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Research Article

Quality of Extemporaneous Preparation Containing Theophylline, Salbutamol Sulphate and Methylprednisolone

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ABSTRACT

Capsule preparations containing theophylline, salbutamol sulfate, and methylprednisolone were frequently prescribed in a private hospital in Yogyakarta. Theophylline is a narrow therapeutic index drug. Extemporaneous preparation products that contain narrow therapeutic index drugs have to meet the quality requirement. This study aimed to evaluate the quality of the capsule preparations. The sample was taken from a private hospital in Yogyakarta. The samples were assessed for physical characteristics, content uniformity, and chemical stability during storage. The result found that the physical characteristics of the product were good. The coefficients of variance of the content uniformity percentage for theophylline, salbutamol sulfate, and methylprednisolone were 11.96%, 3.33%, and 45.74%, respectively. During 30 days of storage, the content of theophylline, salbutamol sulfate, and methylprednisolone decreased by 1.44%, 7.64%, and 15.7%, respectively. Capsule preparations containing theophylline, salbutamol sulfate, and methylprednisolone did not meet the quality requirement.

INTRODUCTION

Extemporaneous preparation products were still in high demand, particularly for medicines that were not available on the market (Yuliani et al., 2020a). The healthcare professionals responsible for the quality of extemporaneous preparation products are pharmacists (Gani et al., 2022). The appearance of the product, active ingredient uniformity, active ingredient stability, and compatibility are the parameters of the quality of extemporaneous preparation products (Naveed et al., 2017; Riswanto et al., 2017). A previous study stated that the compounding process leads to an increase in the risk of instability of active ingredients (Yuliani et al., 2020b). The information about incompatibility between the active ingredient and the active ingredient excipient was limited. The interaction between the active ingredient and another compound in the mixture will influence the dose of the drug. It may affect the efficacy and safety of the extemporaneous preparation products (Narang et al., 2012; Panakanti and Narang, 2012; Yuliani et al., 2022, 2020b).

The quality of the extemporaneous preparation product is determined by the stability of the active ingredient, which is measured by the concentration in the dosage forms (Bajaj et al., 2012). Drug-excipient interaction can lead to instability of the product as well as the environment (Darji et al., 2017; De Winter et al., 2013; Narasimha Murthy and Repka, 2017). Drug-excipient interaction should be considered in the selection of excipients added in the compounding preparation to avoid instability events (Dave et al., 2015). Inappropriate storage temperatures may influence the physical and chemical stability of drug products (De Winter et al., 2013).

This study was concerned with capsule preparations containing theophylline, salbutamol sulfate, and methylprednisolone. The prevalence of capsule preparation is not high in practice compared with the divided powder (Kristina et al., 2018). However, this capsule preparation is the most frequently prescribed in a private hospital in Yogyakarta, given to an adult patient with allergic rhinitis. According to Ezeamuzie and Shihab (2010), there is no clinical interaction between theophylline and salbutamol. The combination of theophylline and methylprednisolone results in a positive effect on the respiratory system (Yuzkat et al., 2016). Theophylline is a narrow therapeutic drug (Handiana and Indriyati, 2018). On the other hand, the inappropriate concentration of salbutamol can lead to electrolyte disturbance. Therefore, the compounding preparation of the capsules containing theophylline, salbutamol sulfate, and methylprednisolone should be able to ensure their quality in terms of efficacy and safety. Previous studies indicated that the content uniformity of extemporaneous preparation products is not matched to the requirement (Gani et al., 2022; Yuliani et al., 2022). In the case of the capsule preparation of theophylline, the concentration of the active ingredient in each capsule should be uniform according to its narrow therapeutic index. A high variation in theophylline content may cause harm to the patient. For these reasons, a study about the quality of capsule preparations containing theophylline, salbutamol sulfate, and methylprednisolone has to be done.

METHODS

Materials

The materials used in this study were theophylline powder (PT Brataco), salbutamol sulfate tablet 4 mg (PT. Yarindo), methylprednisolone tablet 4 mg (PT. Yarindo), theophylline WS 100% (PT Dexa Medika), salbutamol sulfate WS 100,3% (PT Dexa Medika), methylprednisolone WS 100,2% (AVIK Pharmaceutical), and methanol p.a. (Smartlab Indo).

