DETERMINATION OF PARACETAMOL LEVELS IN TABLETS AND ORAL SOLUTIONS BY HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

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ABSTRACT
According to RI Law no. 36 of 2009, determining the level of efficacious substances from a drug preparation is one of the requirements that must be carried out to ensure the quality of the drug preparation. Drug preparations of good quality will provide the expected effect and one of the parameters is the level of the active substance of the drug must meet the level requirements listed in the Indonesian Pharmacopeia or other standard books. The purpose of this study was to determine the levels of Paracetamol in tablet preparations and oral solution by high-performance liquid chromatography. The determination of the concentration was carried out by the HPLC method using a 2.5 mm x 25 cm VP-ODS shim pack column with water-methanol as a mobile phase (3:1), a flow rate of approximately 1.5 ml/minute, and the detection was carried out at a wavelength of 243 nm. The advantage of the HPLC method is the separation system with high speed and efficiency because it is supported by advances in column technology, high-pressure pump systems, and highly sensitive and diverse detectors so that they are able to analyze various samples qualitatively and quantitatively, back in single or mixed components. The results showed that all the specified samples met the content requirements according to the Indonesian Pharmacopeia IV edition 1995, namely not less than 90.0% and not more than 110.0% of the amount stated on the label. The results of the Validation test method carried out obtained a recovery percent of 99.96% with an RSD (Relative Standard Deviation) of 1.81% so that it can be concluded that this method has good sensitivity and accuracy, with a LOD (limit of detection) 0.76 g/ml and LOQ (limit of quantitation) 2.56 g/ml.

Keywords : Paracetamol, tablets, oral solution, High-Performance Liquid Chromatography, and validation

INTRODUCTION
Paracetamol is a metabolite of phenacetin with the antipyretic effect that has been used since 1893. The aminobenzene group causes the antipyretic effect. Paracetamol in Indonesia is known as an antipyretic and is available as an over-the-counter drug in tablet preparations and oral solutions (Wilmana, 2007). According to RI Law no. 36 of 2009, determining the level of efficacious substances from a drug preparation is one of the requirements that must be carried out to ensure the quality of the drug preparation. Drug preparations of good quality will provide the expected effect, and one of the diameters is the level of the drug's active substance must meet the level requirements listed in the Indonesian Pharmacopeia or other standard books (Depkes RI, 2009). According to the Indonesian Pharmacopoeia IV edition 1995, Paracetamol tablets and oral codam solution were determined by High-Performance Liquid Chromatography using an L1 column (3.9 mm x 30 cm) with a motion of a water-methanol mixture P (3:1), a flow rate of approximately 1.5 ml/min, and the detection was carried out at a wavelength of 243 nm. Judging from the structure of Paracetamol, which has chromophore and autochrome groups, it is possible to determine the levels by UV spectrophotometry. According to Moffat (2004), Paracetamol can provide a spectrum at a wavelength of 245 nm with Ai 1 668a in 0.1 N HCL solvent and at 257 nm with Ai 715a in 0.1 N NaOH.
solvent. This group can be hydrolyzed into primary amines to determine their levels by titrimetry.

The requirements for Paracetamol levels in tablet preparations and oral solutions according to the Indonesian Pharmacopeia IV edition of 1995, namely containing Paracetamol, C8H9NO2, are not less than 90.0% and not more than 110.0% of the amount stated on the label. Based on the above, the researchers tried to determine the levels of Paracetamol in tablet preparations and oral solutions produced by several Pharmaceutical Industries in Medan City by HPLC using a VP-ODS shim pack column (2.5 mm x 25 cm) using the water-methanol mobile phase. (3:1) and determine the suitability of the obtained levels with the requirements of the levels set by the Indonesian Pharmacopeia IV edition of 1995.

MATERIALS AND METHODS

The equipment used in this research is an HPLC unit (Shimadzu) which consists of a vacuum degasser, pump, integrator, Shim Pack VP-ODS column (2.5 mm x 25 cm), microliter injector (100 NI), Bransonic, electric balance, and glassware. The ingredients used are Aqua Bidestilata (PT. Ikapharmindo Putramas), Methanol gradient grade for liquid chromatography (E. Merck), Paracetamol (BPFI), Paracetamol tablets and generic oral solution (PT. Varse, PT. Universal), and tablets with the name trade (PT. Mutifa). The samples used were two generic Paracetamol tablets, one trade name produced by several Pharmaceutical Industries in Medan City, and two generic Paracetamol oral solution preparations, each produced by Pharmaceutical Industries in Medan City.

