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Research Article

Beyond Use Date of Pulverized Rifampicin and Its Influencing Factors

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ABSTRACT

Inaccurate drug dosage during Tuberculosis (TB) therapy is one of the factors causing TB resistance, especially for drugs that undergo a compounding process, which are often prescribed for children. Inappropriate storage of drugs during therapy can cause a reduction in drug content, which results in changes in drug dosage. Accordingly, drugs should be used within a certain time limit or what is known as the Beyond Use Date (BUD). This study aims to determine the BUD in rifampicin powder preparations from a hospital in the Bogor district. Rifampicin powder preparations are packaged in three types of packaging (paper silk, parchment and capsules). Storage was varied at two temperatures, namely room temperature 25-28 ˚C and warm temperature 30-35 ˚C. Rifampicin levels were analyzed using High Performance Liquid Chromatography (HPLC). The results showed that the BUD of paper silk, parchment and capsule packaging at room temperature were 8, 11, and 14 days, while storage at warm temperatures was 11, 10, and 12 days, respectively. This study determined that rifampicin powder preparations should be used for 7-13 days. Factors that affect BUD are the moisture content of the preparation, the container (type of packaging) and the storage conditions (temperature).

INTRODUCTION

The results of the Health Research of the Republic of Indonesia on Tuberculosis (TB) cases from year to year have increased, and in 2022 it increased by 58.47%. The research stated that one of the provinces that experienced the highest increase with a range of 30% - 40% was the West Java province. The research also described that the range of children suffering TB in the West Java Region included children under 1 year of age as much as 0.08%, children aged 1-4 years as much as 0.78%, and children aged 5-14 years as much as 0.53% (Ministry of Health of the Republic of Indonesia, 2019). The cases of TB sufferers which always increase every year are certainly related to cases of Drug Resistant Tuberculosis (TB DR) patients. Based on the World Health Organization (WHO) Global TB Study, it was determined that the Indonesian population experiences an incident of TB DR cases of 8.8% out of 100,000 people who experience TB, including the pediatric patients (WHO, 2024).

One of the causes of TB DR in pediatric patients is the inappropriate dosage of Anti-Tuberculosis Drug (OAT) therapy. Isoniazid, rifampicin, pyrazinamide and ethambutol are first-line OAT for TB therapy. OAT in pediatric patients requires dose adjustments, so that it undergoes a compounding process from tablet preparations to become divided powder preparations/pulverized (Siahaan and Mulyani, 2013).

According to Feinstein *et al*., (2015), the use of powder preparations was most widely used in pediatric patients, reaching 38% compared to other preparations such as syrup, injection, inhalation, and capsules. The use of powder is widely used in pediatric patients and is closely related to the advantages of the powder dosage form, namely easy to use/easy to swallow. This is because these pediatric patients still find it difficult to swallow tablets or capsules

so that this powder preparation is suitable for children and it is also easy to adjust the dose to optimize the treatment therapy process (Saristiana *et al*., 2023).

The content of active substances (dosage) in the preparation will decrease during the storage period due to several factors, including storage temperature conditions, humidity and the type of packaging used. Preparations stored in inappropriate conditions can cause a decrease in the quality of the preparation, so this needs to be considered to maximize treatment therapy (Septiasari, 2018). Expiration Date (ED) is an indicator commonly used by the public as a time limit for drug use. However, preparations that have gone through the compounding process or have been opened from the primary packaging, the drug usage limit will change and will be shorter than ED. This term is known as the Beyond Use Date (BUD) (USP, 2019). If the drugs have changed physical or chemical properties, it can certainly affect the patient's treatment therapy and there is a possibility of failure in the course of the treatment (Mustafa, 2019), and as a result, the possibility of resistance will increase.

In the first-line treatment of TB in children, many doctors still prescribe the use of powder compared to reconstituted syrup, because it has a better BUD. Rifampicin is an effective antituberculosis drug with excellent sterilization activity (Ryoo and Jnawali, 2013). Siahaan and Mulyani (2013) stated that rifampicin should not be mixed in one powder mixture with other OATs. Therefore, researchers aimed to determine the BUD on several packages of rifampicin powder preparations that are compounded at a hospital in Bogor Regency. The results of this study are expected to be used to reduce the potential for cases of resistance to TB treatment in pediatric patients.

