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EVALUATION AND FORMULATION OF RIFAMPICIN TABLET

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ABSTRACT
Rifampicin is a broad spectrum of an antibiotic and commonly used as a fire line therapy for Mycobacterium tuberculosis infection and is a first-line form of treatment for tuberculosis. Rifampicin tablets were made with the active ingredient of rifampicin, filler and disintegrant mixture of starch and lactose. The tablets exhibited good physical quality and dissolution. The physical properties and dissolution profile analysis of rifampicin tablets were done using DDSolver, WinSAAM, and Monolix software. Rifampicin tablet formula was made using the wet granulation method. The evaluation of the physical properties of rifampicin tablets was done by testing several parameters including hardness, friability, disintegration time, and dissolution. Dissolution profile results were analyzed using DDSolver software to determine the kinetics of drug release, WinSAAM to investigate the compartment model of conventional rifampicin tablets, and Monolix to determine the dissolution profile and rifampicin compartment model easily and practically using population-based approaches. The results showed that rifampicin tablets from the formula had a mixture of starch and lactose disintegrant was exhibit a have good physical quality and dissolution profile and meet the requirements of the Indonesian Pharmacopoeia thus, it has better efficacy.

KEYWORDS: Rifampicin, Starch, Lactose, Tablet, Physical properties. Dissolution.

INTRODUCTION

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis and is an infectious disease that has affected millions globally. Rifampicin is a primary anti-tuberculosis drug used for tuberculosis therapy and is the first-line drug for the treatment of short-term tuberculosis (Katzung, 2010).

There are things that need to be considered in tablet formulation, such as the selection of excipients. Starch can be used as fillers, binders, and disintegrant. Lactose is often used as the main excipient in tablet formulations for drugs which have low solubility property because lactose is easily soluble so that it is suitable if used as an excipient of rifampicin tablets that belonging to BCS class II which has low solubility (Rowe et al., 2009).

The drugs which have low solubility and high permeability, the absorption rate of the drug is determined or limited by the rate of dissolution of the drug in the liquid where the drug is absorbed. Thus an efforts are needed to improve solubility and dissolution (Dressman and Kramer, 2005).

Population-based modeling analysis is a method for modeling, identifying and explaining the relationship between the physiological characteristics of subjects and drug treatment. The practicality of a population-based modeling approach is the focus of analysis on the subject population and not on the subject per individual. Ironically, this population-based analysis is still very limited in use in Indonesia. The impression that modeling analysis is expensive, complicated, and not easy to operate may still be a negative stigma that needs to be corrected. However, on the other hand, this is also an opportunity for researchers in Indonesia to utilize and develop this population-based analysis (Zhang et al., 2010).

MATERIAL AND METHOD

Materials

The materials used in this research are rifampicin (provided by Mersi Farma distributor) with fillers such as starch (Pharmaceutical grade), lactose (Pharmaceutical grade), magnesium stearate (Pharmaceutical grade), talc (Pharmaceutical grade), ac-di- sol (Pharmaceutical grade), gelatin (Pharmaceutical grade), aquades, and 37% HCl (E Merck P.a).

Method

1. Preparation of rifampicin tablet

Tablets were made by direct compression method, tablet making was done in two batches with one formula made by the author shown in table 1.

Tabel 1: Formula.

Ingredient	Amount
Rifampicin	450 mg
Starch	90 mg
Lactose	48 mg
Mg Stearat	3 mg
Talk	3 mg
Ac-di-sol	1 mg
Gelatin	35,5 mL

2. Physical properties evaluation

Hardness test, friability test, disintegration time test, weight uniformity, content uniformity, hardness, friability, disintegration time test were done according to steps as in Indonesian Pharmacopoeia V.

3. Dissolution study

Dissolution media containing 0.1 N hydrochloric acid was prepared. The evaluation was carried out using 900 ml of 0.1 N HCl, 0.1 N HCl was chosen because HCl is acidic, whereas rifampicin is alkaline, so that if rifampicin tablets dissolved in acid can make rifampicin soluble since rifampicin ionizes in acidic solution. The temperature of the liquid during the dissolution process was maintained at 37oC and the rotation was set at 100 rpm for one hour. A 5 ml sample was withdrawn at 2, 5, 10, 20, 30, 45, and 60 minutes with the replacement of physiological fluids in a dissolution device, analyzed immediately with a UV-Vis spectrophotometer with a wavelength of 471 nm.

4. Determination of tablet dissolution kinetic using DDSolver

The kinetics and dissolution models were analyzed with zero, first order, higuchi, peppas korsemayer, and weibul dissolution models using DDSolver. Kinetics and zero and first order dissolution models by comparing the adjusted R2 and AIC values obtained from the two models.