**Determination of the concentration of Paracetamol tablets**

Weigh and powdered not less than 20 tablets, then carefully weighed the amount of powder equivalent to approximately 25 mg of Paracetamol, and put into a 50 ml volumetric flask with added solvent, shaken (C = 500 g/ml). Then filtered, in a pipette, 5 ml of the filtrate was put into a 50 ml volumetric flask, supplemented with solvent to the marked line (C = 50 g/ml). This solution was pipette 2 ml, put into a 10 ml volumetric flask, filled with solvent to the marked line, filtered with 0.2 m cellulose membrane, and injected into the HPLC system (C = 10 g/ml).

**Determination of Paracetamol syrup concentration**

Pipette 1 ml of Paracetamol oral solution (each 5 ml contains 120 mg of Paracetamol) is put into a 100 ml volumetric flask, and then the solvent is added to the marked line. Furthermore, 1 ml of the solution was pipetted, put into a 25 ml volumetric flask diluted with water-methanol (3:1) solvent to the marked line, filtered with 0.2 m cellulose membrane, and injected into the HPLC system.

**Method Validation Test Method**

A validation test was carried out on samples of Paracetamol tablets from PT. Mutifa with trade name Omegrip in specific ranges of 80%, 100%, and 120%.

1. **Specific range 80%**

**Working procedure before adding standard comparison**

Weighed Paracetamol powder equivalent to 0.2800 g Paracetamol with a weight of 0.3381 g paracetamol, put into a 50 ml volumetric flask, added solvent, and shaken (C = 5600 g/ml), then filtered. A 4.5 ml pipette is put into a 50 ml volumetric flask, filled with solvent up to the marked line (C = 504 g/ml), then 5 ml is pipetted into a 50 ml volumetric flask, made up to the marked line (C = 50, 4 g/ml), and a 2 ml pipette was put into a 10 ml volumetric flask, then filtered with 0.2 m cellulose membrane, then injected into the HPLC system (C = 10.08 g/ml). This procedure was carried out three times.

**The working procedure of adding a standard comparison was**

Weighed Paracetamol powder equivalent to 0.2800 g of Paracetamol with a weight of 0.3381 g. Paracetamol added 0.1200 g of comparison standard (BPFI), put into a 50 ml volumetric flask, then added solvent and shaken (C = 8000 g/ml), filtered. A 2 ml pipette was put into a 10 ml volumetric flask, filtered with 0.2 m cellulose membrane, then injected into the HPLC system (C = 10.08 g/ml). This procedure was carried out three times.
2. Specific range 100 %
Working procedure before standard adder comparison
Weighed Paracetamol powder equivalent to 0.3500 g Paracetamol with a weight of 0.4226 g paracetamol, put into a 50 ml volumetric flask, added solvent, and then shaken (C = 7000 g/ml), filtered, then 4.5 ml pipette was added. Into a 50 ml volumetric flask, filled with solvent to the marked line (C = 630 g/ml), then 5 ml was pipetted into a 60 ml volumetric flask, made up to the marked line (C=63 g/ml), and pipette 2 ml was put into a measuring flask of 10 ml filled to the marked line and filtered with 0.2 m cellulose membrane. The HPLC system (C = 12.6 g/ml), all this procedure was carried out three times.

The working procedure of adding a reference standard
Weighed Paracetamol powder equivalent to 0.3500 g Paracetamol with a weight of 0.4226 g paracetamol then added a standard 0.1500 g put into a 50 ml volumetric flask Add solvent and shake (C = 10000 g/ml), then filtered and pipetted 3 ml was put into a 50 ml measuring flask, filled with solvent up to the marked line (C = 900 g/ml), then 5 ml pipette was put into a 50 ml volumetric flask, then filtered with 0.2 m cellulose membrane, then injected into the HPLC system (C = 18 g/ml). This procedure was carried out three times.

