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# Chemometrics-assisted content uniformity evaluation of extemporaneous preparation containing ambroxol HCl, pseudoephedrine HCl, and triprolidine HCl

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**ABSTRACT**: Split powder preparations containing ambroxol HCl, pseudoephedrine HCl, and triprolidine HCl were frequently dispensed at a private hospital in Semarang, Central Java, Indonesia. Triprolidine HCl was reported to have a low composition in the divided powder. Content uniformity is one of the most important characteristics of extemporaneous formulations, especially for low-dose active ingredients. The aim of this study was to evaluate the dose uniformity of the divided powder preparation containing ambroxol HCl, pseudoephedrine HCl, and triprolidine HCl prepared by a pharmacist in a private hospital in Semarang, Central Java, Indonesia. In this study, the spectrophotometric method was used in combination with the chemometric analysis to determine the drug concentration in the divided powder. The accuracy of the models was evaluated by the highest value of the coefficient of determination of calibration, cross-validation and validation, while the precision of the models was evaluated by the lowest value of the mean square error of calibration, cross-validation and prediction. The selected model for each compound was used to build predictive models for quantitative analysis. It was found that the content of ambroxol HCl, pseudoephedrine HCl, and triprolidine HCl in the subdivided powder samples were 8.120 ± 1.167 mg, 30.142 ± 3.965 mg, and 1.193 ± 0.221 mg, respectively. The results on the uniformity of the content did not meet the requirements, as it was found that the coefficient of variance of these determinations was more than 5%. Surprisingly, the divided powder can be considered as a safe and acceptable dosage form due to its wide therapeutic window.

**KEYWORDS**: Ambroxol HCl; pseudoephedrine HCl; triprolidine HCl; divided powder; quality.

## 1. INTRODUCTION

Extemporaneous preparation was still needed especially for pediatric patient since the license drug for pediatric was limited [1]. Many problems have been identified in the formulation of pediatric medicines [2]. Extemporaneous preparation for children were unique due to their physical and chemical properties. Pharmacists must ensure that the quality of the drug, especially its stability and tolerability, is met. [3]. The lack of information on stability, bioavailability, pharmacodynamics, pharmacokinetics, effectiveness and safety data makes it important to develop an appropriate pediatric therapeutic formulation [4]. Hence, it is important to guarantee the safety, efficacy and quality of extemporaneous preparation in the community service.

The quality of extemporaneous preparation can be recognized by its appearance, uniformity of active ingredient, stability of active ingredient, and compatibility between active ingredient and excipient [5,6]. The manipulation to the license drug during extemporaneous preparation will change the specification of the drug including the stability of the active ingredient in the dosage forms [7]. The incompatibility of the other active ingredient was also unknown [8,9]. The compatibility between active ingredient and active ingredient-excipient will affect the dose of the drug in the preparation and potentially impact the safety and effectiveness of the pharmaceutical dosage form [10,11].

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Extemporaneous preparation of divided powder is still widely used in Indonesia, especially for pediatric patient. The mixture of ambroxol hydrochloride (HCl), pseudoephedrine hydrochloride (HCl), and triprolidine hydrochloride (HCl) is high frequency drug combination to treat cough in the pediatric patient. Ambroxol is found in numerous over-the-counter dosage forms as a mucolytic agent [12]. A study engaging 1300 pediatric patients indicated that ambroxol is well tolerated, even in the early infant for acute and chronic respiratory disease [13]. On the other hand, pseudoephedrine and triprolidine are frequently formulated as a combination dosage form. Pseudoephedrine is considerably safe as a nasal decongestant among children aged 6 to <12 years with the common cold [14,15]. Triprolidine HCl is the first generation of antihistamine indicated for allergic rhinitis [16]. The previous study observing the pharmacokinetic of triprolidine in the combination of triprolidine and pseudoephedrine reported that the level of triprolidine was higher in combination than in single agents [17]. However, the dosage variant increases the risk of under- or overdosing of the individual components. Remarkably, the combination of antihistamine and decongestant in children increase dystonic reaction and sympathomimetic toxicity [18–20].

