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SYSTEMATIC LITERATURE REVIEW OF PARACETAMOL, GLYCERIL GUAIACOLATE, PHENYLPROPANOLAMINE HCL, DEXTROMETORPHAN HBR AND CHLORPHENIRAMINE MALEATE IN DRUG WITH HPLC

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ABSTRACT

Determination of compounds level in a drug needed to be done to maintain the quality of the drug. However, drug preparations containing a mixture of various active substances can cause problems when determining the concentration. This research was done by using the SLR (Systematic literature review) method. The data sources used scientific databases to obtain relevant sources related to paracetamol, glyceryl guaiacholate, phenylpropanolamine HCl, dextromethorphan HBr and chlorpheniramine maleatee in medicinal preparations, the optimum conditions of HPLC for the analysis of these compounds, as well as the selected analytical method that met the validation requirements.

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The results of literature study of paracetamol, glyceryl guaiacolate, phenylpropanolamine HCl, dextromethorphan HBr and chlorpheniramine maleateeanalyzedin drugs using the High Performance Liquid Chromatography method simultaneously generally using reverse phase chromatography. Where the stationary phase uses an octadecyl silica or C18 column, the mobile phase uses a mixture of phosphate buffer with methanol or acetonitrile. With a buffer concentration of 0.01 M and in pH range of 4 to 7. The flow rate was generally 1 ml/min and the wavelength detectionwas in the range of 210-270 nm. From the optimum conditions, the retention time (tR) of paracetamol was 3-6 minutes, glyceryl guaiacolatewas 4-8 minutes, phenylpropanolamine HCl was 4-6 minutes, dextromethorphan HBr was 9-10 minutes and chlorpheniramine maleateewas 5-8 minutes. Validation of the method qualified of selectivity, accuracy, precision, linearity, LOD and LOQ parameters.

Introduction

Determination of compounds levels in a drug needed to be done to maintain the quality of the drug. However, drug preparations containing a mixture of various active substances can cause problems when determining the concentration. This is because the active substances can mix with each other while determine the compounds levels, so each component of the substance must be separated first. The method that often used to determine the concentration of a mixture of active substances in a drug is High Performance Liquid Chromatography (HPLC), with this method the active substances can be separated and each active substance can be analyzed individually (Gandjar, 2012). Using the HPLC method requires a lot of money, so it is necessary to develop alternative methods in order to save costs.

Determining the concentration of compounds simultaneously by high performance liquid chromatography method, based on differences interaction of compounds with the stationary phase. This will result different retention times for each compound. The mobile phase which is polar and the stationary phase which is non-polar is called reverse phase chromatography. In the reverse phase, highly polar substances will elute first than less polar substances (Ardrey, 2003).

The development of analysis methods for mixed drugs simultaneously with HPLC has been widely done. Nalini et al., 2014, analyzed paracetamol, guaifenesin, phenylephrine HCl, chlorpheniramine maleatee and bromhexine HCl using a C8

column (150 X 4.6 mm, 3.5 m) and using methanol as a mobile phase: acetonitrile (3 : 2). The results obtained where the validation parameter requirements including accuracy, precision and robustness are met. Siregar, 2018 determined the levels of phenylephrine, paracetamol, glyceryl guaiacholate and chlorpheniramine maleatee simultaneously in tablet preparations using the HPLC method. The analysis was done at the mobile phase pH 4.1; 4.3; 4.6 with the addition of phosphoric acid as buffer. The optimum condition in this study was the stationary phase using a C18 column (250 x 4.6 mm, particle size 10 m), the mobile phase was a mixture of phosphate buffer pH 4.3 : methanol (60:40), flow rate 1.0 ml /min and wavelength detection of 263 nm.

Research by Ellora et al., 2018 was done to optimization of the mobile phase of HPLC to determine the levels of paracetamol, glyceryl guaiacolate, chlorpheniramine maleatee and phenylephrine HCl in tablets simultaneously. In this study, the optimum conditions for the mobile phase were obtained using methanol: phosphate buffer pH 4.3 (60: 40), with a flow rate of 1.0 ml/min and detection at 263 nm.

