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DEVELOPMENT AND VALIDATION OF KETOROLAC TROMETHAMINE ANALYSIS METHODS USING HPLC AND TEST ITS STABILITY

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ABSTRACT

Determination of ketorolac tromethamine levels based on United States Pharmacopeia (USP) using L7 column 4.6 mm x 25 cm; 5 µm with mobile phase tetrahydrofuran and buffer (30:70). Tetrahydrofuran has oxidative properties and has a high UV limit and the presence of peroxide impurities in it can affect the stability of the analyte so that the use of tetrahydrofuran is often avoided. Therefore, a method for analyzing ketorolac tromethamine was developed by applying of High Performance Liquid Chromatography (HPLC) using C18 column with acetate buffer pH 4.2 and methanol (20:80) as mobile phase, flow rate 1.0 mL/minute, wavelength 318 nm, and 10 µL injection volume. The validation results obtained a linearity value (r) 0.9982, value of LOD is 9.61 µg/mL and LOQ is 29.11 µg/mL. The results of precision test obtained %RSD equal to 0.776% and the accuracy test of the sample concentrations 80%, 100% and 120% show the %recovery are 94,79%, 99,42% and 92,83%, respectively. New degradants were formed with acid exposure of 80.66%, base exposure of 59.30%, temperature exposure (70-90°C for 3 hours) are 1.28%, 15.06%, and 18.40 %, respectively. Oxidation exposure (H_2O_2 1%, 3% and 5%) are 11.36%, 13.98% and 14.79%, respectively. All the research results can be concluded that the method development and validation results can be used for the analysis of ketorolac tromethamine and testing its stability.

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INTRODUCTION

Ketorolac tromethamine has the molecular formula $C_{15}H_{13}NO_3.C_4H_{11}NO_3$ with the chemical compound name (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizin-1-carboxylic acid, mixed with 2-amino-2-(hydroxymethyl)-1,3-propandiol with a molecular weight of 376.40 which is used as a pain reliever due to its strong analgesic influence (Depkes RI, 2020). Ketorolac tromethamine is a member of the heterocyclic acetic acid derivative family used as an analgesic with capabilities close to the opioid class and has strong antipyretic and anti-inflammatory effects, mainly used for short-term treatment of postoperative pain because it is highly selective for cyclooxygenase (COX-1) enzymes. Ketorolac tromethamine works by inhibiting the cyclooxygenase enzyme (COX-1) which is involved in prostaglandin biosynthesis pathways. Prostaglandins are compounds that play a role in responding to inflammation, pain and fever. Prostaglandins also play a role in increasing sensitivity to pain by reducing peripheral pain. The use of ketorolac tromethamine is generally used only in short-term treatment i.e. used no more than 5 days (Octasari & Inawati, 2021).

Ketorolac tromethamine has been reported to be significantly degraded and unstable under oxidation conditions followed by acidic condition (Uzzaman & Uddin, 2019)). This oxidation reaction can have an impact on drug stability because it has the potential to break down drug compound molecules. Instability of drug products can cause a decrease in effectiveness, loss of efficacy to cause drugs to turn toxic so that they can cause adverse effects (Oktami et al., 2021). Determination of levels is important to determine the consequences of the influence of instability of medicinal products. Method of determining ketorolac tromethamine levels based on United States Pharmacopeia (USP) using HPLC method with tetrahydrofuran mobile phase and buffer (30:70) using 313 nm UV detector, L7 column 4.6 mm x 25 cm, flow rate 1.5 mL/minute. Tetrahydrofuran is a chemical compound that has oxidative properties so that it can damage the column and the use of tetrahydrofuran in routine analysis may decrease column performance (Kurnia et al., 2019). Tetrahydrofuran has a high UV limit and the presence of peroxide impurities in tetrahydrofuran can affect the stability of analytes so the use of tetrahydrofuran is often avoided.