Children are vulnerable patients. The limited communication with patient may lead to the adverse effect of the treatment they receive [7]. The problems that are often encountered in the preparation of compound pediatric preparations are achieving dose uniformity [21]. Hence, it is necessary to study the quality of the extemporaneous preparation of divided powder containing ambroxol HCl, Pseudoephedrine HCl and Triprolidine HCl. The quality in this study was defined as the uniformity of active ingredient during administration of the preparation.

Chemometric, a combination of mathematical and statistical techniques to solve several problems in chemistry, was stated as a powerful tool to predict and classify drug concentration in pharmaceutical formulas [22,23]. Previous study proved that chemometrics techniques were successfully applied for determining the content of paracetamol and tramadol concentration divided powder dosage form [24]. The other study revealed that the combination of UV spectroscopic techniques and chemometrics was a favorable tool to predict the concentration of acetaminophen, caffeine, and propyphenazone in tablet samples [25]. Ultraviolet (UV) spectroscopic method and chemometrics techniques allowed a rapid and efficient analytical stage to be developed, compared to the other analytical technique such chromatographic method which requires more stages to separate one analyte from the others with the similar sample matrices [26-28]. A fast, simple and effective method was developed for pharmaceutical analysis by combining UV spectroscopic technique and chemometrics of multivariate calibration in order to determine the content of ambroxol HCl, pseudoephedrine HCl and triprolidine HCl in extemporaneous preparation of divided powder.

## 2. RESULTS

Drug combination composed by ambroxol HCl, pseudoephedrine HCl and triprolidine HCl were commonly prescribed for pediatrics in a private hospital in Semarang, Central Java, Indonesia. Since it was important to maintain patient obedience, divided powders containing ambroxol HCl, pseudoephedrine HCl, and triprolidine HCl were prescribed for children. Tablets of ambroxol HCl were compounded with commercial tablets containing pseudoefedrin HCl of 60 mg and triprolidine HCl of 2.5 mg to produce divided powders for pediatric patients. The potential interaction between drug and excipient may have occurred during the preparation of the dosage form. Uniformity of drug content plays an important role for good quality of therapy.

The multivariate calibration techniques were implemented in this study. Two multivariate calibration models namely principal component regression (PCR) and partial least square (PLS) were applied as chemometrics techniques to build predictive models for amboxol HCl, pseudoephedrine HCl, and triprolidine HCl. Spectral preprocessing of the UV spectroscopic data was carried out to achieve various types of spectra including original, first derivative, second derivative, standard normal variate (SNV), and Savitzky-Golay(SG). The accuracy of the models was assessed by evaluating the highest value of coefficient of determination ($R^2$) including coefficient of determination of calibration ($Rcal^2$), coefficient of determination of cross validation ($RCV^2$), and coefficient of determination of validation ($Rval^2$), whereas the precision of the models were assessed by evaluating the lowest value of root mean square error of calibration (RMSEC), root mean square error of cross validation (RMSECV), and root mean square error of prediction(RMSEP). Performance of the multivariate calibration models are presented in Table 1.

**Table 1.** The performance of PCR and PLS for predicting the content of ambroxol HCl, pseudoephedrine HCl, and triprolidine HCl

