Jurnal Sains Farmasi & Klinis
p-ISSN: 2407-7062 | e-ISSN: 2442-5435
homepage: http://jsfk.ffarmasi.unand.ac.id

ORIGINAL ARTICLE Vol. 5 No. 2 (Agustus 2018) | pp. 94–101 |

Development and Validation of Loperamide Hydrochloride Tablet Analysis Method with Absorbance and Area under Curve Methods Spectrophotometrically

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ABSTRACT: Development and validation of loperamide hydrochloride tablet method of analysis have been done by using the absorbance method and area under the curve method. This study used methanol and hydrochloric acid 0.1 N (9: 1) as the best solvent with maximum absorption at wavelength 259.00 nm. The linearity of loperamide hydrochloride was obtained in the concentration range 200-600 ppm with a correlation coefficient value with the absorbance method and the areas under the curve method were 0.9998 and 0.9865, respectively. The results showed that the levels of loperamide hydrochloride in generic tablets obtained by absorbance method and the area under the curve method were 105.71% and 96.20%, respectively. The results of determination of loperamide levels in tablets of trademark obtained by absorbance method and the area under the curve method were 102.85% and 98.57%, respectively. The level of both samples met the requirements of Pharmacopoeia Indonesia edition V that is 90%-110%.

Keywords: Loperamide hydrochloride; absorbance method; area under the curve method; spectrophotometry; development; validation; analysis.

Introduction

The most effective antidiarrheal drugs are the opioids and derivatives of opioids that have been selected for maximal antidiarrheal and minimal central nervous system effect. Of the latter group, the most important are diphenoxylate and loperamide, meperidine analogs with weak analgesic effects. Diphenoxylate is formulated with antimuscarinic alkaloids (e.g., atropine) to reduce the likelihood of abuse; loperamide is formulated alone [1]. Loperamide hydrochloride has molecular formula C29H33ClN2O2.HCl and molecular weight 513,51 g/mol. Chemically, loperamide hydrochloride is 4-(p-Chlorophenyl)-4-hydroxy-N,N-dimethyl-α,α-diphenyl-1-piperidine butyl amide monohydrochloride [34552-83-5] as presented in Figure 1. The physicochemical properties for loperamide hydrochloride are powder; white to slightly yellow; melt at a temperature of approximately 225 oC with decomposition; readily soluble in methanol, in isopropyl alcohol and chloroform; challenging to dissolve in water and dilute acid [2].

Loperamide hydrochloride in the form of pharmaceutical raw materials can be determined by the method of water-free titration, whereas in the form of pharmaceutical preparations of tablets and capsules can be determined with high-performance liquid chromatography [2-4]. A quantitative method using silica gel high-performance thin layer chromatography plates with fluorescent indicator, automated sample application, and automated ultraviolet absorption densitometry of the fluorescence quenching zones was developed and validated for the determination of loperamide hydrochloride in anti-diarrheal medications [5]. Two new loperamide potentiometric electrodes were prepared and used for pharmaceutical analysis [6]. Two simple, economical, precise and reproducible visible spectrophotometric methods have been developed for the estimation of loperamide hydrochloride in tablet formulation [7, 8].

Among the various methods used in the determination of drug levels, UV-Vis spectrophotometry is still very popular. In our previous research, we have developed several analytical methods using the absorption method and the area measurement method under the curve with ultraviolet-visible spectrophotometry [9 - 16]. In

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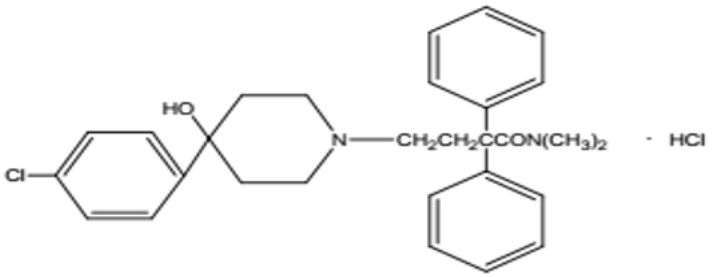

Figure 1. Chemical structure of loperamide hydrochloride

this research, the best solvent search for loperamide hydrochloride analysis was done, and then developed a method for determination of loperamide hydrochloride concentration by UV-Vis spectrophotometry. The method developed is the method of absorbance and method of the area under the curve.