METHODS

Instrumentation and materials

The instruments used in this research were reversed phase high-performance liquid chromatography (RP-HPLC) instruments (Jasco®), sonicators (Branson®), moisture balances (KERN®), membrane filters, micropipettes, analytical scales, stability chambers and glassware. The materials used in this research were rifampicin standards (Solarbio®), methanol (Merck®), and acetonitrile (Merck®).

Research Design

The pulverized rifampicin was made by a hospital in Bogor Regency, which is packaged in three different types of packaging, namely paper silk, parchment and capsule packaging. The number of samples from each package type is 70. Evaluation of the quality of the preparation is done by testing the uniformity of weight, organoleptic, moisture content and rifampicin. Weight uniformity testing is conducted using the procedure from Ministry of Health of the Republic of Indonesia (2020). Organoleptic, moisture content and rifampicin content testing are conducted on samples stored at two different temperatures, namely room temperature and warm temperature (30 °C). Moisture content is determined using a moisture balance. Rifampicin content is determined using verified standard methods from Ministry of Health of the Republic of Indonesia (2020). The determination of BUD is based on the decrease in the level of rifampicin content (t90).

Rifampicin Analysis

Analysis of rifampicin was done using RP-HPLC. Separation was done using an ODS-3 column (150 x 4.6 mm; 5 µm). Detection was performed at a wavelength of 254 nm. Methanol and acetonitrile (95:5) were used as the mobile phase at a flow rate of 1.0 mL/minute and an injection volume of 10 µL. Verification of the analysis method was done on the accuracy and precision parameters by sample spike, as well as linearity parameters.

The rifampicin content from the analysis results was used to determine the order of the reaction rate of the active substance decomposition. The decomposition rate of solid preparations generally has characteristics such as order 1 or a sigmoid curve (Ministry of Health of the Republic of Indonesia, 2020). The BUD of the sample is determined when the rifampicin content is less than 90.0% (Ministry of Health of the Republic of Indonesia, 2020) of the compound dose (60 mg).

RESULTS AND DISCUSSION

Physical Characteristic

Organoleptic tests are conducted to test the quality of the preparation from the physical properties by ensuring that the preparation has met the standards in the Indonesian Pharmacopoeia VI Edition (Ministry of Health of the Republic of Indonesia, 2020), based on the standards of the Indonesian Pharmacopoeia VI Edition stating that rifampicin powder is a crystal powder with a reddish brown color. As for the results of observations of this organoleptic test on days 1 to 21 (Table 1), it showed a dark reddish brown color with a powder form, which

means that the physical properties of this rifampicin powder preparation did not change.

The results of the determination of moisture content showed that rifampicin powder stored at room temperature experienced an increase in each package (Table 1). The parchment packaging has the highest increment of the moisture content, and becomes more sensitive to humidity than paper silk and capsule packaging. Parchment is more sensitive to humidity because based on the packaging process of the drug preparation, for parchment itself it does not go through a pressing stage to cover the incoming air, but only goes through the folding stage, so that parchment has many cavities that can be passed through by air into the preparation, which causes the preparation packaged in this parchment packaging to experience a fairly drastic increase in moisture content.

In warm temperature storage, the moisture content decreases (Table 1). This occurs because the temperature factor used in the stability oven is 30 °C, so that the preparation is slightly heated at that temperature and the moisture content gradually decreases. Similar to room temperature storage, the moisture content in paper silk packaging is higher than the other packaging. From each storage, it can be seen that parchment packaging is more sensitive to storage temperature and humidity, followed by paper silk and capsule packaging.

Uniformity Assay

Assays to assess uniformity of weight are done to ensure that each pack/capsule does not have a weight that deviates according to the Indonesian Pharmacopoeia VI Edition. The weight of the sample is related to the dosage content of each package of preparation. If the weight of the preparation is not uniform, it can cause a lack of therapeutic effect. This weight uniformity is carried out on each dose unit of the drug packaged in three types of packaging, namely paper silk, parchment, and capsules, as well as variations in two storage temperatures, namely room temperature and warm temperature. Each was assessed on as many as 10 packs, but because the test results of 10 packs did not meet the requirements, so an additional test of 20 packs was conducted with a total test of the preparation, namely 30 packs for each type of packaging and storage temperature. The results of the weight uniformity test can be seen in Table 1. The acceptance value referred to the Indonesian Pharmacopoeia VI Edition.