Based on the background above, the researchers conducted a literature study on the analysis of paracetamol, glyceryl guaiacholate, phenylpropanolamine HCl, dextromethorphan HBr and chlorpheniramine maleatee in drugs using the High Performance Liquid Chromatography method simultaneously.

Method

This study used a Systematic Literature Review (SLR), which is a systematic, clear, comprehensive synthesis of literature studies, by identifying, analyzing, evaluating through the collection of existing data with an explicit search method and involving a critical review process in the selection of studies.

The data sources selected were research articles in Indonesian and English, published in 2010-2020, available in full-text. After the application of a search based on predetermined criteria, then the articles obtained were evaluated for relevant studies that qualified the inclusion criteria.

The data sources used scientific databases to obtain relevant articles related to the analysis of paracetamol, glyceryl guaiacholate, phenylpropanolamine HCl, dextromethorphan HBr and chlorpheniramine maleatee using high performance liquid chromatography, namely ScienceDirect, Springer, Elsevier and Scopus.

Research subjects inclusion criteria:

a. Research articles that discuss method optimization
analysis of paracetamol, glyceryl guaiacholate, phenylpropanolamine HCl, dextromethorphan HBr and chlorpheniramine maleatee simultaneously using high performance liquid chromatography.

b. Research article that discusses method validation
analysis of paracetamol, glyceryl guaiacholate, phenylpropanolamine HCl, dextromethorphan HBr and chlorpheniramine maleatee simultaneously using high performance liquid chromatography.

c. Research articles can be accessed in full text form.

d. Research articles published in the last 10 years, namely 2010 to 2020.

Data Collection Technique and Analysisliterature search in the ScienceDirect, Springer, Elsevier and Scopus databases using keywords, for example: "HPLC method for simultaneous analysis of paracetamol, dextromethorphan HBr and chlorpheniramine maleatee" or "paracetamol, guaiphenesin, phenylpropanolamine HCl, HPLC".

1. Recording the amount of literature obtained from the results of searching.
2. The selection of literature is only in the form of research articles.
3. Screening of literature according to research objectives by reading the title and/or research abstract, which did not qualified the inclusion criteria were excluded.
4. Extracting data on selected research articles and those available in full text to record identity (researcher name and year), research methods, and resume of research results.
5. Summarizing the important points of the article and looking for interrelationships between the articles through the research results obtained in order to obtain a summary that discusses the problems that have been formulated.
6. Preparation and writing of results was done descriptively.

Result and Discussion

This literature study aimed to evaluate the analysis of paracetamol, glyceryl guaiacholate, phenylpropanolamine HCl, dextromethorphan HBr and chlorpheniramine maleatee in drugs by simultaneous high performance liquid chromatography.

The design of this research is a literature study. Previous research criteria for review

were selected based on the following search criteria: only research articles, in English and Indonesian, published between 2010 to 2020 and available in full text. After applying the search based on the criteria, then the results are selected to be evaluated against relevant studies and qualified inclusion criteria.

Sources were taken from scientific databases to obtain relevant research related to the specific problem of analyzing paracetamol, glyceryl guaiacholate, phenylpropanolamine HCl, dextromethorphan HBr and chlorpheniramine maleatee in drugs by simultaneous high performance liquid chromatography. The scientific databases used are ScienceDirect, Springer, Elsevier and Scopus.

The search was done between November and December 2020 using the keywords: paracetamol, dextromethorphan HBr and chlorpheniramine maleatee, HPLC" or "paracetamol, guaiphenesin and phenylpropanolamine HCl, HPLC".

Determination of the optimum wavelength of research was not done at one of the maximum wavelengths of compounds because the wavelength of one compound was only sensitive to changes in the concentration of the compound concerned. So it was done at the optimum five-compounds wavelength.