Materials and Methods

Drug and chemicals

The materials used in the present study were pure substance loperamide hydrochloride (PT Vasudha Pharma), Imodium® tablet 2 mg (PT Taiso Pharmaceutical Indonesia), and generic tablet loperamide hydrochloride 2 mg (PT Ifars), methanol (PT Merck), hydrochloric acids (PT Merck), citric acid (PT Merck), sodium hydroxide (PT Merck). The chemicals were used as received without purification before analysis.

Preparation of Solvents

0.1 N Sodium hydroxide solution

162 grams of sodium hydroxide were dissolved in 150 mL of carbon dioxide-free water. The solution was cooled to room temperature, filtered through filter paper. The clear filtrate was put as much as 54.5 mL into a tightly sealed container and dilute it with carbon dioxide-free water up to 1000 mL. The solution was pipetted as many 100 mL, inserted into 1000 mL volumetric flasks, and added with carbon dioxide-free water until the boundary mark, and homogenized.

0.1N Hydrochloric acid solution

85 mL of concentrated hydrochloric acid was diluted with distilled water up to 1000 mL. 100 mL of the solution were put in 1000 mL volumetric flask and added with carbon dioxide-free distilled water until the boundary mark, then homogenized.

0.1 M Citric acid solution

19.21 grams of citric acid was dissolved in carbon-dioxide free distilled water up to 1000 mL. 100 mL of the solution was put in a 1000 mL volumetric flask, and added with carbon dioxide-free distilled water until the boundary marks, and homogenized.

Preparation of 1000 µg / mL loperamide hydrochloride solution in various solvents

- In 0.1 N HCl, 0.1 N NaOH, 0.1 M citric acid, and methanol

  A standard solution of pure loperamide hydrochloride was prepared with a concentration of 1000 µg/mL, by carefully weighing 100 mg pure loperamide hydrochloride using an analytical scale, inserted into a 100 mL volumetric flask, then added in portions each with 0.1 N HCl, 0.1 N NaOH , 0.1 M citric acid, and methanol. These solutions were shaken until dissolve, then added each solvent to the limit.
- In methanol : 0.1 N HCl

  A standard solution of pure loperamide hydrochloride of 400 ppm was prepared by carefully weighing 40 mg of loperamide hydrochloride using an analytical scale, inserted into a 100 mL volumetric flask, then added a portion of methanol : 0.1 N HCl (9 : 1), shake until dissolved and then completed with methanol : 0.1 N HCl (9 : 1) to the limit mark, and shake homogeneously.

Determination of maximum absorption wavelength of loperamide hydrochloride

Each standard solution of 1000 ppm loperamide hydrochloride in various solvents (0.1 N HCl, 0.1 N NaOH, methanol, and citric acid) was diluted to 100 ppm and then diluted again to 10 ppm with each solvent. The absorption is measured at wavelengths between 200-400 ppm. The measurement of the four solvents was not obtained by the

best solvent to make a methanol solvent mixture: 0.1 N HCl (9: 1) with a concentration of 400 ppm. Absorbance is measured in the wavelength range 200 - 400 nm with an ultraviolet spectrophotometer.