RESULT AND DISCUSSION

1. Physical evaluation

Tabel 1: Physical evaluation result.

Properties	Batch 1	Batch 2
Weight uniformity (mg)	1,54% ± 0,64	2,02% ± 0,84
Content (%)	92,13% ±4,19	92,61% ± 0,79
Hardness ((Kg/cm2)	6,9636 ± 0,326	6,2727 ± 0,276
Friability (%)	0,17% ± 0,004	0,09% ± 0,063
Disintegration time (s)	332,67 ± 16,862	326,67 ± 8,144

The weight uniformity test of tablets can be used as an initial indicator of uniformity of active substances in tablets with the assumption of homogeneous of ingredients was achieved. Tablets that have a uniform weight will have a uniform active ingredient too. The results of the analysis showed that the weight of the tablets in the two different batches was not significant, as evidenced by the NP values that were less than 15%, (1.54% and 2.02%). Weight uniformity of the tablet can be achieved because the mixture of materials has good flow properties so that it can fill the molding chamber (die) with a constant weight (Ministry of Health of Indonesia, 2014).

Content uniformity analysis showed no significant difference between each tablet, it showed that the mixture of starch and lactose as fillers did not affect the uniformity of tablet content in each batch. Table 2 shows that both batches have a CV value of less than 5%, thus it can be said that the active substance content of each batch is uniform and meets the requirements (Ministry of Health of Indonesia, 2014).

Hardness has parameters that describe the resistance of the tablet against mechanical stresses such as shock, impact and cracking of the tablet during packaging, storage, transportation to the hands of consumers. The analysis showed that the hardness of the two batches of tablets gave good results and was met the requirements of the Indonesian Pharmacopoeia (Indonesian Ministry of Health, 2014).

The friability of the tablet affects the handling of the tablet during the packaging and distribution process. The tablets must remain intact until they are used by the patient. The acceptable friability value is ≤1%, the results of the study in table 2 show that rifampicin tablets met the fragility requirements of the tablet (Ministry of Health, Republic of Indonesia, 2014).

Disintegration time is the time required for a tablet to disintegrate into finer granules or aggregates when in contact with the media. A mixture of starch and lactose as a good disintegrant in rifampicin tablets thus shortening the disintegration time due to the ability to

absorb water from starch is high. In the Indonesian Pharmacopoeia V Edition (2014) the requirements for disintegration of non-coated tablets are less than 15 minutes or 900 seconds. Disintegration time test results showed that rifampicin tablets have a disintegration time of fewer than 15 minutes or 900 seconds so that they met the disintegration time requirements of non-coated tablets as listed in the Indonesian Pharmacopoeia V Edition (Ministry of Health Republic of Indonesia, 2014).

The results of rifampicin scanning by spectrophotometer showed that rifampicin absorbs at a wavelength of 471 nm. This value approaches the rifampicin wavelength value at USP 29, that rifampicin in 0.1 N HCl has a maximum wavelength at 475 nm. This difference in results is due to the influence of the instruments, and the purity of the material used.

Equation of the rifampicin standard curve in HCl 0.1 N with a spectrophotometer, yields the equation Y = 0.01088x + 0.0884.

Drug release from preparations has an important role in the delivery of drugs orally and determine the therapeutic effect of drugs. In vitro drug release studies are a prerequisite for obtaining accurate predictions for designing and testing drug activity in vivo (Zhang et al., 2010).

According to Indonesian Pharmacopoeia Edition V, conventional rifampicin tablets must be able to release the drug as much as no less than 80% within 45 minutes. The dissolution profile in figures 5 and 6 shows that each batch gives a release pattern that is not different from each other. It was seen that each tablet in both batches had released the drug more than 80% at the 30th minute. This shows that rifampicin tablets can provide fast drug release and met the standard (Zhang *et al*., 2010).

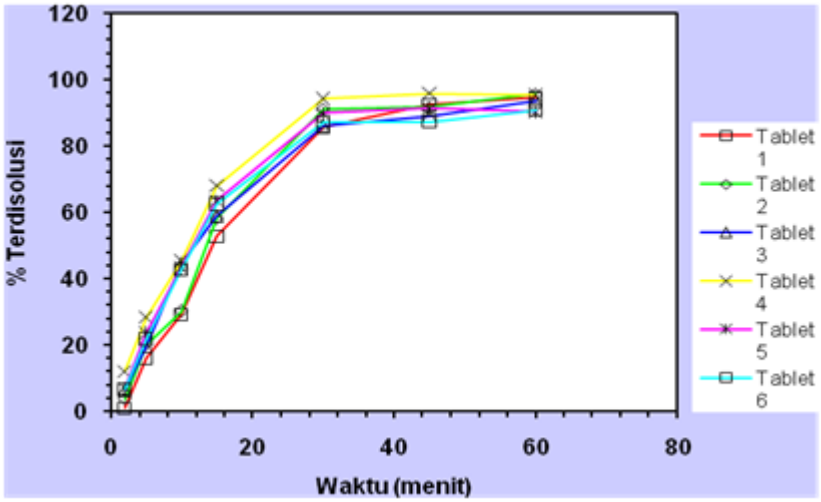

Figure 1: Dissolution profile of batch 1 rifampicin tablets.