| Analytes | Multivariate calibration | Types of spectra | Number of components | $R_{cal}^2$ | RMSEC | $R_{CV}^2$ | RMSECV | $R_{val}^2$ | RMSEP |
|---|---|---|---|---|---|---|---|---|---|
| AMB | PCR | Original | 2 | 0.989 | 0.500 | 0.986 | 0.574 | 0.992 | 0.578 |
| | | First derivative | 2 | 0.991 | 0.463 | 0.987 | 0.549 | 0.993 | 0.512 |
| | | **Second derivative** | **8** | **0.994** | **0.366** | **0.988** | **0.535** | **0.993** | **0.543** |
| | | SNV | 9 | 0.970 | 0.837 | 0.938 | 1.202 | 0.969 | 1.110 |
| | | SG | 2 | 0.989 | 0.502 | 0.986 | 0.576 | 0.992 | 0.581 |
| | PLS | Original | 2 | 0.989 | 0.500 | 0.986 | 0.574 | 0.992 | 0.577 |
| | | First derivative | 2 | 0.991 | 0.463 | 0.987 | 0.550 | 0.993 | 0.512 |
| | | Second derivative | 2 | 0.992 | 0.451 | 0.986 | 0.566 | 0.994 | 0.504 |
| | | SNV | 4 | 0.958 | 0.997 | 0.932 | 1.262 | 0.952 | 1.383 |
| | | SG | 2 | 0.989 | 0.502 | 0.986 | 0.576 | 0.992 | 0.581 |
| PSE | PCR | Original | 11 | 0.955 | 1.415 | 0.891 | 2.197 | 0.965 | 1.106 |
| | | First derivative | 16 | 0.972 | 1.120 | 0.833 | 2.721 | 0.896 | 1.892 |
| | | Second derivative | 24 | 0.992 | 0.596 | 0.780 | 3.127 | 0.287 | 4.959 |
| | | SNV | 7 | 0.868 | 2.425 | 0.760 | 3.265 | 0.805 | 2.595 |
| | | **SG** | **8** | **0.952** | **1.467** | **0.902** | **2.089** | **0.919** | **1.669** |
| | PLS | Original | 5 | 0.951 | 1.471 | 0.892 | 2.188 | 0.974 | 0.940 |
| | | First derivative | 5 | 0.970 | 1.154 | 0.830 | 2.747 | 0.894 | 1.908 |
| | | Second derivative | 3 | 0.845 | 2.621 | 0.765 | 3.230 | 0.887 | 1.975 |
| | | SNV | 5 | 0.883 | 2.277 | 0.720 | 3.525 | 0.802 | 2.613 |
| | | SG | 7 | 0.957 | 1.388 | 0.897 | 2.142 | 0.901 | 1.849 |
| TRP | PCR | Original | 2 | 0.992 | 0.263 | 0.990 | 0.289 | 0.938 | 0.608 |
| | | First derivative | 14 | 0.996 | 0.192 | 0.985 | 0.348 | 0.926 | 0.667 |
| | | Second derivative | 4 | 0.985 | 0.359 | 0.975 | 0.455 | 0.929 | 0.652 |
| | | SNV | 4 | 0.943 | 0.693 | 0.914 | 0.850 | 0.882 | 0.844 |
| | | SG | 2 | 0.992 | 0.263 | 0.990 | 0.289 | 0.939 | 0.608 |
| | PLS | Original | 2 | 0.992 | 0.263 | 0.990 | 0.289 | 0.938 | 0.608 |
| | | First derivative | 3 | 0.990 | 0.283 | 0.985 | 0.348 | 0.933 | 0.635 |
| | | Second derivative | 2 | 0.984 | 0.362 | 0.976 | 0.448 | 0.931 | 0.642 |
| | | SNV | 4 | 0.944 | 0.682 | 0.913 | 0.852 | 0.884 | 0.834 |
| | | **SG** | **2** | **0.992** | **0.263** | **0.990** | **0.289** | **0.939** | **0.608** |

Note: Selected model of calibration for each compound were marked with bold. AMB: ambroxol HCl; PSE: pseudoephedrine HCl; TRP: triprolidine HCl; PCR: Principal Component Regression; PLS: Partial Least Squares; SNV: Standard Normal Variate; SG: Savitzky-Golay smoothing with polynomial order of 3 and window width of 11 points.