Instrumentations

Shimadzu Spectrophotometer UV-Visible 1800 type, cuvette, personal computer (HP), Minitab 19, Excel 2019, Moisture analyzer (Kern MLS), Disintegration tester (Shanghai Develop Machinery BJ-2), analytical balance 0.0001 (Pioneer), micropipette (Socorex) 0,5-10 µL, 10-100 µL, 20-200 µL, dan 100-1000µl; blue and yellow tip (Biologic), droplet pipette; beaker glass (Pyrex); volumetric flask (Pyrex) 5 mL, 10 mL, dan 25 mL; glass funnel (Pyrex), filter paper (Whatman) no 41, mortar and stamper.

Preparation of sample for quality test

The samples tested in this study were capsules with the active substances theophylline, salbutamol sulfate, and methylprednisolone, which were prepared at the pharmacy department at a private hospital in Yogyakarta with the following prescription:

R/ Pulvis theophylline 3.9 g
Salbutamol tab 4 mg 15 Tab
Methylprednisolone 4 mg 30 Tab
m.f Caps no 60
S b dd 1 Caps

Ten capsules were used for the physical appearance test, 12 capsules for the disintegration time test, 6 capsules for the moisture content test, and 30 capsules for the content uniformity test.

Preparation sample for stability test

The samples were prepared by weighing 65 mg of theophylline powder, crushing and weighing tablets of salbutamol equivalent to 1 mg, and tablets of methylprednisolone equivalent to 2 mg. The three substances were mixed to make one capsule. Twenty capsules for the stability study were obtained by repeating the procedure.

Physical Characteristic test

The physical characteristic test is done by observing the physical appearance and measuring the moisture content and disintegration time of the capsule. The physical appearance of the capsule is determined by visual observation, while moisture content and disintegration time are determined by the moisture balance and disintegration tester, respectively.

Preparation of calibration and validation solution

Twenty-five solutions of the calibration series and nine series of validation were prepared by making a standard solution for each substance. The standard solution was made by diluting 10.0 mg of each working standard substance with 10.0 mL of methanol. Calibration and validation set solutions were created by combining synthetic combinations of theophylline, salbutamol sulfate, and methylprednisolone from standard solutions to create 35 different standard solution mixture

compositions, as shown in Table 1. The absorbance of 25 solutions of the calibration series and 10 validation series was measured using a UV-Vis spectrophotometer with a wavelength range of 200–400 nm and a selected measurement interval of 2 nm. All of the absorbance values were collected and processed using R statistical software 4.1.2.

Uniformity test

The net weight of the capsule contents was calculated by subtracting the weight of the capsule shell from the gross weight of each capsule. Each capsule powder was put into 10 different 25 mL volumetric flasks, then dissolved using methanol, diluted to the mark, and then the solution was filtered using filter paper. Each sample solution was pipetted as much as 125 µL into a different 5 mL volumetric flask, then diluted with methanol to the mark. The absorption value was read using a UV-VIS spectrophotometer, with a wavelength of 200-400 nm and a measurement interval of 2 nm.

Stability test

The sample was put into three different 25-mL volumetric flasks, then dissolved using methanol, diluted to the mark, and then the solution was filtered using filter paper. Each sample solution was pipetted as much as 125 µL into a different 5 mL volumetric flask, then diluted with methanol to the mark. The absorption values were read using a UV-VIS spectrophotometer and an HP computer set, with a wavelength of 200–400 nm and a measurement interval of 2 nm.

RESULTS AND DISCUSSION

Physical Characteristic

The organoleptic test on the first and 30th days showed that all samples had white powder, crystalline powder, and hard capsules and were well preserved (Table 2). There was no odor in all the samples. The organoleptic stability of the blended capsules during the storage period indicated that the powder in the capsules was physically stable because they could maintain their physical form.