Table 1. Optimum Wavelength

Author	Sample	Method	Wavelength (nm)
Siregar, 2018	Phenylephrine, paracetamol, glyceryl guaiacholat and chlorpheniramine maleatee	Reverse phase HPLC using C_{18} column	263
Ellora *et al.*, 2018	Paracetamol, glyceryl guaiacholat, chlorpheneramine maleatee and phenylephrine HCl	Reverse phase HPLC using VP-ODS column	263
Rasal *et al.*, 2014	Chlorpheniramine maleatee, phenylpropanolamine	Reverse phase HPLC using C_{18} Thermo Hypersil	217

	HCl and paracetamol	Gold column	
Goyal, 2013	Guaifenesin, chlorpheniramine maleatee and dextrometorphan HBr	Reverse phase HPLC using Purospher star RP-18e column	225
Nalini *et al.*, 2014	paracetamol, guaifenesin, phenylephrineHCl, chlorpheniramine maleatee and bromhexin HCl	Reverse phase HPLC using Symmetry C_8 column	220
Abdulbari, 2013	Chlorpheniramine maleatee, paracetamol, phenylpropanolamin HCl and caffeine	Reverse phase HPLC using Inertsil C_{18} column	220

Optimization of High Performance Liquid Chromatography Conditions variations of one test variable at a time can be used to optimize HPLC conditions, while other variables are conditioned to still the same, the response that occurs then recorded. Flow rate, stationary or mobile phase composition, temperature, detection wavelength, and pH are examples of these variables. Retention time, resolution value, peak shape, column capacity, number of plates, detection limit, quantification limit, and other separation parameters must be maximized in optimizing HPLC conditions until the values obtained were qualified (Gandjar and Rohman, 2007).

Table2. Mobile PhaseComposition

Author	**Sample**	**Method**	**Mobile Phase Composition**
Ellora *et al.*, 2018	Paracetamol, glyceryl	Reverse phase	Methanol : buffer

	guaiacholat, klorfeneramin maleate and phenylephrine HCl	HPLC using VP-ODS column	phosphate 0,01 M pH 4,3 (60:40)
Siregar, 2018	Phenylephrine, paracetamol, glyceryl guaiacholat and chlorpheniramine maleate	Reverse phase HPLC using C_{18} column	Buffer phosphate pH 4,3 : methanol (60:40)
Rasal*et al.*, 2014	Chlorpheniramine maleate, phenylpropanolamine HCl and paracetamol	Reverse phase HPLC using C_{18} Thermo Hypersil Gold column	Methanol : buffer phosphate 0,01M pH 7 (70:30)
Acheampong *et al.*, 2016	Chlorpheniramine maleate, paracetamol and caffeine	Reverse phase HPLC using Phenomenex C_{18} column	Methanol : buffer phosphate 0,05 M pH 4,0 (30:70)
Al-Rimawi, 2010	Pseudofedrin HCl, dextrometorphan HBr, chlorpheniramine maleate and paracetamol	Reverse phase HPLC using Nova-pak column	Methanol : buffer phosphate (90:10)
Redasani*et al.*, 2013	Chlorpheniramine maleate, phenylephrine HCl, paracetamol and caffeine	Reverse phase HPLC using Inertsil ODS C_{18}	Buffer phosphate 0,05M pH 4,0 : acetonitril (93:07)
Renu*et al.*, 2013	Chlorpheniramine maleate, paracetamol and phenylephrine HCl	Reverse phase HPLC using C_8 column	Buffer phosphate 0,01 M pH 3 : acetonitril (70:30)
Zahoor *et al.*,	Chlorpheniramine	Reverse phase	Buffer phosphate