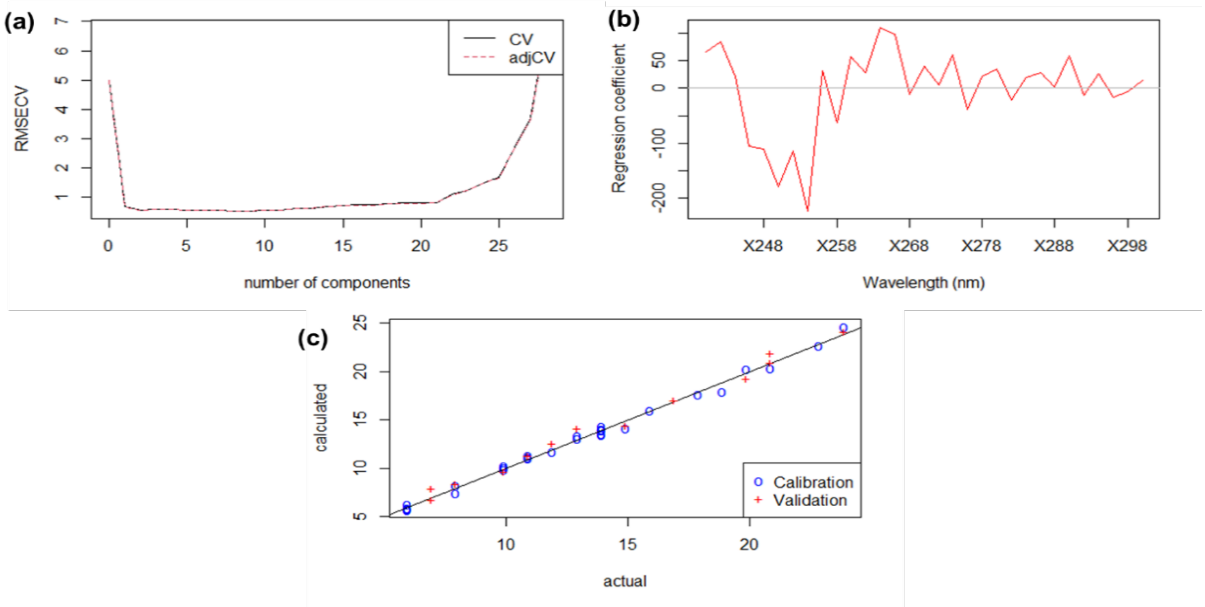


**Figure 1**. Variable selection plot (a), regression coefficient plot (b), and multivariate calibration plot (c) of ambroxol HCl

According to the data presented in Table 1, it was obtained that the selected model for ambroxol HCl was PCR model on second derivative spectra with the $Rcal^2$, $RCV^2$ and $Rval^2$ were 0.994, 0.988, and 0.993, respectively. The error of the model was expressed from the RMSEC, RMSECV, and RMSEP with the value of 0.366, 0.535, and 0.543, respectively. Multivariate predictive equation for ambroxol HCl was y = 1.002x - 0.386. The variable selection plot, regression coefficient plot, and multivariate calibration plot of ambroxol HCl were depicted in Figure 1.

The selected model for pseudoephedrine HCl was PCR model on SG spectra with the $Rcal^2$, $RCV^2$ and $Rval^2$ were 0.952, 0.902, and 0.919, respectively. The error of the model was expressed from the RMSEC, RMSECV, and RMSEP with the value of 1.467, 2.089, and 1.669, respectively. Multivariate predictive equation for pseudoephedrine HCl was y = 1.078x - 3.832. The variable selection plot, regression coefficient plot, and multivariate calibration plot of pseudoephedrine HCl were depicted in Figure 2.

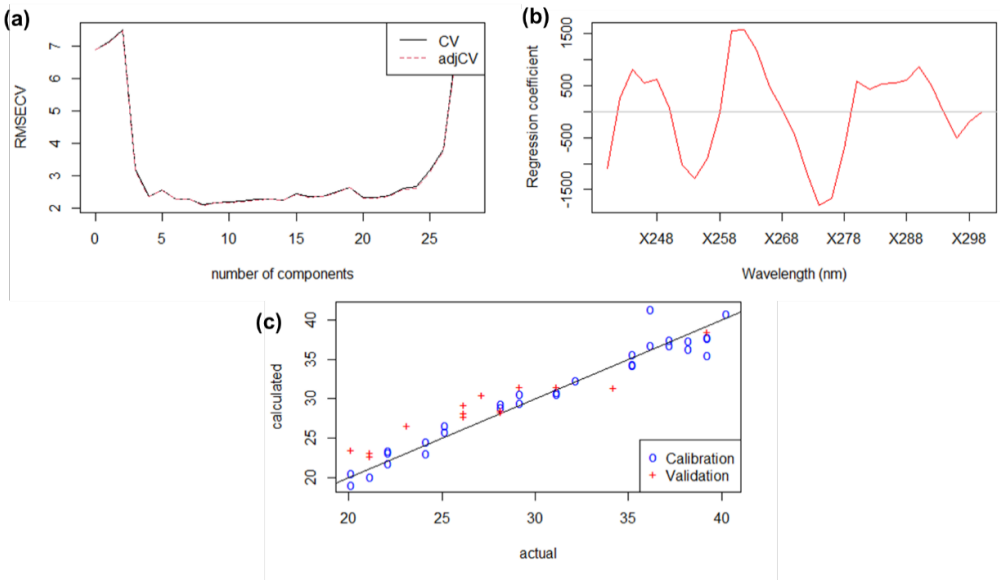


**Figure 2.** Variable selection plot (a), regression coefficient plot (b), and multivariate calibration plot (c) of pseudoephedrine HCl