Table 1. A Series of calibration and validation solutions

No	Calibration solution series (ppm)			Validation solution series (ppm)		
	Theophylline	Salbutamol sulphate	methylprednisolone	Theophylline	Salbutamol sulphate	methylprednisolone
1.	140	1.8	4.6	151	1.8	2.8
2.	36	0.6	2.4	64	1.4	2.6
3.	135	2.0	3.6	57	1.4	1.8
4.	161	2.0	3.2	84	1.6	2.6
5.	124	1.8	2.4	67	1.6	2.0
6.	128	1.8	4.2	100	1.8	3.2
7.	148	1.4	3.2	79	1.6	1.0
8.	69	0.6	4.8	91	1.4	3.4
9.	49	1.2	2.2	142	2.0	3.6
10.	82	1.6	2.2	101	1.8	2.6
11.	61	1.6	1.8			
12.	54	1.4	2.0			
13.	156	1.8	2.2			
14.	134	1.8	2.8			
15.	153	1.6	3.2			
16.	48	1.4	1.2			
17.	157	2.0	3.6			
18.	158	1.8	4.2			
19.	41	1.2	1.6			
20.	114	1.6	1.6			
21.	121	1.8	3.4			
22.	93	1.4	3.6			
23.	98	1.8	3.4			
24.	140	1.8	3.8			
25	59	1.2	2.8			

All of the capsules met the requirements for the moisture content of the preparation, which was less than 5% (Table 2). Moisture content increases on the day of the 30th. Drugs in the form of salt pick up moisture more easily than the parent form. There was an increase of 0.5 percent in moisture content during storage. The increasing moisture content may lead to interactions between capsule preparations and water molecules in the storage environment and affect the stability of the active ingredient (Armstrong et al., 2014).

The capsule preparation is declared to meet the disintegration time test requirements if the hard capsule can completely disintegrate within 15 minutes. The preparation is declared to be disintegrated if the remaining preparation left on the gauze of the test instrument is a soft mass with no clear core (Ministry of Health of the Republic of Indonesia, 2020). Table 2 showed that the capsule preparations containing theophylline, salbutamol sulfate, and methylprednisolone meet the disintegration time requirements for solid oral dosage forms. Results showed no change in capsule disintegration time during storage.

Calibration and Validation Model

Table 3 shows the RMSEC value and the R^2 value. A good RMSEC value closer to 0, or smaller, may result in a smaller error rate in predicting the model (Utami, Ryandita, and Sundhani, 2019). The RMSEC value of theophylline is 0.3227, the RMSEC value of salbutamol sulfate is 0.0877, and the RMSEC value of methylprednisolone is 0.1135. In the calibration model, the R^2 value is obtained where a good value is close to 1 (Riswanto et al., 2021). The coefficient of determination of calibration (R_{cal}^2) value on theophylline calibration is 0.9999, the $Rcal^2$ value of salbutamol sulfate is 0.9125, and the R_{cal}^2 value of methylprednisolone is 0.9847. Table 3 shows the R_{pred}^2 values of theophylline, salbutamol sulfate, and methylprednisolone have good values because they are close to 1. The good PRESS (predictive residual error sum of squares) value is smaller. The PRESS values obtained by theophylline, salbutamol sulfate, and methylprednisolone were already the most optimal values obtained.

Table 2. Physical characteristics of an extemporaneous preparation capsule

Physical Characteristics	Day 1	Day 30
Physical appearance	Color : white Shape : hard Smell: no smell	Color : white Shape : hard Smell: no smell
Moisture content (%)	3,80± 0.03	4.33± 0.11
Disintegration Test	completely destroyed preparations	completely destroyed preparations

Table 3. Results of Calibration and Validation Multivariate

Analytes	Calibration					Validation	
	$Rcal^2$	RMSEC	$Rpred^2$	PRESS	RMSECV	$Rval^2$	RMSEP
Theopylline	0.9999	0.3227	0.9977	200.17	0.9955	0.9923	2.5914
Salbutamol	0.9125	0.0877	0.9555	0.3194	0.9071	0.9182	0.0618
Methylprednisolone	0.9847	0.1135	0.9870	1.6763	0.9274	0.9280	0,1542

Table 4. Chemical Stability Testing of an Extemporaneous Preparation Capsule

Analyte	Day 1 (%w/w)	Day 30 (%w/w)	Degradation (%w/w)
Theophylline	90.42 ± 0.99	88.98 ± 1.02	1.44
Salbutamol	164.78 ± 14.99	157.14 ± 4.18	7.64
Methylprednisolone	103.77 ± 10.69	87.98 ± 1.35	15.79

*X±SD, X is the average of 3 time measurements.