Preparation of calibration curve of loperamide hydrochloride

Preparation of the calibration curve of loperamide hydrochloride by carefully weighing 100 mg of loperamide hydrochloride using an analytical scale, insert it into a 100 mL measuring flask, then add in portion, methanol solvent: 0.1 N HCl (9: 1) shake until dissolved and then sufficient with methanol: HCl 0.1 N (9: 1) to the limit mark, shake homogeneously. Then a standard solution of 1000 ppm loperamide hydrochloride was taken with a 2 mL, 3 mL, 4 mL, 5 mL, and 6 mL volume pipettes, each fed into a 10 mL measuring flask and sufficient with a methanol solvent: 0.1 N HCl (9: 1) until the homogeneous boundary mark until obtained the concentration of 200 ppm, 300 ppm, 400 ppm, 500 ppm, and 600 ppm. The absorbent and area under the curve were measured for each solution at the maximum wavelength of loperamide hydrochloride.

Determination of levels of loperamide hydrochloride in tablets

Determination of loperamide hydrochloride levels in tablets was done by grinding 20 tablets then weighed the equivalent of 2 mg of pure loperamide hydrochloride. Dissolve with some methanol: 0.1 N HCl (9: 1) in 10 mL measuring flask, sonication for 1 hour until dissolved, then add solvent to the limit. The absorbance and area under the curve were measured with the ultraviolet-visible spectrophotometer at the maximum wavelength of loperamide hydrochloride. Determine levels of loperamide hydrochloride based on the linear regression equation of loperamide hydrochloride.

Validation of Analysis Methods

Linearity Test

The measurement data of the calibration curve was analyzed by linear regression so that it obtained the correlation coefficient (r) which showed its linearity. The value of good linearity is $0.999 \leq r \leq 1$ [17].

Limit of Detection (LOD) and Limit of Quantification (LOQ)

The limit of detection (LOD) and the limit of quantification (LOQ) are determined from the regression of the standard curve obtained. The value of LOD = 3.3 (SD / S) and LOQ = 10 (SD / S). The standard deviation (SD) is determined by the standard deviation of the residual and the slope (S) is the slope of the line (b) of the linear regression $y = a + bx$ [17].

Test Accuracy

The accuracy test is carried out by the spiking test which is by adding a standard solution of loperamide hydrochloride to a test solution where the level is known. The concentrations of standard solutions added were 80%, 100% and 120% with three repetitions. Furthermore, the computed raw material recovery values added to the test solution are expressed as percent recovery. Validation methods are eligible if percent recovery shows a range of 80% - 120% [17].

Precision Test

The precision test was performed at the repeatability level by measuring the concentration of test solution of loperamide hydrochloride with a concentration of 200 ppm, 300 ppm, and 400 ppm at three different times in one day (intraday) with repetition every three times. Measurement of loperamide hydrochloride test solution with the same concentration was also performed on three consecutive days (interday) with repetition of each three times. RSD values between 1 - 2% are usually required for large amounts of active compounds, whereas for compounds with a certain amount of content, RSD ranges from 5 to 15% [17].

Statistical analysis

Statistical analysis was performed on the determination of the content, accuracy test, intraday and interday precision test of the absorbance method and the area-wide method under the curve in the sample. Both of these methods were compared by using the two paired t-test using SPSS 22 [18].

Results and Discussion

Determination of solvent used in this study was done by testing some solvents. The solvents tested were 0.1 N HCl, 0.1 N NaOH, citric acid, methanol, and methanol: 0.1 N HCl (9: 1). The best solvent determination of some of the solvents was seen from the maximum wavelength, and the absorbance of 0.1 N HCl, 0.1 N NaOH, citric acid and methanol for a standard solution of 10 ppm loperamide hydrochloride. Furthermore, the maximum wavelengths are measured in the range of 200-400 nm each. For a standard solution of loperamide hydrochloride in methanol: 0.1 N HCl (9: 1) at a concentration of 400

ppm, absorbance was measured at a wavelength of 200-400 nm.

The results of measurements in a 0.1 N HCl solvent showed a maximum absorption wavelength at 258.80 nm and an absorbance of 0.027; in 0.1 N NaOH showed 231.40 nm and absorbance of 0.030; in a citric acid solvent showing 264.80 nm and an absorbance of 0.010; in a methanol solvent of 392.60 nm and an absorbance of 0.003. Meanwhile, the measurement results in methanol solvent: 0.1 N HCl (9: 1) showed 259.00 nm and the absorbance of 0.469. Of the several solvents, the methanol solvent: 0.1 N HCl (9: 1) shows the best maximum absorption wavelength and absorbance represents a range ranging from 0.2-0.8. Therefore, methanol: 0.1 N HCl (9: 1) is selected as the best solvent (see Figure 2).