HPLC works by separating molecules in solids according to their affinity, with solids acting as stationary or stationary phases while liquids separated are liquid phases (Willian & Pardi, 2022). HPLC is used for ketorolac tromethamine analysis because it has the advantages of being able to separate molecules in a mixture, has a high analysis speed, high sensitivity, is able to prevent decomposition or ruffling of the analyzed material, provides good resolution, can integrate with various types of detectors and reusable columns (Hujjatusnaini et al., 2021). Research on the stability of ketorolac tromethamine has been conducted using HPLC with a C18 neosphere column measuring 4.6 mm x 250 mm and a particle size of 5 μm with a mobile phase of water: methanol: acetonitrile (53:23:24) with 0.5% formic acid. The stability test was performed using (2 N HCl) (2 N NaOH), water and 3% H_2O_2.

Stability test results showed ketorolac tromethamine was found to transform into many degradation products under oxidation conditions (Uzzaman & Uddin, 2019). There has not been much research on the development of methods for determining the levels and stability of ketorolac tromethamine. Methods are often developed to be able to adapt the conditions to the equipment available in the testing laboratory. The development carried out must also be

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validated to ensure the implementation of tests carried out according to the established analysis methods. In this study, a method will be developed to determine ketorolac tromethamine levels and test its stability by developing columns, mobile phases, flow rates, and stability testing with exposure to acids, bases, oxidation, and temperature.

METHODS

Tools and Materials

Tools

HPLC (Shimadzu LC 2030) with UV detector and C18 Coloumn (YMC-Triart HPLC Coloumn), sonicator (Vevor Brand), 0.45µm PTFE membrane filter, analytical balance (Shimadzu Corporation ATX224), beaker glass (Pyrex), volumetric flask (Pyrex), micropipette (Dragon Lab), measuring cup (Pyrex), hot plate (Shimadzu), thermometer, weighing bottle and stopwatch.

Materials

Standard ketorolac tromethamine BPFI (BPOM), methanol HPLC grade (Merck), acetate buffer pH 4.2 HPLC grade, NaOH 1 N, HCl 1 N, aqua pro injection, H2O2 1%, 3% and 5%.

Preparation of standars stock solution

Standard stock solution of ketorolac tromethamine was prepared with a concentration of 412 µg/mL in the mobile phase. A total of 10.3 mg of ketorolac tromethamine was weighed and transferred into a 25 mL measuring flask. Add 15 mL of mobile phase methanol, sonicated for 5 min, then added solvent to mark and filtered with 0.45 µm membrane filter and put back into measuring flask.

Determination of Maximum Wavelength

Standard solutions of ketorolac tromethamine in methanol solvents concentrations of 5 µg/mL, 7.5 µg/mL and 10 µg/mL were then observed for absorption by UV spectrophotometry in the wavelength range of 200 to 400 nm with methanol used as blanks.

Mobile Phase Optimization

A standard solution of ketorolac tromethamine was injected as much as 10 µL with the mobile phase composition of acetate buffer: methanol at a ratio of (80:20); (50:50); (20:80) with flow speeds of 0.50 mL/min, 0.75 mL/min and 1.0 mL/min. The parameters of determining the optimum conditions of HPLC are the fastest retention time, tailings factor ≤ 2.0 and theoretical plot number ≥ 2000 (Priya & Vaishali, 2022).

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Validation Methods

1. Linearity and range
   Linearity tests were carried out by diluting the parent solution of ketorolac tromethamine into several concentration variations, namely 20.6 µg/mL, 41.2 µg/mL, 61.8 µg/mL, 82.4 µg/mL, 103 µg/mL, 123.6 µg/mL, and 144.2 µg/mL. Each concentration is carried out 3 times replication and the peak area results are made a curve against the concentration of the working raw solution. Linearity is determined through statistical analysis of linear regression ($y = bx + a$).

2. Limit of Detection (LoD) and Limit of Quantification (LoQ)
   This test is carried out by measuring the lowest standard concentration that can be detected in area.
   LoD can be calculated by the formula:
   $$LoD = 3.3 \times SD$$
   LoQ can be calculated by the formula:
   $$LoQ = 10 \times SD$$
3. Accuracy
   Accuracy testing is carried out by simulation methods (Spiked placebo recovery) by adding standard ketorolac tromethamine standards of 80%, 100% and 120% of the concentrations used in injection samples placebo. The method can be considered accurate if the presentation of analyte recovery is close to the correct value. The validation method qualifies if the percent of recovery is in the range of 85-110% for analytes with a concentration of 0.01% (AOAC, 2019).