3. Specific Range 120% 
Fun procedure before adding the reference standard
Weighed the powder equivalent to 0.4200 g Paracetamol with a weight of 0.5071 g Paracetamol, put into a 50 ml volumetric flask, added solvent, and shaken (C = 8400 g/ml), then filtered. In a pipette, 3 ml was put into a 50 ml volumetric flask, filled with solvent up to the marked line (C = 756 g/ml), then 5 ml was pipetted into a 50 ml volumetric flask, made up to the marked line (C = 75.6 g/ml), and a 2 ml pipette, put into a 10 ml volumetric flask, then filtered with 0.2 m cellulose membrane, then injected into the HPLC system (C = 18 g/ml). This procedure was carried out three times.
The procedure for adding a comparison standard
Weighed the powder equivalent to 0.4200 g Paracetamol with a weight of 0.3381 g Paracetamol was added as a comparison standard 0.1800 g was put into a 50 ml volumetric flask then added the solvent and was shaken (C = 12000 g/ml), then filtered and pipetted 3 ml was put into a 50 ml volumetric flask, filled with solvent up to the marked line (C = 1080 g/ml), then 5 ml pipette was put into a 50 ml volumetric flask, made up to the marked line (C = 108 g/ml), and a 2 ml pipette, put into a 10 ml volumetric flask, then filtered with 0.2 pm cellulose membrane, then injected into the HPLC system (C = 21.6 g/ml). This procedure was carried out three times.

Percent recovery can be calculated by the formula:
\[ \frac{AB}{C} \times 100\% \]
Where
A = Concentration obtained after adding raw materials
B = Concentration before adding raw materials
C = concentration of added raw materials

4. The precision
The test is determined by the RSD parameter (Relative Standard Deviation) with formula:
\[ \text{RSD} = \frac{SD}{X} \times 100\% \]
Where: RSD = Relative Standard Deviation
SD = Standard Deviation
X = Average level in the sample

5. Determination Limit Detection (LOD) and Limit Quantity (LOQ)
To determine the limit of detection (LOD) and limit of quantitation (LOQ) formula can be used
\[ \text{LOD} = \frac{3 \times \text{Sy} \times X}{\text{Slope}} \]
\[ \text{LOQ} = \frac{10 \times \text{Sy} \times X}{\text{Slope}} \]
Information:
\[ \frac{\text{Sy}}{X} = \text{Standard deviation of residual} \]
LOD = Limit of Detection
LOQ = Limit of Quantity

RESULTS AND DISCUSSION
According to the Indonesian
Pharmacopeia IV edition 1995, Paracetamol was determined by High Performance Liquid Chromatography using shim pack column L1 (3, 9 mm x 30 cm) with a water-methanol mixture of P (3:1), a flow rate of approximately 1.5 ml/min, and the detection was carried out at a wavelength of 243 nm. In this study, the procedure used is different from the procedure contained in the Indonesian Pharmacopeia IV edition 1995, in terms of column size, which is the VP-ODS shim pack column (2.5 mm x 25 cm).

To test the validity of this method, a validation test was carried out with validation test parameters carried out, namely accuracy test, precision test, detection limit (LOD) and quantitation limit (LOQ). The results of the BPI Paracetamol Identification Test with the retention time parameter were obtained at 3.8 minutes. The retention time of this comparison standard is almost the same as the retention time of all the specified samples, this means that all samples contain Paracetamol.

Table 1. Data retention time of Paracetamol BPFI and Paracetamol in tablet and syrup preparations produced by several pharmaceutical industries in Medan City.

| Preparation          | Treatment | Retention Time |
|----------------------|-----------|----------------|
| Paracetamol          | 1         | 3.878          |
|                      | 2         | 3.862          |
|                      | 3         | 3.852          |
|                      | 4         | 3.868          |
|                      | 5         | 3.847          |
| Paracetamol Tablet   | 1         | 3.823          |
| PT. Mutifa (Omegrip) | 2         | 3.827          |
|                      | 3         | 3.832          |
|                      | 4         | 3.830          |
|                      | 5         | 3.831          |
|                      | 6         | 3.836          |
| Paracetamol Tablet   | 1         | 3.866          |
| PT. Varse (generic)  | 2         | 3.865          |
|                      | 3         | 3.861          |
|                      | 4         | 3.862          |
|                      | 5         | 3.852          |
|                      | 6         | 3.847          |
| Paracetamol Tablet   | 1         | 3.902          |
| PT. Universal (generic) | 2     | 3.904          |
|                      | 3         | 3.889          |
|                      | 4         | 3.889          |
|                      | 5         | 3.876          |
|                      | 6         | 3.876          |
| Paracetamol Syrup    | 1         | 3.834          |
| PT. Universal (generic) | 2    | 3.846          |
|                      | 3         | 3.838          |
|                      | 4         | 3.833          |
|                      | 5         | 3.815          |
|                      | 6         | 3.818          |
| Paracetamol Syrup PT.| 1         | 3.811          |
| Varse (generic)      | 2         | 3.815          |
|                      | 3         | 3.820          |
|                      | 4         | 3.811          |
|                      | 5         | 3.816          |
|                      | 6         | 3.809          |
From the identification results, the chromatogram is not symmetrical but still within acceptable limits because the tailings factor parameter is 2; the tailings factor data can be seen in Table 2 below this.