Preparation of calibration curve of a standard solution of loperamide hydrochloride was made by making series of the standard solution with concentration 200, 300, 400, 500, and 600 ppm using methanol: HCl 0.1 N (9: 1) as a solvent. The solution measured the absorbance and area under the curve at the maximum wavelength of loperamide hydrochloride in methanol: 0.1 N HCl (9: 1). On the measurement of correlation between concentration with absorbance, the absorbance value is 0,262, 0,367, 0,464, 0,557 and 0,660 so that the linear regression equation obtained is $y = 0.00099x + 0.06769$ and $r = 0.9998$ (Figure 3). While the measurement of the relationship between the concentration with the area under the curve obtained the value of the area under a curve respectively 0.181, 0.249, 0.275, 0.358, and 0.442 so that the linear regression equation obtained is $y = 0.000631x + 0.0486$ and the value $r = 0.98653$ (Figure 4).

Determination of levels of loperamide hydrochloride in generic tablets (PT Ifars) showed absorbance rate of 105.71% ± 0.005% (Table 1) and with the method of the area under the curve showed the level of 96.20 % ± 0.000% (Table 2). Determination of levels of loperamide hydrochloride in tablets under the trade name Imodium® (PT Taiso Pharmaceutical Indonesia) showed levels with absorbance method of 102.85% ± 0.015% (Table 3), whereas with the method of the area under the curve showed a level of 98.57% ± 0.014% (Table 4).

The determination of loperamide hydrochloride levels in generic tablets by absorbance method and by the area under the curve method satisfies the requirements by the Pharmacopoeia of Indonesia edition V that is 90-110% [2]. Determination of levels of loperamide hydrochloride in tablets by trade name by absorbance method and by the area under the curve method fulfills the requirements by Pharmacopoeia of Indonesia edition V that is 90-110% [2].

From the statistical analysis data for determination of the generic content of loperamide hydrochloride tablet got the value of T calculated = 32.628 with Sig. = 0.001 (<0.05), which means that Ho is rejected or shows the levels obtained from both methods are significantly different. Meanwhile, the determination of loperamide hydrochloride tablet with the trade name Imodium obtained T value = 91.571 with Sig. = 0.000 (<0.05), which means that Ho is rejected or shows the levels obtained from both methods are significantly different.

Linearity is determined by processing the data between concentration (x) with absorbance (y) and concentration (x) with the area under the curve (y) obtained from the calibration curve using a linear regression equation, to obtain correlation coefficient value. The result of the calibration curve with absorbance method gives a direct result with r value = 0.9998 while with the method of the area under the curve gives a result which not linear with value r = 0.98653. The correlation coefficient obtained by the absorbance method gives a linear result because it meets the acceptance criteria with a correlation coefficient value of $0.99 \leq r \leq 1$ whereas with the method of area under the curve gives results that are not linear because it does not meet the acceptance criteria with a correlation coefficient value of $0.99 \leq r \leq 1$ [18].

The limits of detection and limit of quantification of loperamide hydrochloride by absorbance method were 217.5622 ppm and 659.2795 ppm, respectively. While the limits of detection and the limits of quantification by the method of the area under the curve are 172.9710 ppm and 524.1546 ppm, respectively.

Accuracy is measured as the number of recovered analytes. The determination of recovery was done by adding the standard solution of loperamide hydrochloride by 80%, 100% and 120% into the generic sample of tablet loperamide hydrochloride. Percent recovery by absorbance method was 99.16%, 99.56%, 99.82% with average percentage was 99.51%. While the method of the area under the curve obtained percent recovery of 100.21%, 100.49%, 100.44% with the average recovery percentage is 100.38%. Percent recovery for the sample by trade name is made in the same way as in generic samples. Percent recovery was 99.23%, 99.19%, 99.30%, and the average was 99.24% with the absorbance method. The recovery was 102.21%, 102.41%, 102.98 % and the average is 102.53% with the method of the area under the curve.