4. Precision
   The precision test method uses a sample solution of ketorolac tromethamine in injection preparations. Tests are conducted on the same day and different days during 3 days of repetition. Precision expressed by percent Relative Standard Deviation (RSD). Percent RSD is declared to meet method validation if the RSD value ranges < 4% for analytes with a concentration of 0.01% (AOAC, 2019).

5. Robustness
   Testing robustness carried out by injecting ketorolac tromethamine solution at a concentration of 103 µg/mL at flow rates of 0.9 mL/minute and 1.1 mL/minute and the composition of the mobile phase of acetate buffer : methanol (17:83), and acetate buffer: methanol (23: 77). The chromatogram results were recorded and measured the main peak response, then looked at the effect on the analyte retention time tested (Depkes RI, 2020).

Degradation Test

1. Acid Degradation
   Acid forced degradation test used a standard ketorolac tromethamine solution of 20 µg/mL and added 1 mL HCl to 1N and shaken in an ultrasonic water bath for 60 min at room temperature (±30°C). Take 10 µL of acid degradation samples analyzed under optimized chromatographic conditions (Uddin et al., 2019).

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2. Base Degradation
   Base forced degradation test used a standard 20 µg/mL ketorolac tromethamine solution with 1 mL NaOH 1N added and shaken in an ultrasonic water bath for 60 min at room temperature (±30°C). Take 10 µL of base degradation samples analyzed under optimized chromatographic conditions (Uddin et al., 2019).
3. Oxidation Degradation
   Oxidation forced degradation test using standard 20 µg/mL ketorolac tromethamine solution added 1 mL H_2O_2 concentration 1%, 3% and 5% and stored at room temperature (±30°C) for 1 hour. Take 10 µL of oxidation degradation samples from each concentration and analyze under optimized chromatographic conditions (Uddin et al., 2019).
4. Thermal Degradation
   Thermal forced degradation test using standard 20 µg/mL ketorolac tromethamine solution and heated at 70°, 80° and 90°C in hot plate for three hours. Take 10 µL of temperature degradation samples and analyze them under optimized chromatographic conditions (Uddin et al., 2019).

RESULT AND DISCUSSION

Determination of Maximum Wavelength

Determination of the maximum wavelength of ketorolac tromethamine compounds was carried out using UV-Vis spectrophotometry set in the wavelength region of 200 – 400 nm. The determination of this maximum wavelength aims to determine the optimal wavelength that produces the maximum emission intensity from ketorolac tromethamine solution using methanol solvent. Methanol is used as a solvent due to the easily soluble ketorolac tromethamine property in methanol (Depkes RI, 2020). The results of determining the maximum wavelength of ketorolac tromethamine using several concentration series showed that the compound ketorolac tromethamine has a maximum wavelength at 318 nm.

Mobile Phase Optimization

The mobile phase is an important parameter in separation with HPLC. The determination of the mobile phase used is based on consideration of the polarity properties of the sample to be separated. The separation system commonly used in the analysis of ketorolac tromethamine with HPLC is the reverse phase. The stationary phase used is the C18 column which is non-polar. The elution method used for mobile phase optimization uses the isocratic elution method. The results of optimization of HPLC conditions obtained the composition of the mobile phase of the acetate buffer pH 4.2 – methanol (20:80) at a flow rate of 1.0 mL/minute obtained tailings factor results ≤ 2.0 theoretical plots of ≥2,000 and a resolution value of ≥ 1.5.

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Table 1. Optimization of mobile phase composition and flow rate

Flow rate mL/min	Comparison of acetate buffer : methanol	Flow rate mL/min	Comparison of acetate buffer : methanol	Flow rate mL/min	Comparison of acetate buffer : methanol
0,5	80 : 20	0,75	80 : 20	**1,0**	80 : 20
	50 : 50		50 : 50		50 : 50
	20 : 80		20 : 80		**20 : 80**

Notes : The standard solution used concentration is 100 ppm, Wavelength 318 nm and injection volume 10 µL.