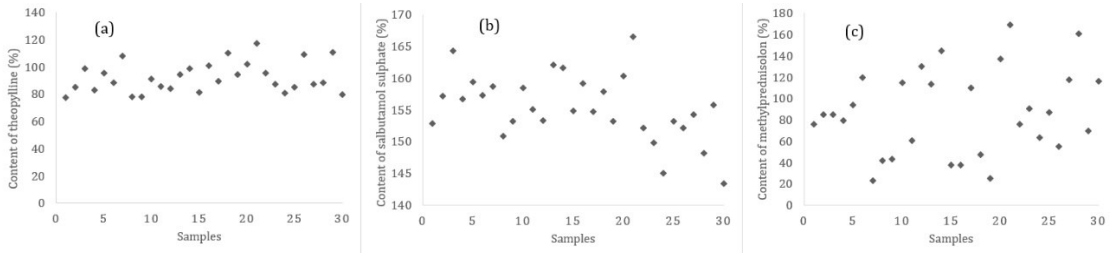


Figure 1. The result of content uniformity test of theophylline (a), salbutamol sulfate (b), and methylprednisolone (c).

Table 3 shows the validation results of the multivariate calibration model as indicated by the coefficient of determination calibration (R_{cal}^2) and the RMSEP (Root Mean Square Error of Prediction) value. The coefficient value (R_{cal}^2) of the determination obtained is close to 1, which indicates that the multivariate calibration model can predict well. The RMSEP value is said to be good if the value is close to 0. The RMSEP value obtained in the model validation can be said to be good because it is close to 0.

Content Uniformity

The content uniformity of each active ingredient was determined by the multivariate calibration models of each substance. The content of the active ingredients was expressed as the percentage of the levels that should be in the capsule. The variance in each dose of each active ingredient in the capsule is presented in Figure 1.

The theophylline, salbutamol sulfate, and methylprednisolone content requested in the prescription are 65 mg, 1 mg, and 2 mg, respectively. Theophylline, salbutamol sulfate, and methylprednisolone found in the samples were 59.78±7.17 mg, 1.55±0.05 mg, and 1.74±0.80 mg, respectively. Content uniformity is achieved when the variation in content is less than 5% (Nguyen et al., 2009). The coefficient of variance of the samples was 11.96%, 3.33%, and 45.77% for theophylline, salbutamol sulfate, and methylprednisolone. The coefficient of variation of salbutamol sulfate was the lowest among the two other active ingredients and met the requirement. However, the average percentage content was 155%, which was not acceptable. Theophylline is a drug with a narrow therapeutic index; high content variation will cause the patient to receive an overdose or underdose of the drug, which may be harmful to the patient. Content uniformity is very important for drugs with narrow therapeutic indexes.

Stability of Active Ingredient

The chemical stability test of the active ingredients was carried out on day 30 due to the duration of the therapy. Pharmaceutical dosage forms still meet the requirement of chemical stability if the decrease in the active ingredient content is less than 10% (RI, 2020). The results of chemical stability testing are presented in Table 4. The content of theophylline, salbutamol sulfate, and methylprednisolone decreased by 1.44%, 7.64%, and 15.7%, respectively. Theophylline and salbutamol sulfate decreased by less than 10%, but methylprednisolone decreased by more than 10%; therefore, this extemporaneous preparation capsule didn't meet the requirement.

CONCLUSIONS

The physical characteristics were evaluated based on the capsule preparation. It was found that the capsule preparation has good physical characteristics. The content uniformity and chemical stability were also assessed. The coefficients of variance of content uniformity percentage were 11.96%, 3.33%, and 45.77% for theophylline, salbutamol sulfate, and methylprednisolone, respectively. Hence, the content uniformity of the product didn't meet the requirement. During 30 days of storage, the content of theophylline decreased by 1.44%, while salbutamol sulfate and methylprednisolone decreased by about 7.64% and 15.7%, respectively. It also didn't meet the chemical stability requirement because one of the active ingredients decreased the content by more than 10%. Extemporaneous preparation products that contain narrow therapeutic index drugs should meet all the requirements, especially content uniformity and chemical stability. Compounding pharmacists need to improve their knowledge and skills to prepare high-quality extemporaneous preparation products.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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