Table 2. Data for tailings factor Paracetamol BPFI and Paracetamol in tablet and syrup preparations produced by several pharmaceutical industries in Medan City

| Preparation                  | Treatment         | Factor Tailings |
|------------------------------|-------------------|-----------------|
| Paracetamol                  | 1                 | 1,467           |
|                              | 2                 | 1,492           |
|                              | 3                 | 1,535           |
|                              | 4                 | 1,550           |
|                              | 5                 | 1,572           |
|                              | 6                 | 1,587           |
| Paracetamol Tablet           | PT. Mutifa (Omegrip) |                 |
|                              | 1                 | 1,617           |
|                              | 2                 | 1,546           |
|                              | 3                 | 1,584           |
|                              | 4                 | 1,591           |
|                              | 5                 | 1,587           |
|                              | 6                 | 1,584           |
| Paracetamol Tablet           | PT. Varse (generic) |                 |
|                              | 1                 | 1,503           |
|                              | 2                 | 1,520           |
|                              | 3                 | 1,527           |
|                              | 4                 | 1,532           |
|                              | 5                 | 1,509           |
|                              | 6                 | 1,590           |
| Paracetamol Tablet           | PT. Universal (generic) |            |
|                              | 1                 | 1,463           |
|                              | 2                 | 1,459           |
|                              | 3                 | 1,468           |
|                              | 4                 | 1,472           |
|                              | 5                 | 1,479           |
|                              | 6                 | 1,489           |
| Paracetamol Syrup            | PT. Universal (generic) |         |
|                              | 1                 | 1,587           |
|                              | 2                 | 1,573           |
|                              | 3                 | 1,569           |
|                              | 4                 | 1,571           |
|                              | 5                 | 1,588           |
|                              | 6                 | 1,580           |
| Paracetamol Syrup            | PT. Varse (generic) |               |
|                              | 1                 | 1,594           |
|                              | 2                 | 1,601           |
|                              | 3                 | 1,600           |
|                              | 4                 | 1,590           |
|                              | 5                 | 1,571           |
|                              | 6                 | 1,575           |

The results of determining the linearity of the BPFI Paracetamol calibration curve in the concentration range of 5 to 25 G/ml, obtained a linear relationship between area and concentration, correlation coefficient $r = 0.9998$.

Table 3. Data on the area of paracetamol calibration BPFI

| No | Concentration (µg/ml) | Area    |
|----|-----------------------|---------|
| 1  | 5,000                 | 381488  |
| 2  | 10,000                | 706766  |
| 3  | 15,000                | 1097102 |
| 4  | 20,000                | 1450600 |
The correlation coefficient obtained is acceptable because it meets the specified requirements $r = 0.995$ (Moffat, 2004). From the calculation results, the regression line equation $Y = 72049.8626X + 5071.2142$.

For tablet preparations and oral solutions with trade names and generic names, the results of data processing and the results of determining the average levels of Paracetamol in tablets and oral solutions can be seen in the table below:

**Table 4. Results of data processing from tablets and oral solution Paracetamol**

| Name dosage                        | Area (mm$^2$) | Contents (%) | content (%) | Range of concentrations (%) |
|------------------------------------|---------------|--------------|-------------|-----------------------------|
| **Paracetamol tablets PT. Mutifa (Omegrip)** | 786047        | 108.13       | 107.36      | 107.36 ± 1.40               |
|                                    | 786783        | 108.23       |             |                             |
|                                    | 779367        | 107.20       |             |                             |
|                                    | 784070        | 107.86       |             |                             |
|                                    | 772465        | 106.25       |             |                             |
|                                    | 774107        | 106.48       |             |                             |
| **Paracetamol Tablets PT. Universal (generic)** | 669085        | 91.93        | 91.77       | 91.77 ± 1.05                |
|                                    | 668605        | 91.87        |             |                             |
|                                    | 667560        | 91.72        |             |                             |
|                                    | 668080        | 91.80        |             |                             |
|                                    | 668678        | 91.28        |             |                             |
| **Tablets PT.Varse (Generic)**     | 669696        | 92.02        | 94.64       | 94.64 ± 2.64                |
|                                    | 713066        | 98.02        |             |                             |
|                                    | 684519        | 94.07        | Paracetamo   |                             |
|                                    | 692215        | 95.14        | 94.64       |                             |
|                                    | 682278        | 93.76        |             |                             |
|                                    | 701228        | 96.39        |             |                             |
|                                    | 682931        | 93.85        |             |                             |
| **Paracetamol oral solution PT.Varse (Generic)** | 685572        | 98.14        | 97.98       | 97.98 ± 0.30                |
|                                    | 685059        | 98.07        |             |                             |
|                                    | 687302        | 98.39        |             |                             |
|                                    | 684397        | 97.97        |             |                             |
|                                    | 683354        | 97.82        |             |                             |
|                                    | 683886        | 97.90        |             |                             |
| **Paracetamol oral solution PT. Universal (Generic)** | 667621        | 95.55        | 96.07       | 96.07 ± 0.82                |
|                                    | 668342        | 95.66        |             |                             |
|                                    | 674865        | 96.60        |             |                             |
|                                    | 668309        | 95.65        |             |                             |
|                                    | 674783        | 96.59        |             |                             |
|                                    | 673211        | 96.36        |             |                             |