The determination of intraday precision on a generic sample of tablet loperamide hydrochloride was performed in the morning, afternoon and evening with three different

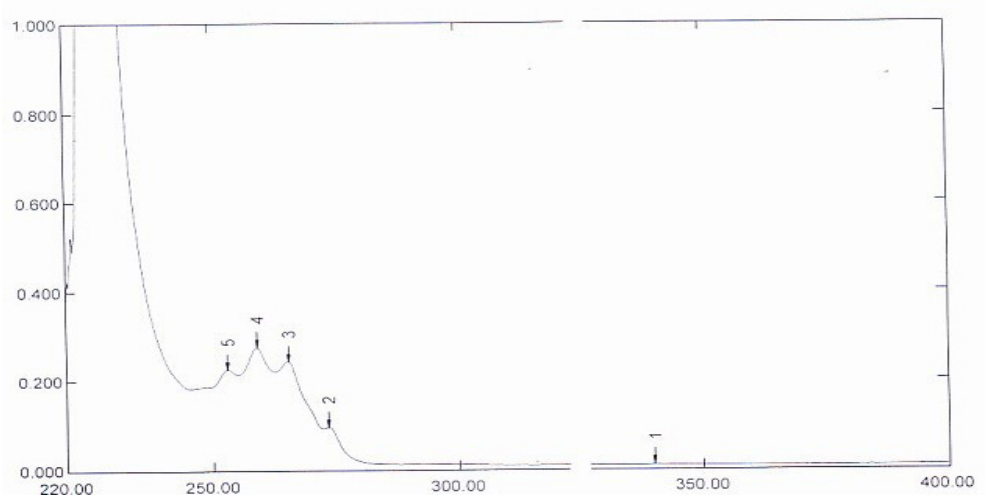

Figure 2. The ultraviolet spectrum of a solution of 400 ppm loperamide hydrochloride in methanol: 0.1 N HCl (9: 1)

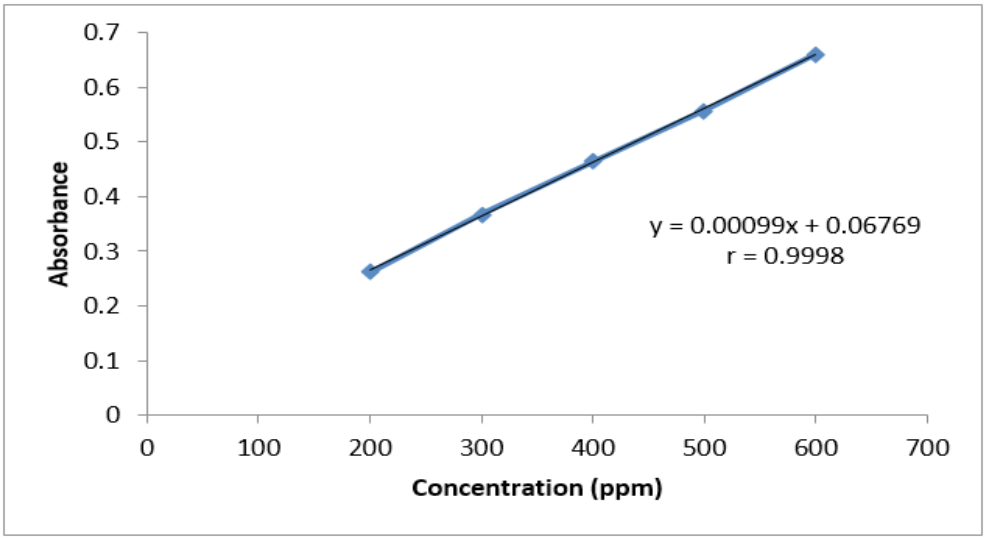

Figure 3. Calibration curve of loperamide hydrochloride in methanol: 0.1 N HCl (9: 1) by absorbance method at maximum wavelength 259.00 nm