Table 1. Uniformity of Weight

Package	Acceptance Value (%)	Active Content (Average ± SD)
Paper Silk	75 – 125	100% ± 15.61457
Parchment		100% ± 13.95463
Capsule		100% ± 13.72455

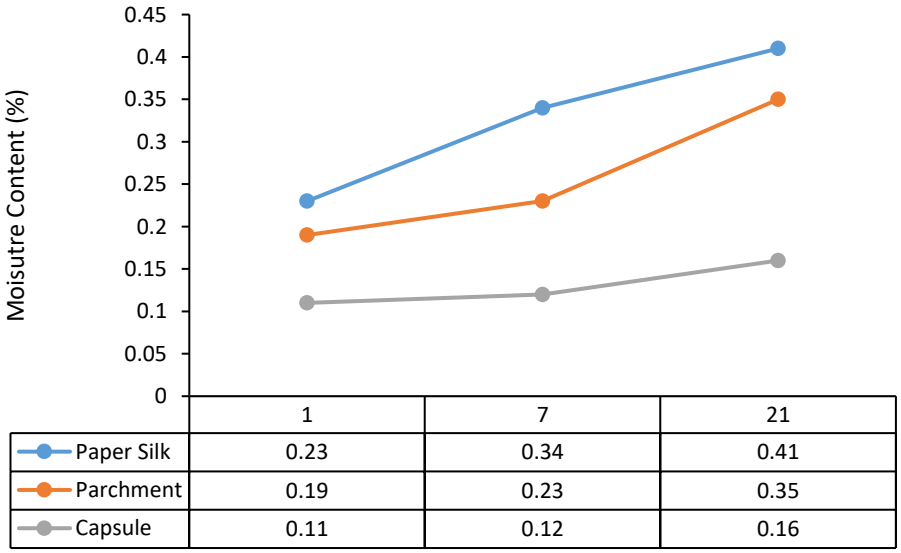
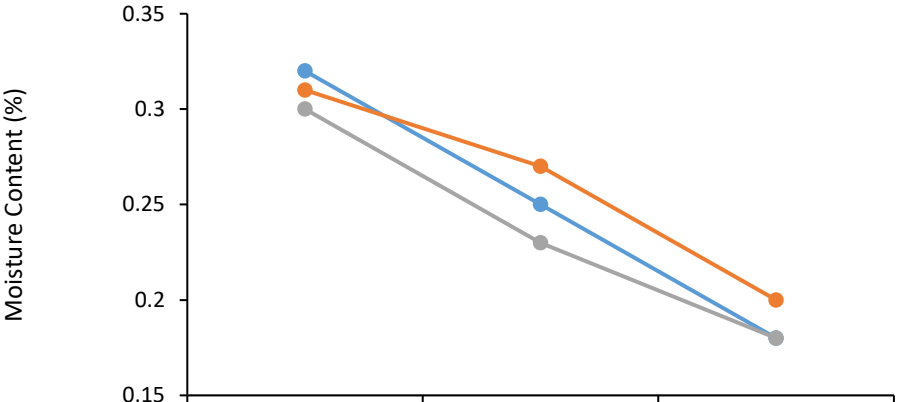


Figure 1. Moisture content at the room temperature storage.



	1	7	21
Paper Silk	0.32	0.25	0.18
Parchment	0.31	0.27	0.20
Capsule	0.30	0.23	0.18

Figure 2. Moisture content at the warm temperature storage.

Moisture Content Assay

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Verifications of Analysis Method

Verification of accuracy and precision parameters using the spike technique at three concentration levels with three replications each. Accuracy is determined based on the % recovery value, while precision is seen based on the % Coefficient of Variation (CV) value. The results of the accuracy test of the analysis method show that the % recovery of the analysis method (Table 2) has met the requirements of AOAC (2016) which states that for analytes in the sample matrix with a concentration of 0.01% - 0.001% or equivalent to 10 - 100 mg / L states that a good average for % recovery is 90 - 107%. Good results are also shown by the results of the verification of the precision level of the analysis method, where the test results state that for the % KV value obtained for the same concentration as the accuracy, it has a %CV value required by AOAC (2016) which is 4% (Table 2). The verification results show that this rifampicin compound analysis method has met the standards, so that the analysis method can be used to analyze rifampicin levels in samples accurately and precisely.