The tailing factor value shows the symmetry of a chromatogram, in the mobile phase composition of the acetate buffer pH 4.2 – methanol (20:80) the flow rate of 1.0 mL/minute shows a tailing factor value of 1.134 meaning that the resulting chromatogram shape is almost symmetrical, so that this mobile phase composition meets all the requirements of the optimum conditions. The fastest retention time resulted from a flow rate of 1.0 mL/min so that the mobile phase composition of the acetate buffer pH 4.2 – methanol (20:80) with a flow rate of 1.0 mL/minute was chosen as the method used for ketorolac tromethamine analysis.

Table 2. Results of Optimization of Mobile Phase Composition and Flow Rate

Variations of the composition of the mobile phase	Flow Rate Variation (mL/min)	Retention Time	*Tailing Factor* (≤ 2.0)	Theoretical plot (≥2,000)	HETP
Acetate Buffer : Methanol (80 : 20)	0,5	3,312	2,875	19162	52,186
	0,75	2,242	2,216	11946	83,708
	1,0	3,337	N/A	13465	74,268
Acetate Buffer : Methanol (50:50)	0,5	3,221	0,998	8693	115,034
	0,75	1,700	N/A	144	6964,547
	1,0	1,708	N/A	3782	264,407
Acetate Buffer : Methanol (20 : 80)	0,5	4,123	1,131	13965	71,606
	0,75	2,795	1,117	12676	78,891
	1,0	2,154	1,134	12214	81,874

Notes : The standard solution used concentration is 100 ppm, Wavelength 318 nm and injection volume 10 µL.

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Linearity and range

The linearity test of a method aims to see the linear relationship between the actual analyte concentration and the response of the tool. The value of the correlation coefficient (r) is a parameter that shows a linear relationship between the area and the concentration of analytes. The calibration curve equation obtained obtained linear regression equation y = 68973x – 172551 with the value of the coefficient of determination (r^2) = 0.9964 and the correlation coefficient (r) = 0.9982 in the range of 20.6 µg/mL - 144.2 µg/mL. A method can be said to have good linearity if the equation of the calibration curve has a correlation coefficient r > 0.99. A correlation coefficient (r) close to 1 indicates a linear relationship between concentration and the area produced. Figure 1 shows a proportional relationship between standard ketorolac tromethamine and area which can be seen from increasing area as the concentration of standard ketorolac tromethamine increases.

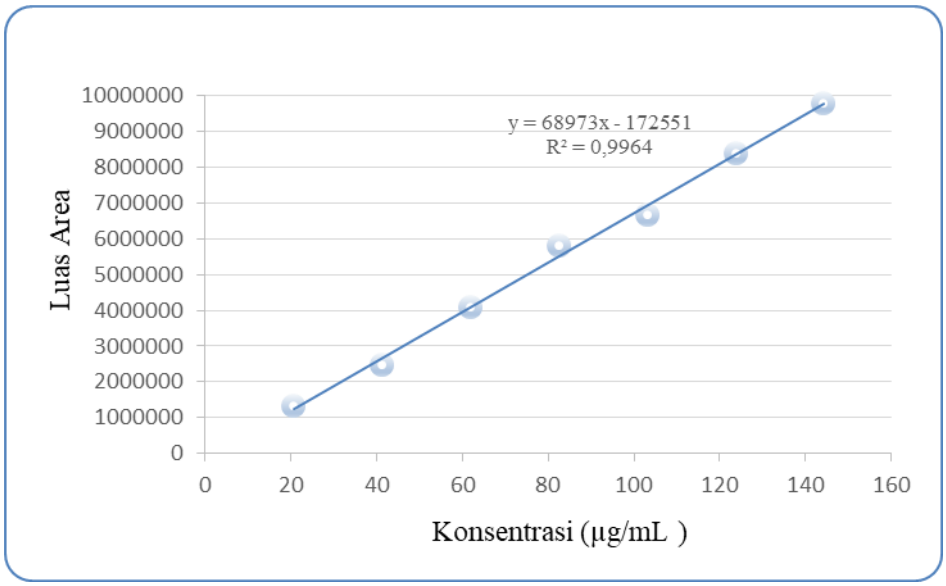

Figure 1. Standard Curve of Ketorolac Tromethamine

In Figure 1 it can be seen that the resulting calibration curve has a linear tangent line, the shape of the resulting curve has followed the Lamber-Beer law, namely increasing concentration, the resulting area is also higher. These results show that the tool used has a good response to the sample.

