 µg/mL), and mixture of PAR and IBU(4 µg/mL), then made the first derivative of the absortion spectrum of each solution of PAR and IBU. Further superimposed, the same was done for the second derivative absorption spectrum. To determine the wavelength of the analysis carried out by observing wavelengths showed absoprtion zero partner compounds uptake and absorption there of has a value equal or nearly equal. The wavelength analysis of PAR and IBU can be seen Figure 4.

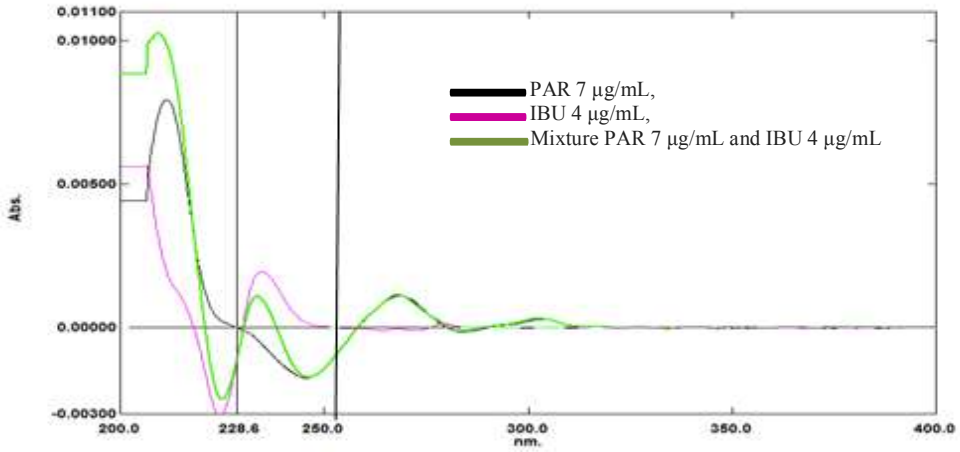



**Figure 4. The wavelength analysis spectrum for PAR( at λ 253.4 nm) and IBU (at λ 228.6 nm)**

**Figure 4. Zero Crossing Second Derivatives of Ibuprofen**

In the Figure 4, it can be seen that the wavelength analysis of PAR and IBU that can be used is the second derivative absorption. It is known by wavelength selection for each derivative analysis. The wavelength is obtained by determining the zero crossing for PAR and IBU.

Determination of the wavelength of the analysis can be by riding overlaid absorption spectrum of each derivative PAR, IBU and a mixture of PAR and IBU further observation wavelength showed absorption compound partner zero and uptake of compounds another and mixtures there of having absorption value equal oe nearly equal. At first derivative absorption, the wavelength analysis of IBU was not found, so the assay of IBU can not be done on the first derivative absorption spectrum. Thus proceed to the second derivative absorption spectrum.

At the second derivative absorption spectrum, it is known that PAR and IBU has a wavelengthmore than one. Ride overlaid with second derivative absorption spectrum of PAR, IBU and a mixture of PAR and IBU, so it can be seen that at a wavelength of 253.4 nmand 228.6 nm has an absorption zero where as PAR and IBU mixture of PAR and IBU have almost the same absorption.

**Table 1. Wavelength analysis and absorbance of Paracetamol and Ibuprofen at second derivative**

| Wavelength (nm) | Absorbance | | |
|---|---|---|---|
| | **Paracetamol (7 µg/mL)** | **Ibuprofen (4 µg/mL)** | **Mixture PARand IBU** |
| 218.0 | 0.00324 | 0.00001 | 0.00342 |
| **228.6** | **0.00000** | **-0.00112** | **-0.00115** |
| 230.0 | -0.00007 | 0.00002 | -0.00024 |

| **253.4** | **-0.00086** | **0.00000** | **-0.00086** |
|---|---|---|---|
| 258.2 | -0.00001 | 0.00000 | 0.00001 |
| 275.8 | 0.00045 | 0.00000 | 0.00045 |
| 280.0 | 0.00000 | 0.00014 | 0.00008 |
| 286.4 | -0.00011 | 0.00000 | -0.00007 |
| 290.0 | 0.00001 | -0.00000 | 0.00002 |
| 321.8 | 0.00000 | -0.00000 | -0.00002 |

Based on the Table1. was obtained wavelength analysis of PAR and IBU were use is 253.4 nm and 228.6 nm respectively. At a wavelength of 253.4 nm, IBU absorption value is zero, while the value absorption of PAR and a mixture of PAR and IBU have absorption value equal oe nearly equal in succession namely -0.00086.At wavelength 228.6 nm, PAR absorption value is zero, while the value of absortion of IBU and a mixture of PAR and IBU have absortion value equal or nearly equal in succession namely -0.00112 and -0.00115.