The Pharmaceutical Industry in Medan City complies with the level requirements contained in the Indonesian Pharmacopeia Edition IV 1995, which is not less than 90.0% and not more than 110.0% of the amount stated on the label. Examples of calculations can be seen in Appendix 9, page 63.

The results of the method validation tests carried out on samples of Paracetamol tablets (PT. Mutifa) include accuracy tests with the addition of raw materials, precision tests with RSD (Relative Standard Deviation) parameters, detection limits...
Data validation results can be seen in Table 5 below.

**Table 5. Data on validation test results of High-Performance Liquid Chromatography method on the assay of Paracetamol tablets**

| NO | Specific Range | Area of Concentration (µg/ml) | Standard added (µg/ml) | Obtained Level (%) |
|----|----------------|-------------------------------|-----------------------|-------------------|
|    |                | Before + standard After + standard Without standard + standard (C) |                      |                   |
| 1  | 80%           | 624827 101.42 | 8.58 12.97 | 4.32 | 625037 |
| 2  |               | 940771  624827 | 8.59 12.96 | 4.32 | 625037 |
| 3  |               | 625941  940933 | 8.6052 12.97 | 4.32 | 101.06 |
| 4  | 100%          | 734220  1119800 | 10.10 15.45 | 5.4 | 98.96 |
| 5  |               | 731420  1115934 | 10.06 15.39 | 5.4 | 98.69 |
| 6  |               | 732232  1117639 | 10.07 15.42 | 5.4 | 98.92 |
| 7  | 120%          | 890746  1365218 | 12.27 18.85 | 6.48 | 101.48 |
| 8  |               | 889545  1354237 | 12.25 18.69 | 6.48 | 99.39 |
| 9  |               | 885309  1345704 | 12.20 18.58 | 6.48 | 98.47 |

Mean (%Recovery) 99.96
Standard deviation 1.81
Relative Standard Deviation (%) 1.81
LOD (µg/ml) 0.76
LOQ (µg/ml) 2.56

From the method validation test data, the percent recovery Paracetamol was 99.96% with a standard deviation (SD) of 1.8109, while the precision test with a relative standard deviation of (RSD) was 1.81%. Percent recovery obtained is acceptable because it meets the accuracy-test requirements, wherein the literature, the accuracy-test requirements are (98.0% - 102%), and the allowable RSD value is 2% (Harmita; 2004, Rohman, 2009). Thus it can be concluded that the method validation test for Paracetamol tablets uses the HPLC method; this method provides a good test of accuracy and accuracy, with a detection limit (LOD) of 0.76 g/ml and a quantitation limit (LOQ) of 2.56 g/ml.

**CONCLUSION**

From the results of the study, it can be concluded that all Paracetamol tablets and oral solution, both generic and trade names, were determined by HPLC using a VP-ODS shim pack column (2.5 mm x 25 cm) with water-methanol solvent (3:1) at a rate of flow of approximately 1.5 ml/minute, meeting the levels according to the Indonesian Pharmacopeia Edition IV 1995, which is not less than 90.0% and not more than 110.0% of the amount stated on the label. The results of the method validation test carried out obtained recovery percent with RSD (Relative Standard Deviation) 1.81% or in other words, this method provides determination and accuracy that meets the requirements and from the calculation results obtained LOD (Limit of detection) 0.76 g/ml and LOQ (limit of quantitation) 2.56 g/ml.

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