Limit of Detection (LoD) and Limit of Quantification (LoQ)

Limit of detection (LoD) indicates the lowest concentration of an analyte in a detectable sample, although it cannot always be quantified. The LOD value is calculated from 3.3 x SD and the LoD value is 9.61 µg/mL, while limit of quantification (LoQ) indicates the lowest concentration of an analyte in the sample that can be determined with acceptable precision

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and accuracy under the operational conditions of the method used. The LOQ value is calculated from 10 x SD and the LOQ value is 29.11 µg/mL.

Accuracy

Accuracy tests were carried out on 3 sample concentrations, namely 80%, 100% and 120%. Then calculated the percentage value of recovery (%recovery). A recovery percentage value that is close to 100% means that the method used has good accuracy and shows the suitability of the value of a measurement that is comparable to the actual value.

Table 3. Accuracy test results

Simulation	**%*Recovery***
80%	94,79
100%	99,42
120%	92,83
Average	**95,68**

In Table 3 obtained percentage values *Recovery* with simulation method (Spike placebo recovery) has an average Recovery 95,68%. This result meets the requirements of the validation method, which is entered in the range value of 85-110% for solutions with an analyte content of 0.01% (AOAC, 2019).

Precision

Precision is expressed as Standard deviation (SD) or Relative Standard Deviation (RSD). Precision tests were carried out on the first, second and third days in a row by injecting a solution of ketorolac tromethamine samples with levels of 120 µg/mL As many as 6 repetitions, the area obtained from the injection results is calculated on average and the %RSD value produced. % RSD from the precision measurement of ketorolac tromethamine on the first day was 1.351%, day two was 0.550% and day three was 0.472%. The results of the first, second, and third day RSD % were then averaged until the average % RSD from the ketorolac tromethamine precision test was 0.776%. The precision value meets the requirements of good precision, where the precision is expressed as good if the RSD value < 4% for the analyte concentration in the sample is in the range of 0.01% (AOAC, 2019).

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Robustness

Robustness is carried out to determine the magnitude of the influence that occurs in a method by making slight changes in small methods such as the composition of the mobile phase and the flow rate in a proportional range. The robustness test in this study was carried out on changes in flow rates of 0.9 mL/minute and 1.1 mL/minute and the composition of the mobile phase of acetate buffer: methanol (17:83) and acetate buffer: methanol (23:77). The results of the robustness test can be seen in Table 4 where the parameters of this test are %recovery and %RSD of the resulting concentration.

Table 4. Robustness test result

Parameters	%Recovery	%RSD
Flow rate 0.9 mL/min	110,96	1,481
Flow rate 1.0 mL/min	101,97	1,114
Flow rate 1.1 mL/min	91,94	0,254
Acetate buffer : methanol (17:83)	97,91	4,482
Acetate buffer : methanol (20:80)	101,97	1,114
Acetate buffer : methanol (23:77)	100,11	2,175

Robustness It is the ability of the method to remain stable and not be affected by a small variation in the parameters of the method. Testing robustness is performed by modifying certain operational analysis variables such as flow rate, column, oven temperature, detection wavelength, and mobile phase while analyzing reference solutions under normal operating settings (Priya & Vaishali, 2022). Test robustness This study was carried out by changing the ratio of mobile phases slightly and varying the flow rate from normal conditions, then measuring the effect on separation. In this test it is expected to give a % valueRecovery and %RSD which is not much different in conditions before variation. Testing robustness Get Results %Recovery within the required range of 85-110% and the result of %RSD value in all variations is < 4% so that the method carried out can be declared to meet the requirements of the method endurance test.