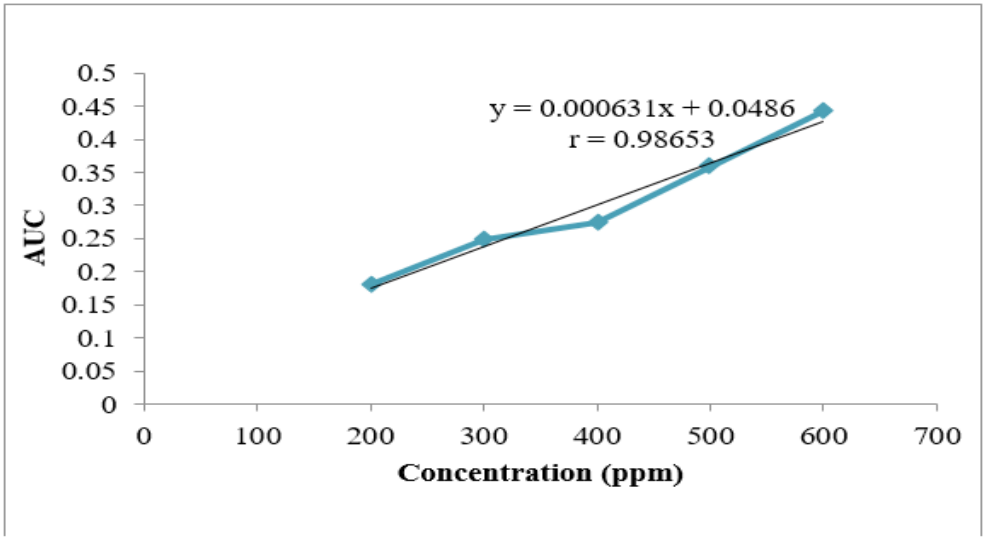

Figure 4. Calibration curve of loperamide hydrochloride in methanol: 0.1 N HCl (9: 1) with the method of the area under the curve

concentrations. The percentage of RSD obtained by absorbance method at a concentration of 200 ppm was 1.26%, 0.30% and 0.30%, respectively; at a concentration of 300 ppm by 0.20%, 0.72% and 0.34%, respectively; at concentrations of 400 ppm by 0.15%, 0.15% and 0.15%, respectively so that the mean RSD percentage is 0.40%. The percentage of RSD obtained by the method of area under the curve at a concentration of 200 ppm was of 0.99%, 0.50%, and 0.50%, respectively; at a concentration of 300 ppm by 0.88%, 1.00%, and 0.57%, respectively; at concentrations of 400 ppm by 0.50%, 0.25%, and 0.50%, respectively, so the mean percentage of RSD is 0.63%.

Determination of intraday precipitation of tablet loperamide hydrochloride under the trade name Imodium® is performed in the same manner as a generic sample. The percentage of RSD obtained by absorbance method at the concentration of 200 ppm was 0.59%, 0.60%, and 0.30%, and the concentration of 300 ppm was 0.58%, 0.39%, and 0.20%. At concentrations of 400 ppm RSD percentage of 0.88%, 0.14% and 0.67%, so the average RSD percentage is 0.48%. The percentage of RSD obtained by the method of the area under the curve at a concentration of 200 ppm of 0.99%, 1.00%, and 0.51%, and a concentration of 300 ppm of 0.65%, 0.94%, and 0.32%. At a concentration of 400 ppm, RSD percentage is 0.70%, 0.47% and 0.70%, so the mean percentage of RSD is 0.70%.