### 3.4Determination Results Linearity Calibration Curves

The linearity of the calibration curve showed a linear relationship between the absorbance with concentration. PAR regression equation is $Y = (-12.4X + 1).10^{-5}$ with a correlation coefficient, r = 0.99990 andIBU, $Y = (-27.7X + 0.3).10^{-5}$ with a correlation coefficient, r = 0.99999. R values > 0.995showed a linear correlation relationship between X and Y value.

### 3.5Application of the Method in Commercial Tablet

Assay of PAR and IBU done using NR® tablet and OS®tablet. Created test solution so that where there is a concentration of PAR and IBU7 µg/mL and 4 µg/mL respectively.Furthermore, the absorption spectrum is transformed into a second derivative absorption spectrum with$\Delta\lambda$ = 8 nm a wavelength 253.4 nm and 228.6 nm for PAR and IBU respectively.

**Table 2. Content of Paracetamol and Ibuprofen in Tablets**

| **Name** | **NR® Tablet** | **OS® Tablet** | **Label claim (mg)** | **Requirements (%)** |
|---|---|---|---|---|
| PAR | (100.03 ± 1.28) % | (100.11 ± 1.55) % | 350 | 90-110 |
| | (345.62 – 354.58) mg | (344.96 – 355.81) mg | | |
| IBU | (101. 15 ± 1.00) % | (100.89 ± 0.57) % | 200 | 90-110 |
| | (200.30 – 204.30) mg | (200.64 ± 202.92 ) mg | | |

From Table 2. can be seen content of PAR and IBU in NR® Tablet and OS® Tablet meet the requirements which containts is not less than 90.0% and not more than 110.0% of the amount listed on the label[3].

**Table 3. Result Recovery of Paracetamol and Ibuprofen**

| **Specific Ranges (%)** | **% Recovery of** | |
|---|---|---|
| | **Paracetamol** | **Ibuprofen** |
| 80 | 102.69 | 101.61 |
| | 10269 | 102.00 |
| | 97.90 | 97.45 |
| 100 | 99.46 | 99.15 |
| | 99.46 | 100.09 |
| | 103.29 | 102.47 |
| 120 | 102.56 | 99.61 |
| | 99.37 | 99.34 |
| | 102.56 | 101.85 |

| | | |
|---|---|---|
| % Recovery | 101.11 | 100.40 |
| StandardDeviation (SD) | 2.02 | 1.68 |
| Relative Standart Deviation | 2.00 | 1.67 |

Based on Table 3 above shows that the average % recovery for PAR and IBU is 101.11% and 100.40% respectively, has been qualified to validate the accuracy of analytical procedures because the average is between the range of 98%-102%[21].

Test accuracy with parameter percent recovery is done by using standart solutionNR® Tablet. Standart addition method by adding a certain amount standard to the sample which has addition to make three samples with the analyte concentration of a specific range of 80%,100% and 120%. Then the solution is measured absorbance wavelength coresponding analysis used.

Based on calculation of data, precision (%RSD) obtained for PAR and IBU is 2.00% and 1.67% respectively. The RSD for of the two substances which meet the requairement of ≤ 2%[21].

**Table 4. Validation Parameters for Derivative Spectrophotometric**

| Parameters | Paracetamol | Ibuprofen |
|---|---|---|
| Corr. Coef. (r) | 0.99990 | 0.99999 |
| Accuration (%) | 101.11 | 100.40 |
| LOD (µg/mL) | 0.242 | 0.111 |
| LOQ (µg/mL) | 0.806 | 0.369 |

In Table 4 above shows that PAR and IBU can be detected and quantited using derivative spectrophotometric with zero crossing method. It can be concluded that determination of PAR and IBU in tablet has been done to meet the requirements validation test with good accuracy and precision.

**Table 5 . Several Studies on the Assay of Paracetamol and Ibuprofen**

| Method | Solvent | References |
|---|---|---|
| UV Spectrophotometry,PAR at 248 nm and IBU at 220 nm | Ethanol 99,9% | Reference[16] |
| UV Spectrophotometry with zero crossing, PAR at 271.2 nm, IBU at 242.4 nm and caffeine at 302.4 nm | Phosphat buffer pH 7.2 | Reference[17] |
| UV Spectrophotometry with ratio spectra | Methanol | Reference[18] |
| UV Spectrophotometry with zero crossing, PAR at 253.4 nm and IBU at 228.6 nm | Methanol and Distilled water | This Work |

## 4. Conclusion

Based on the research conducted, it can be concluded assay of PAR and IBU in tablet using methanol and distilled water can be simultaneous analysis by derivative spectrophotometric with zero crossing method. The proposed method is simple as there is no need for solvent extraction, rapid, low cost and could be opplied in quality control laboratories.

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