Acid Degradation

In the acid degradation study of ketorolac tromethamine can be seen in The Figure 2. A decrease in pH of 3 is used to obtain ketorolac tromethamine in acididc conditions. The chromatogram from the acid forced degradation study showed that there were 5 new peaks formed. The degradation product has retention times of 2,821 minutes, 3,849 minutes, 4,847 minutes, 6,255 minutes, and 6,679 minutes against the peak of ketorolac tromethamine which has a retention time of 2,130 minutes.

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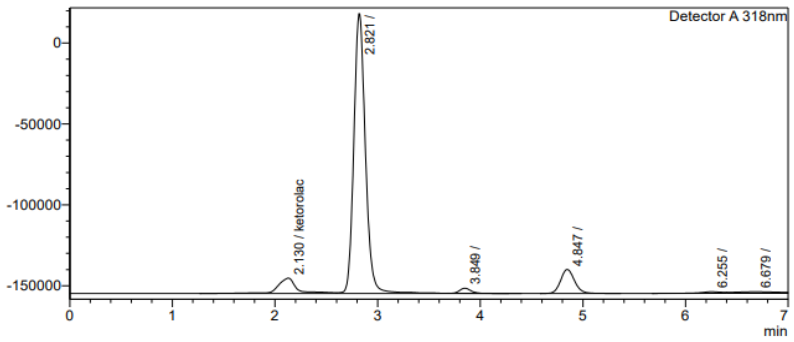

Figure 2. Acid Degradation Test Chromatogram

The result of forced degradation of this acid resulted in a decrease in ketorolac tromethamine levels by 19.34% and degradan formation by 80.66%. Ketorolac tromethamine shows higher degradation results likely due to the presence of pyrrole rings that tend to polymerize under acidic conditions.

Base Degradation

In the base degradation study of ketorolac tromethamine can be seen in The Figure 3. The addition of a pH of 3 is used to obtain ketorolac tromethamine in base conditions. The chromatogram of the base forced degradation study shows that there are 2 new peaks formed. The degradation product has a retention time of 2,702 minutes and 3,131 minutes against the peak of ketorolac tromethamine which has a retention time of 2,248 minutes.

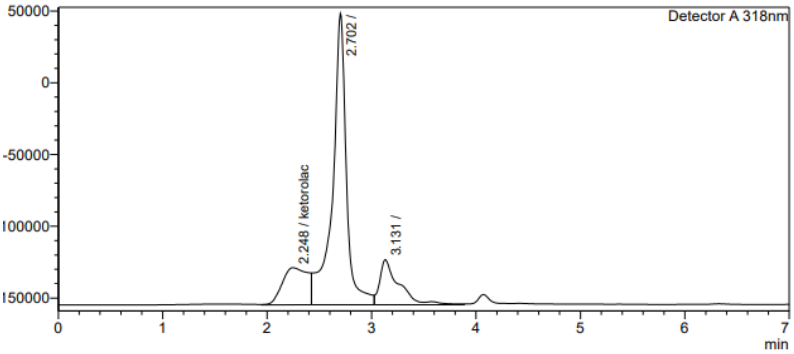

Figure 3. Base Degradation Test Chromatogram

The results of the base degradation chromatogram can be seen that ketorolac tromethamine has been split into several new peaks. Previous studies in degradation tests under base conditions using 0,1 N NaOH obtained 2 new peaks of degradants with retention times of 2,603 and 3,631 (Uddin et al., 2019). The result of forced degradation of this base resulted in a decrease in ketorolac tromethamine levels by 40.70% and degradan formation by 59.30%.

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Thermal Degradation

The chromatogram of forced thermal degradation studies with several temperature variations, namely 70° C, 80° C and 90° C did not show new peaks formed but there was a decrease in levels of ketorolac tromethamine after forced degradation tests. The result of forced degradation of temperature with a temperature variation of 70° C resulted in a decrease in ketorolac tromethamine levels by 98.72% and the formation of new degradant by 1.28%. Then with a temperature variation of 80° C resulted in a decrease in tromethamine ketorolac levels by 84.94% and new degradans were formed by 15.06% and with a temperature variation of 90° C resulted in a decrease in tromethamine ketorolac levels by 81.60% and new degradans were formed by 18.40%.