Linearity of the method described correlation coefficient value (r) in Table 3. The results of observations in this linearity test obtained linear curve results with a correlation coefficient value of 0.9989 with a linear regression equation Y = 706396 + 25911.4X. According to Harmita (2004), a good correlation coefficient is close to 1, so from the results obtained in this linearity test it has been linear and meets the requirements.

Rifampicin Content and BUD Determination

The RP-HPLC system showed a good relative standard deviation for replicate injections of standard (Figure 3) which was less than 1.0%,

Table 2. Accuracy and Precision

Concentration (mg/L)	Replication	Recovery (%)	Coefficient of Variation (%)
48	1	96.3395	1.62
	2	97.6526	
	3	94.5414	
60	1	95.0953	1.32
	2	96.4829	
	3	97.6517	
72	1	95.3778	1.45
	2	92.8272	
	3	93.2683	

Table 3. Linearity

Concentration	Area	Slope	Intercept	R^2	R
20	1223043	25911.4	706396	0.9978	0.9989
40	1797404				
80	2886835				
160	4598426				
320	9091338				

and the resolution was more than 4.0. These results give information that the system was suitable for use in analysis. The injected sample is shown in Figure 4. The results of the analysis of rifampicin contents showed a decrease (Table 4). This decrease in levels was due to changes in the structure of the rifampicin compound. Pyta *et al*. (2012) determined that the piperazine ring of rifampicin can be hydrolyzed into an aldehyde group called rifaldehyde (Figure 5). In addition, rifampicin can also undergo oxidation of the alcohol group to a ketone called rifampicin quinone as shown in Figure 6 (Acuña *et al*., 2019).

The decomposition of compounds can also be affected by the container (Rayfield *et al*., 2021). Storage containers can be associated with the type of packaging. Packaging functions to protect the preparation and prevent decomposition of compounds that can damage the quality of the preparation. The use of inappropriate packaging can cause the drug preparation to be more susceptible to changes in physical and chemical properties. The container and storage conditions for this rifampicin preparation, according to the Indonesian Pharmacopoeia Edition VI are storage in a tightly closed container, protected from light and humidity with a temperature of 15–25 °C.

According to the Indonesian Pharmacopoeia Edition VI, rifampicin content is not less than 90% and not more than 110%, so that the determination of BUD is by determining the time when the content reaches 90% or also known as t90. The BUD value obtained in this study was decimal, so it was reported as the lower value, because the principle of BUD is best used before the expiration date. If the BUD used the upper value, then the rifampicin compound content is less than 90% of the amount stated on the label, which will affect the therapeutic effect of the drugs.