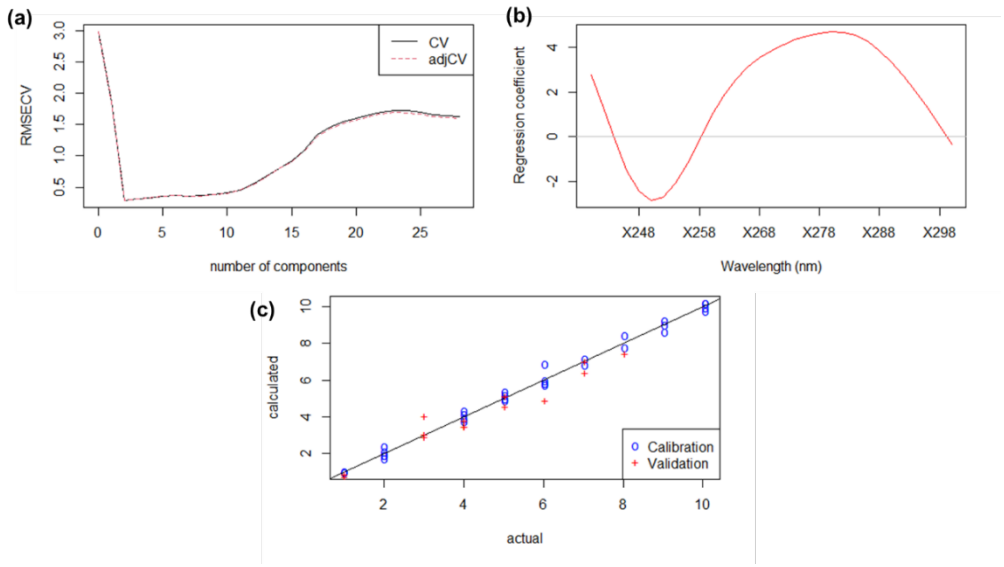


**Figure 3.** Variable selection plot (a), regression coefficient plot (b), and multivariate calibration plot (c) of triprolidine HCl

The selected model for triprolidine HCl was PLS model on SG spectra with the $Rcal^2$, $RCV^2$ and $Rval^2$ were 0.992, 0.990, and 0.939, respectively. The error of the model was expressed from the RMSEC, RMSECV, and RMSEP with the value of 0.263, 0.289, and 0.608, respectively. Multivariate predictive equation for triprolidine HCl was y = 0.8906x + 0.636. The variable selection plot, regression coefficient plot, and multivariate calibration plot of tripolidine HCl were depicted in Figure 3.

## 3. DISCUSSION

Aided by the selected models for ambroxol HCl, pseudoephedrine HCl, and triprolidine HCl, the content uniformity of the samples was evaluated. The sample used in this study were compounded to the target content of 10 mg, 30 mg, and 1.25 mg for ambroxol HCl, pseudoephedrine HCl, and triprolidine HCl, respectively. Content of ambroxol HCl, pseudoephedrine HCl, and triprolidine HCl found in divided powder samples were 8.120±1.167 mg, 30.142±3.965 mg, and 1.193±0.221 mg, respectively. Graphical results of content uniformity were presented in Figure 4.