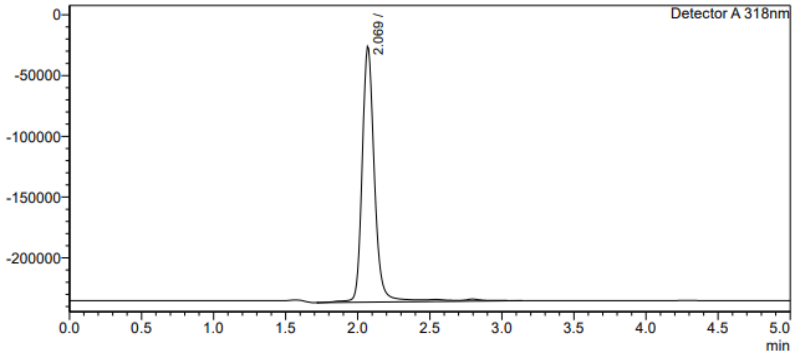

Figure 4. Temperature Degradation Test Chromatogram

Oxidation Degradation

Chromatogram results of oxidation forced degradation studies with concentrations of H_2O_2 1%, H_2O_2 3% and H_2O_2 5% showed that there was 1 new peak formed. The result of forced degradation of oxidation with a concentration of H_2O_2 1% resulted in a decrease in ketorolac tromethamine levels by 88.64% and degraded by 11.36%. Then with a concentration of H_2O_2 3% resulted in a decrease in ketorolac tromethamine levels by 86.02% and the formation of new degrant by 13.98% and with a concentration of H_2O_2 5% resulted in a decrease in ketorolac tromethamine levels by 85.21% and degradan formation by 14.79%.

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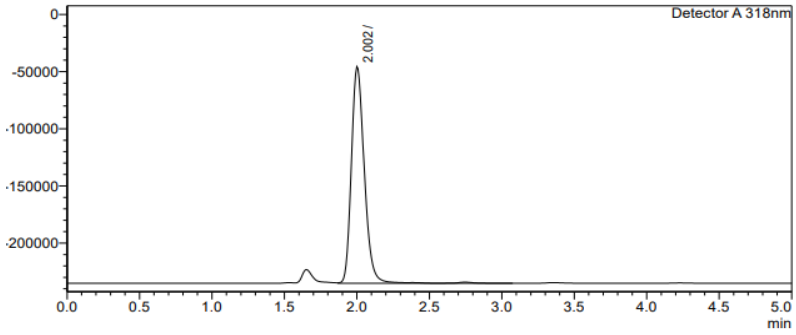

Figure 5. Chromatogram Oxidation Degradation Test

The chromatogram results in this study contained 1 new peak formed through an oxidation process and other peaks are not visible because the concentration is so small that it is not detected in instrument.

CONCLUSION

Based on the results of the study can be concluded:

1. The optimum conditions for the development of the ketorolac tromethamine analysis method with the HPLC method using the YMC-Triart C18 column are using the mobile phase of the acetate buffer pH 4.2 and methanol (20:80) with a maximum wavelength of 318 nm and a flow rate set at a speed of 1.0 mL/minute and an injection volume of 10 µL.
2. The HPLC method was developed linearly with a correlation coefficient value (r) of 0.9982 with a range of 20.6 µg/mL – 144.2 µg/mL with an LoD value of 9.61 µg/mL and LoQ 29.11 µg/mL. The %RSD value was 0.776% and the %recovery from the accuracy test was 95.68% and the method proved to be resilient to changes in the mobile phase ratio of pH 4.2 acetate buffer and methanol and flow rate.
3. The stability of ketorolac tromethamine with acid exposure formed a new degradan by 80.66%, base exposure formed a degradan by 59.30%, exposure to temperatures of 70°C, 80°C and 90°C formed a new degradan by 1.28%, 15.06%, and 18.40% respectively then in exposure to H_2O_2 various concentrations formed a new degradan by 11.36%, 13.98% and 14.79%.

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