2018	maleate, paracetamol and phenylephrine HCl	HPLC using Phenomenex luna column	0,01 M pH 6,2 : acetonitril (70:30)
Goyal, 2013	Guaifenesin, chlorpheniramine maleate and dextrometorphan HBr	Reverse phase HPLC using Purospher star RP-18e column	Buffer phosphate pH 3) :asetonitiril with ratio (74 : 26)
Sirigiri *et al.*, 2017	Chlorpheniramine maleate and dextrometorphan	Reverse phase HPLC using Discovery C_{18} column	water pH 2 : acetonitril (60 : 40)
Nalini *et al.*, 2014	Paracetamol, guaifenesin, phenylephrine HCl, chlorpheniramine maléate and bromhexine HCl	Reversephase HPLC using Symmetry C_8 column	Mobile phase A (buffer phosphate 10 mM KH_2PO_4 and 3,7 mMion pair sulfonicacid) and mobile phase B (methanol :acetonitril (3:2))
Abdulbari, 2013	Chlorpheniramine maleate, paracetamol, phenylpropanolamine HCl and caffeine	Reverse phase HPLC using Inertsil C_{18}	acetonitril : water : methanol (15 : 75 : 10) with addition of buffer solution pH 2,8 that mixed with trietilenamine 0,3 ml and sulfonic acid
Vijay, 2015	Phenylephrine, paracetamol, guaifenesin and dextrometorphan	Reverse phase HPLC using Altima C_{18}	Phosphate acid as solvent A and Acetonitril as solvent B
Swapnil *et al.*, 2015	Paracetamol, guaifenesin,	Reverse phase HPLC using	Buffer phosphate acid 1 M :

	ambroxol HCl, phenylephrine HCl and chlorpheniramine maleate	Zodiac C_{18} column	acetonitril (50 : 50)
Meruva, 2017	Phenylephrine, chlorpheniramine maleate, paracetamol, dextrometorphan	Reverse phase HPLC using C_8 column	Buffer phosphate (20 Mm) pH 6,6 : acetonitril (70 : 30)

Buffer mixtures with methanol or water with acetonitrile combined in the mobile phase are usually used in reverse phase chromatography (Rohman, 2012). In reverse phase HPLC, the mobile phase with more water can resulta longer retention time. When acetonitrile or methanol is mixed with water, it is much easier to control the analyte separation than if only water was used as the mobile phase.

Several studies have used phosphate buffer as a component of the mobile phase. The use of phosphate buffers is considered for pH modification. The position of the pH in an analyte, namely a weak acid or a weak base, is crucial because if the pH of the mobile phase is not adjusted, the analyte will undergo ionization or protonation. The bond of the analyte with the stationary phase can be weaker if it is ionized as a result of non-ionized. Ionized analytes can be eluted faster (Rohman, 2009). The phosphate buffer has pKa value of 2.1 and a pH range of 1.1 - 3.1, according to Kazakevich and Lobrutto (2007). The ability of a buffer to maintain a pH is known as buffer capacity, and is efficient within this pH range.

Based on the literature study, it can be concluded that the optimum conditions for the analysis of paracetamol, glyceryl guaiacholate, phenylpropanolamine HCl, dextromethorphan HBr and chlorpheniramine maleate using high performance liquid chromatography simultaneously generally use reversed phase. Where the stationary phase uses an octadecyl silica or C18 column, the mobile phase uses a mixture of phosphate buffer with methanol or acetonitrile. With a buffer concentration of 0.01 M and pH range 4 to 7. The flow rate is generally 1 ml/min and the detection wavelength is in

the range of 210-270 nm. From the optimum conditions, the retention time (tR) of paracetamol was 3-6 minutes, glyceryl guaiacolatewas 4-8 minutes, phenylpropanolamine HCl was 4-6 minutes, dextromethorphan HBr was 9-10 minutes and chlorpheniramine maleateewas 5-8 minutes.

Method Validation

After the system suitability test was done, the analysis method validation was done. The first validation parameter of the analytical method was done, namely the selectivity test. Selectivity testing was done to determine whether the method used was able to measure the analyte carefully and thoroughly after the addition of other components in the sample.