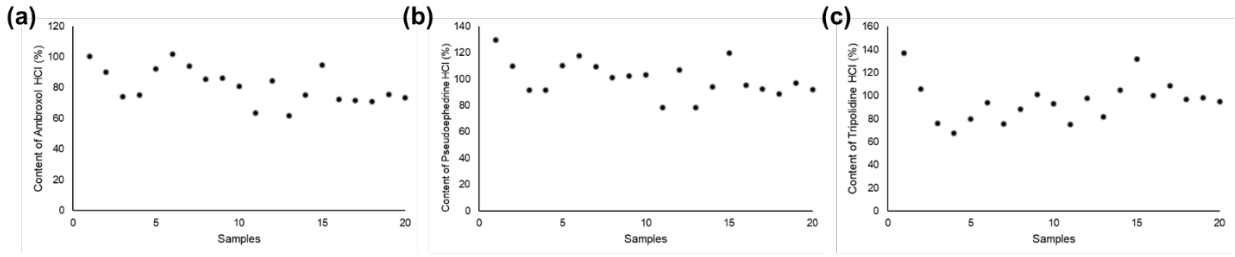


**Figure 4.** Content uniformity evaluation for ambroxol HCl (a), pseudoephedrine HCl (b), and triprolidine HCl (c)

The coefficient of variance for percentage content uniformity of ambroxol HCl, pseudoephedrine HCl, and triprolidine HCl, were 14.002%, 12.822%, and 18.094%, respectively. Pharmaceutical dosage form was stated to have dose uniformity only if the variance of the content was less than 5 % [29]. The coefficient of variance for triprolidine HCl was found in the highest percentage compared to ambroxol HCl and pseudoephedrine HCl. The small amount of triprolidine HCl in the combination of dose may increase the random error of compounding due to the high variance of the samples. Both underdose and overdose therapies are possible if the dose of the active ingredient is present in the sample at the different concentration. However, ambroxol HCl was reported as a well-tolerated drug with low risk of adverse effects even when it was received in higher therapeutic dose [30]. The highest amount of pseudoephedrine HCl found in the sample was 38.90 mg (129.678%). It can be assumed that the maximum daily dose of pseudoephedrine HCl was 116.70 mg since the divided powder has been prescribed for three times a day. The maximum permissible daily dose of pseudoephedrine HCl was 120 mg for children aged 6–12 years [15]. Thus, it can be stated that in the overdose content obtained from the sample, the potential toxicity can be avoided with the consideration of daily dose administration.

## 4. CONCLUSION

Drug combination of mucolytic agent, nasal decongestant, and antihistamine were commonly prescribed for pediatric patients. In a private hospital in Semarang, Central Java, Indonesia, combination of drugs including ambroxol HCl, pseudoephedrine HCl, and triprolidine HCl were frequently prescribed as extemporaneous preparation in the form of divided powder. It was important to ensure the content uniformity of the divided powder in order to enhance the quality of the therapy given. UV spectroscopy method combined with chemometrics techniques were applied to determine content uniformity of the samples. The best predictive models for each compound were selected along with the evaluation of accuracy and precision of the models.

Content uniformity was evaluated from the sample of divided powders. It was found that the coefficient of variance (CV) for percentage content uniformity of ambroxol HCl, pseudoephedrine HCl, and triprolidine HCl, were 14.002%, 12.822%, and 18.094%, respectively. It can be assumed that the sample of divided powders compounded by pharmacist in private hospital did not meet the requirements of content uniformity since the percentage of coefficient of variance were more than 5%. However, the daily doses of therapy of ambroxol HCl, pseudoephedrine HCl, and triprolidine HCl were still in the safety therapeutic range. Pharmacists are strongly encouraged to improve their knowledge and skills in the practice of compounding in order to provide patient-centered health care services.

## 5. MATERIALS AND METHODS

### 5.1. Materials

Materials used in this study were working standard of ambroxol HCl obtained from PT. Ifars Pharmaceutical Laboratories (Surakarta, Central Java, Indonesia), pseudoephedrine HCl and triprolidine

HCl working standards obtained from PT. Dexa Medica (Palembang, South Sumatra, Indonesia). Samples of divided powders were compounded by pharmacist in a private hospital in Semarang, Central Java, Indonesia. These samples were compounded from the ambroxol HCl tablet mixed with Alerfed® tablets containing pseudoephedrine HCl and triprolidine HCl.