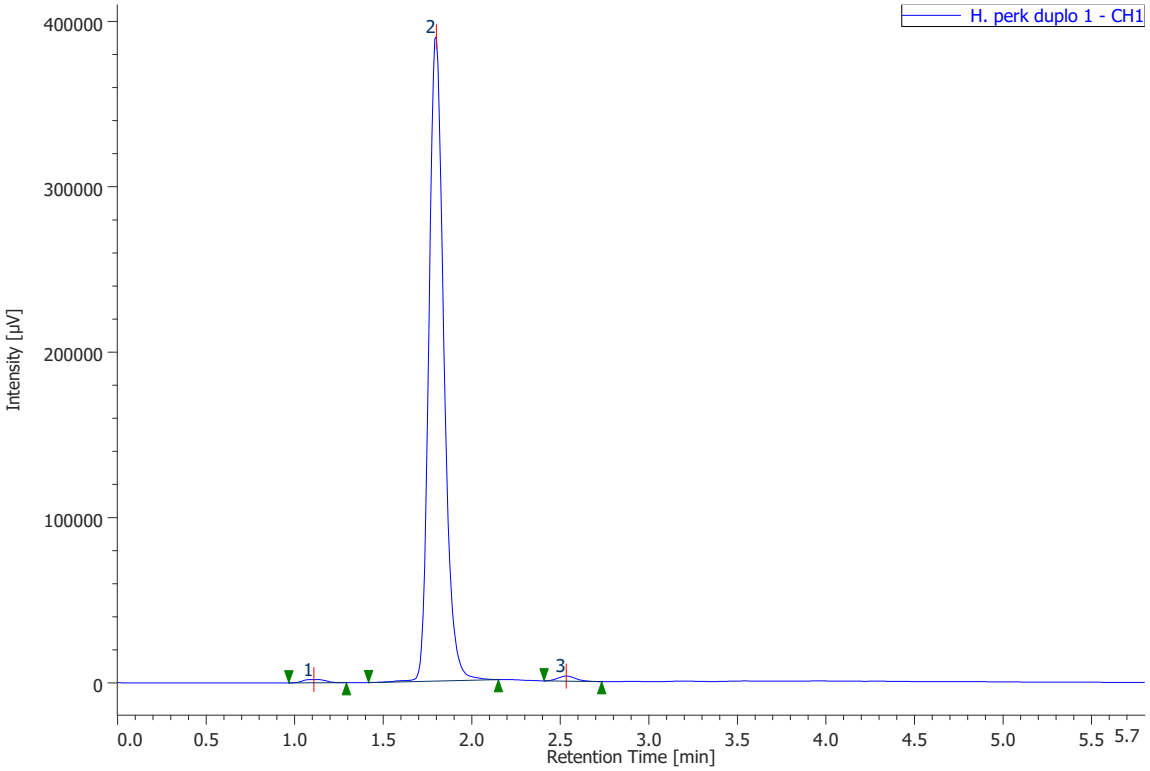

Figure 3. Standard of rifampicin

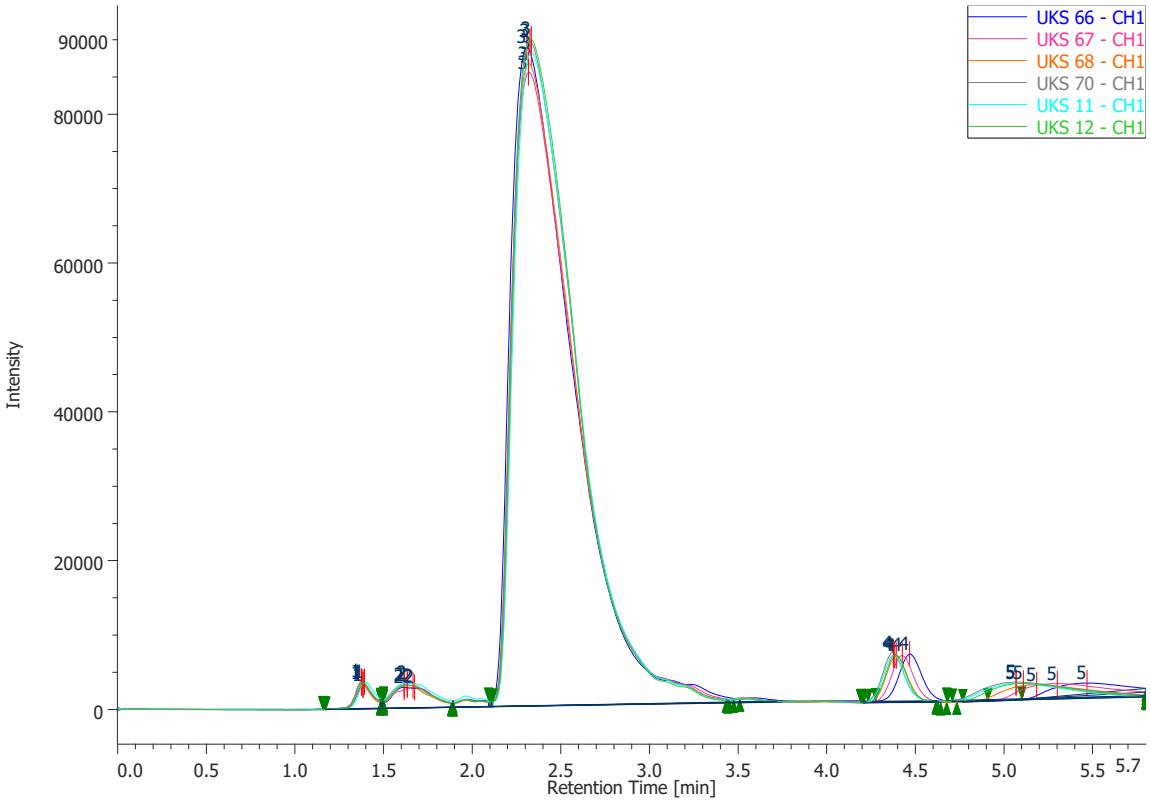

Figure 4. System Suitability Test for Standard.