The determination of interday precision on a generic sample of tablet loperamide hydrochloride was performed for three consecutive days at three different concentrations. At a concentration of 200 ppm on the first, second and third day, RSD was obtained by absorbance method of 1.13%, 0.52%, and 0.52%, respectively, and at a concentration of 300 ppm on the first, second, and third day RSD respectively by 0.73%, 0.69% and 0.80%. At the concentration of 400 ppm on the first, second and third day, RSD was obtained by 0.39%, 0.25%, and 0.39% respectively, so the average RSD percentage was 0.60%. The method of the wide area under the curve, at a concentration of 200 ppm on the first, second, and third were obtained RSD respectively equal to 0.86%, 0.50%, and 0.50%. At a concentration of 300 ppm on the first, second, and the third day were obtained RSD respectively by 1.19%, 1.51%, and 1.32%; at the concentration of 400 ppm on the first, second and third day were obtained RSD respectively of 0.87%, 0.66%, and 0.66%. The average RSD percentage is 0.90%.

The determination of interday precision of loperamide hydrochloride in tablets under the trade name Imodium® is performed in the same manner as the generic sample. Determination of interday precision by absorbance method for the concentration of 200 ppm on the first, second and third day of RSD was obtained by 0.79%, 0.90% and 0.60%, respectively; for the concentration of 300 ppm on the first, second, and third day of RSD obtained by 0.90%, 0.34% and 0.59% respectively. For the concentration of 400 ppm on the first, second and third day, the RSD was 0.58%, 0.88%, and 0.58% respectively. The average percentage of RSD was 0.68%. The determination of interday precision with the area under the curve method for the concentration of 200 ppm on the first, second and third day was obtained RSD at 0.51%, 0.50%, and 0.50%, respectively; for the concentration of 300 ppm on the first, second and third day was obtained RSD at 0.56%, 0.32%, and 0.32%, respectively; for 400 ppm of concentration on the first and second day of RSD obtained by 0.23%, 0.70% and 0.70% respectively. The average RSD percentage was obtained at 0.57%

Table 1. Determination of loperamide hydrochloride levels in generic tablets (PT Ifars) by absorbance method

No	Absorbance	Levels obtained (ppm)	Weight (mg)	% Level
1	0.276	210.414	2.104	105.21
2	0.277	211.424	2.114	105.71
3	0.278	211.434	2.124	106.22
Average			2.114	105.71
SD				0.005

Table 2. Determination of levels of loperamide hydrochloride in generic tablets (PT Ifars) by the method of the area under the curve

No	AUC	Levels obtained (ppm)	Weight (mg)	% Level
1	0.170	192.393	1.924	96.20
2	0.170	192.393	1.924	96.20
3	0.170	192.393	1.924	96.20
	Average		1.924	96.20
	SD		0.000	0.005

Table 3. Determination of loperamide hydrochloride levels in Imodium® (PT Taiso Pharmaceutical Indonesia) trademark tablets with absorbance method

No	Absorbance	Levels obtained (ppm)	Weight (mg)	% Level
1	0.268	202.333	2.023	101.17
2	0.273	207.384	2.074	103.69
3	0.273	207.384	2.074	103.69
	Average		2.057	102.85
	SD			0.015

Table 4. Determination of loperamide hydrochloride levels in Imodium® (PT Taiso Pharmaceutical Indonesia) trademark tablets with an area under the curve method

No	Absorbance	Levels obtained (ppm)	Weight (mg)	% Level
1	0.171	193.978	1.940	96.99
2	0.174	198.732	1.987	99.37
3	0.174	198.732	1.987	99.37
	Average		1.971	98.57
	SD			0.014

Conclusion

The best solvent used for the analysis of loperamide hydrochloride by ultraviolet-visible spectrophotometry method is methanol: HCl 0.1 N (9 : 1). The analysis of loperamide hydrochloride in tablets by ultraviolet-visible spectrophotometry by absorbance method is valid while the area under the curve method is invalid for analysis of loperamide hydrochloride in tablets.

Acknowledgement

The authors would like to thank PT Vasudha Pharma Chem Limited for providing the loperamide hydrochloride for this research.

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