### 5.2. Instrumentation and Software

The UV-Vis Spectrophotometer type UV 1800 (Shimadzu, Japan) with a set of quartz cuvette 1 cm (Hellma, USA), analytical balance of OHAUS® (China) series of PA224C, and a set of Socorex®(Switzerland) micropipettes were used in this study. The UV spectral data were exported to Excel (Microsoft, USA) and converted into .csv formatted files for further data processing. Statistical analysis and multivariate calibrations were performed using R software version 1.4.1717 with "pls" and "prospectr" packages.

### 5.3. Methods

#### *5.3.1. Sample Preparation*

Samples used in this study were divided powder containing ambroxol HCl and commercial tablet (containing pseudoefedrin HCl of 60 mg and triprolidine HCl of 2.5 mg) that prepared by pharmacist in a private hospital in Semarang, Indonesia. This study was approved by the Health Research Ethics Committee of Faculty of Health Science, Universitas Respati Yogyakarta (220.3/FIKES/PL/X/2021). The formula of the divided powder was prescribed as follow:

R/ Ambroxol HCl 30 mg 1/3 tab
Alerfed® ½ tab
Mf. Pulv. dtd no.X

The preparation of divided powder was triplicated, hence a total of 30 dose units were obtained.

#### *5.3.2. Calibration and Validation Solutions*

An accurate weight of 10.0 mg of ambroxol HCl, pseudoephedrine HCl and triprolidine HCl were transferred into three separated 10 mL volumetric flasks for each compound followed by dilution with methanol into the volume. These solutions were labeled as ambroxol HCl, pseudoephedrine HCl and triprolidine HCl stock solution.

Calibration and validation set solutions were prepared by mixing synthetic combination of ambroxol HCl, pseudoephedrine HCl and triprolidine HCl from the stock solutions to obtain 45 compositions of standards solution mixture as presented in Table 2. Each composition was scanned using spectroscopic method at the range of 240-300 nm. The absorbance for each composition were recorded with the interval of 2 nm. The obtained absorbance data for each wavelength were assigned randomly and used for building calibration and validation models.

**Table 2.** Calibration and validation data sets information for developing multivariate calibration models of ambroxol HCl, pseudoephedrine HCl and triprolidine HCl

| Items | Data sets | |
|---|---|---|
| | Calibration | Validation |
| Number of mixture standards | 30 | 15 |
| Ambroxol HCl Concentration (µg/mL) | | |
| Mean | 12.953 | 14.312 |
| Range | 5.96 – 23.85 | 4.97 – 24.85 |
| Pseudoephedrine HCl Concentration (µg/mL) | | |
| Mean | 30.750 | 28.101 |
| Range | 20.12 – 40.24 | 20.12 – 40.24 |
| Triprolidine HCl Concentration (µg/mL) | | |
| Mean | 5.672 | 4.766 |
| Range | 1.01 – 10.07 | 1.01 – 10.07 |
| Multivariate calibration models | PCR | PCR |
| | PLS | PLS |
| Evaluated parameters for model selection | $R^2$ | $R^2$ |
| | RMSEC | RMSEP |
| | RMSECV* | |

Note: * cross validation was performed using leave one out technique

#### *5.3.3. Multivariate Calibration Analysis*

Absorbance data of calibration and validation set solutions were preprocessed into five types of spectra namely normal/original, first derivative, second derivative, SNV, and SG smoothing (window width

of 11 points, polynomial order of 3). Multivariate calibration models namely PCR and PLS were built for ambroxol HCl, pseudoephedrine HCl and triprolidine HCl. The generated multivariate calibration models were statistically evaluated by assessing several performances such as $R^2$, RMSEC, RMSECV, and RMSEP. The selected model for each compound was identified by evaluating the highest value of $R^2$ (near 1) and lowest value of RMSEC, RMSECV, and RMSEP [28].

*5.3.4. Content Uniformity Evaluation*

Selected multivariate calibration model for each compound were used to evaluate the content uniformity of the active pharmaceutical ingredients namely ambroxol HCl, pseudoephedrine HCl, and triprolidine HCl. The actual value of the content was calculated by plotting the predictive value obtained from the multivariate calibration model. Content of ambroxol HCl, pseudoephedrine HCl and triprolidine HCl from twenty samples of divided powders were determined. The mass of each compound was calculated as well as their standard deviation. The percentage of the content was also determined and presented as graphical chart to visually observe the variance occurred in each dose.

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