Table 4. Rifampicin Content

Packaging	Rifampicin content (%)					
	Room Temperature Storage (days)			Warm Temperature Storage (days)		
	1	7	21	1	7	21
Paper Silk	109.47	99.46	84.73	102.84	100.29	85.49
Parchment	106.74	99.25	88.50	109.58	99.54	88.77
Capsule	102.30	95.75	87.73	104.03	96.27	86.66

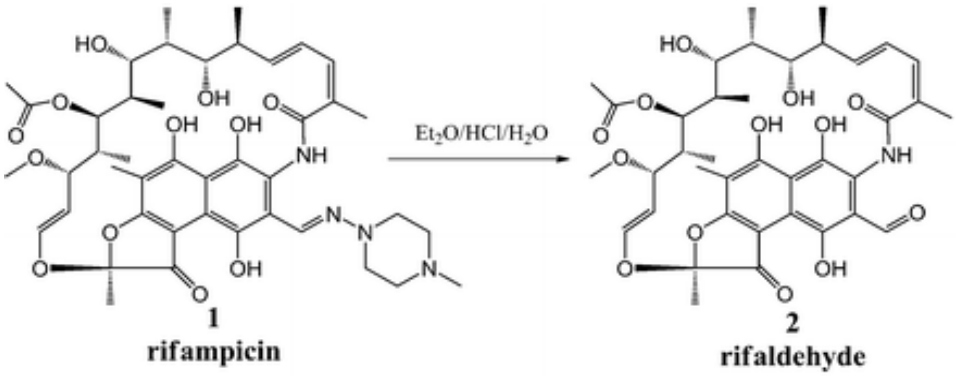

Figure 5. Rifampicin Hydrolysis.

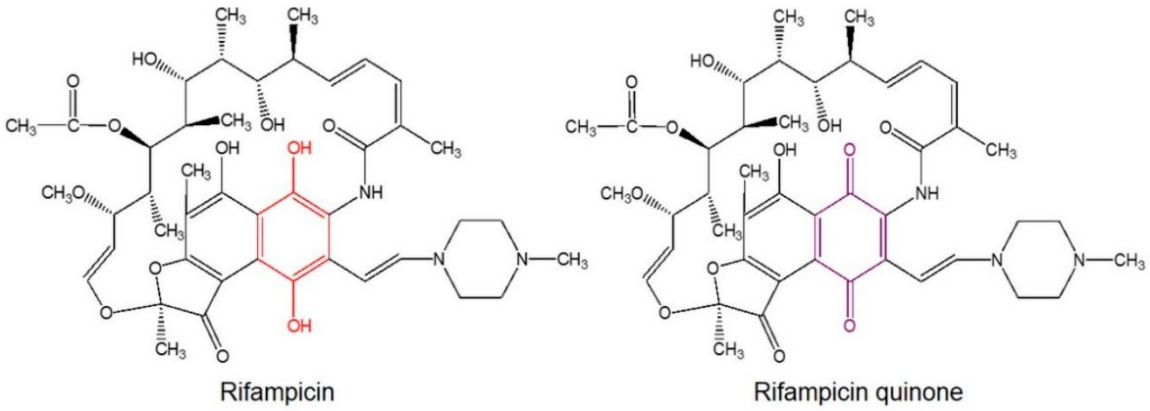

Figure 6. Rifampicin Oxidation.