The validation parameter of the next analytical method is the accuracy test. An accuracy test was done to determine whether the analytical method used could provide closeness between the values obtained from the analysis results and the actual values. Accuracy is expressed as recovery, which is the quotient between the measured value and the actual value multiplied by 100% (Huber, 2007). Recovery requirements for a solution with a concentration of 10 ppm was 80-110% and a concentration of 100 ppm was 90-107% (Huber, 2007). According to (Sudjadi, 2007) which states that the condition for accuracy testing is to look at the relative standard deviation of the results of each measurement whose value was 2.00%.

The validation parameter of the next analytical method is repeatability precisiontest. Precision is the proximity of several measurement values from a homogeneous sample. An analytical method meets the criteria for precision accept anceif the relative standard deviation (RSD) in a solution containing an active substance with a concentration of 10 ppm was< 7.3% and 100 ppm was< 5.3% (Huber, 2007).

The next validation parameter test is linearity test. The linearity parameter was tested to determine the ability to obtain test results that are proportional to the analyte in the sample that used. Linearity is expressed in the form of a linear line between the analyte concentration and the area obtained from the measurement results. Then a calibration curve is made so that the linear equation $y = bx + a$ is obtained and the correlation coefficient (r) is calculated. The value (b) is the slope or slope that shows the magnitude of the change in the value of y as a result of changes in each unit of the value of x. The value (a) is the intercept which is the intersection point between the x-axis and the y-axis, if the value of x is zero, then

the value of y is equal to a. While the value (r) shows the correlation coefficient between the x-axis (concentration) and the y-axis (area). The acceptance requirement of linearity parameter testing is the correlation coefficient value (r) 0.997 (Chan et al., 2004).

The last parameter test is the sensitivity test which consists of LOD and LOQ. The LOD parameter was tested to determine the minimum limit of a substance that can still be detected but does not need to be quantified as an appropriate value using the HPLC analysis method. While the LOQ test is to determine the minimum limit of a substance that can still be detected quantitatively with acceptable accuracy and precision under the conditions of the analytical method used.

Table 3. Validation Parameters

Author	Sample	Mobile Phase	Validation Parameters
Siregar, 2018	Phenylephrine, paracetamol, glyceryl guaiacholat and chlorpheniramine maleate	Buffer phosphate pH 4,3 : methanol (60:40)	Selectivity, linearity, precision, LOD and LOQ
Rasal*et al.*, 2014	Chlorpheniramine maleate, phenylpropanolamine HCl and paracetamol	Methanol : buffer phosphate 0,01M pH 7 (70:30)	Selectivity, linearity, precision, LOD and LOQ
Al-Rimawi, 2010	Pseudofedrin HCl, dextrometorphan HBr, chlorpheniramine maleate and paracetamol	Methanol : buffer phosphate (90:10)	Selectivity, linearity, accuracy, precision
Acheampong *et al.*, 2016	Chlorpheniramine maleate, paracetamol and caffeine	Methanol : buffer phosphate 0,05 M pH 4,0 (30:70)	Selectivity, linearity, accuracy, precision, LOD and LOQ

Conclusion

The results of the literature review analysis of paracetamol, glyceryl guaiacholate, phenylpropanolamine HCl, dextromethorphan HBr and chlorpheniramine maleate simultaneously with high performance liquid chromatography, can be concluded that:

First, paracetamol, glyceryl guaiacholate, phenylpropanolamine HCl, dextromethorphan HBr and chlorpheniramine maleatee were simultaneously analyzed by High Performance Liquid Chromatography.

Second, the optimum conditions for the analysis of paracetamol, glyceryl guaiacholate, guaiacholatewas 4-8 minutes, phenylpropanolamine HCl was 4-6 minutes, dextromethorphan HBr was 9-10 minutes and chlorpheniramine maleateewas 5-8 minutes.

Third, the simultaneous analysis of paracetamol, glyceryl guaiacholate, phenylpropanolamine HCl, dextromethorphan HBr and chlorpheniramine maleate using the High Performance Liquid Chromatography method that qualified the validation parameters, namely selectivity, accuracy, precision, linearity, LOD and LOQ.

Suggestion

It is necessary to develop a simultaneous analytical method to determine drug levels containing more than one compound.

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