Table 5. Beyond Use Date

Storage	Packaging	BUD (days)
Room Temperature	Paper Silk	8
	Parchment	11
	Capsule	14
Warm Temperature	Paper Silk	11
	Parchment	10
	Capsule	12

Based on Table 5, parchment packaging at room temperature has a better BUD (11 days) compared to storage at warm temperatures (10 days). The same thing was also found in the BUD data from capsule packaging at room temperature (14 days), which was better than BUD at warm temperatures (12 days). This is because this study was conducted in the dry season, where room temperature can reach 31-35 ° C, which is higher than warm temperatures (30 ° C). This was not found in the paper silk packaging type, where BUD at room temperature

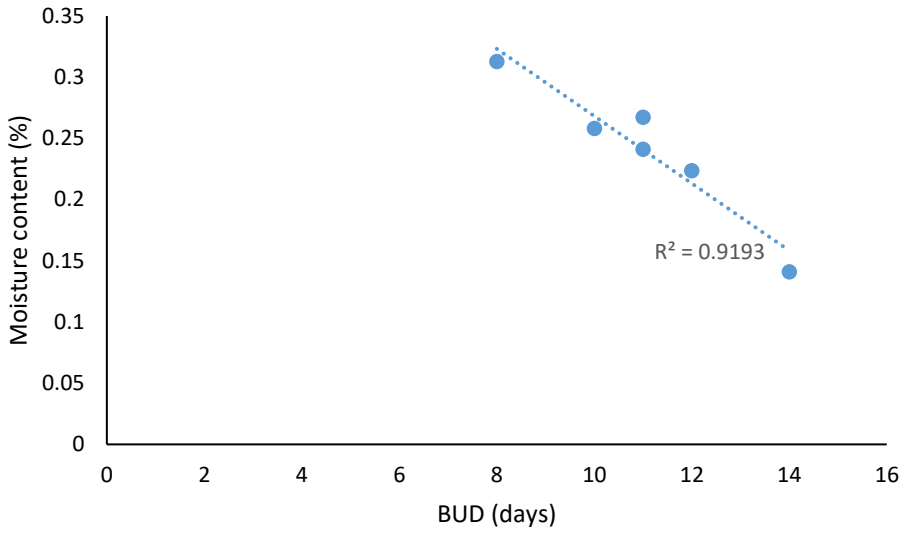

Figure 7. Moisture Content and BUD Correlation.

(8 days) was faster than BUD at warm temperatures (11 days), which was caused by the trapping of some moisture in the packaging, as evidenced by the high-moisture content (0.25%) in this packaging, while parchment and capsule packaging have low moisture content (0.19% and 0.11%).

Further, the correlation between moisture content and BUD values was analyzed (Figure 7). The moisture content at BUD time was predicted based on the relationship between moisture content and time. The results of the determination analysis showed that there was a fairly strong relationship between moisture content and BUD, which was 91.93%. This result supports the findings that the main cause of the difference in BUD is due to the moisture content in the preparation and the decrease in rifampicin levels is due to the hydrolysis reaction. High moisture content can shorten the storage life even shorter. Liu *et al.* (2021) stated that Rifampicin is more easily hydrolyzed than oxidized, so the influence of moisture content is the main factor causing a decrease in rifampicin levels.

Determination of BUD in this study was conducted at natural room temperature, without controlling temperature and humidity, which aims to obtain BUD that is comparable to the storage conditions carried out by consumers/patients. In general, testing the stability of a preparation in the industry was conducted using a chamber that can control temperature and humidity, but consumers do not have such a tool, where consumers tend to store preparations at natural room temperature, so there will be differences in the stability of the tested compound content. The results of the study were obtained by conducting a comparative test with the hospital by interviewing one of the Pharmacists at the Hospital who stated that the BUD of the rifampicin powder preparation lasted for 1 month, while the results of the study determined that the BUD of the rifampicin powder lasted 7-14 days depending on storage conditions and the type of packaging used.

CONCLUSIONS

The moisture content in the powder preparation is one of the factors that causes the decomposition of rifampicin compounds through hydrolysis reactions, which affect the shelf life of the preparation. The type of packaging (container) and storage conditions (temperature) have different characteristics, which can affect the shelf life of the powder preparation.

The BUD of the rifampicin powder preparation prepared by a hospital in Bogor Regency was shorter (8-14 days) than that estimated by the hospital (1 month). The results of the study are expected to be a consideration for the hospital to reconsider the duration of the preparation and delivery of TB drugs, especially rifampicin, so that the therapeutic effect can be optimal and reduce the potential for resistance.

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CONFLICT OF INTEREST

All authors declared no conflict of interest.

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