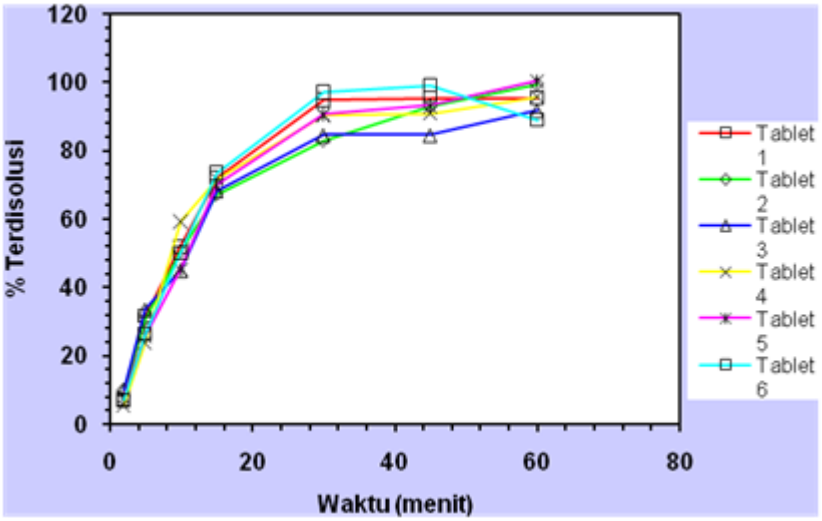

Figure 2. Dissolution profile of batch 2 rifampicin tablets.

2. Determination of the dissolution kinetics of rifampicin tablets with DDSolver

The determination of dissolution speed is assisted using DDSolver software. The kinetics of the dissolution of rifampicin tablets were analyzed by fitting using various release models such as zero order, first order, Higuchi, and Peppas cosmayer models. The determination of the model can be seen from the adjusted R2 and AIC values of the various order models. models with adjusted R2 values get closer to one and AIC (Akaike Information Criterion) values are lower, then the model is stated as suitable to describe the dissolution kinetics (Zhang, et al., 2010). Table 3 shows the R2Adj and AIC values for each batch in 0.1 N HCl using the release kinetics available at DDSolver.

Based on the R2adjusted and AIC values listed in table 3 and figures 4 and 5 the dissolution process of rifampicin tablets both in batch 1 and batch 2 follows the kinetics of Weibull_1 release. This happens to the correlation coefficient obtained, the Weibull_1 correlation coefficient is greater than the other release kinetics correlation coefficient. In choosing the drug release kinetics model, not only can the R2adjusted value be seen as a parameter, but it is also necessary to look at the AIC (Akaike Information Criterion) value where the AIC value because the R2adjusted value tends to increase along with a large number of parameters contained in the release kinetics. Whereas the AIC needs to enter the number of parameters and the number of observed data points to get the value.

There are two kinetic models that have a lower R2 adjusted value but show a lower AIC value so it is necessary to compare the two release kinetics visually using the identity line y = x which shows that the kinetics of weibul release has a point that is closer to the identity line, as shown in Figures 4 and 5. So that it is determined that rifampicin tablets with a mixture of starch and lactose mixtures follow the kinetics of Weibull release with the equation:

$$F = 100.\ [1\text{-}e^{-\frac{t-Ti^{\beta}}{\alpha}}]$$

Whereas t is the time of drug dissolution. Ti is lag time, ie the time lag before the dissolution or the process of releasing drugs into the medium and in most cases the value is close to zero. Whereas α is a parameter that defines the time scale in the dissolution process, α is useful if the process is carried out with 2 different tools. B notation is a parameter that shows the shape of the curve if the value of β = 1 it indicates that the shape of the curve is sigmoid, the value of β> 1 curve shape is parabolic, whereas if the value of β <1 then the shape of the curve is exponential (Zhang, 2010). A β value in the range of 0.69 to 0.75 indicates that drug release follows diffusion ficks, a value of β = 0.75-1 indicates a combined mechanism that is often found in dissolution, and value of β> 1 indicates that the mechanism that regulates release the drug is complex (Papadopulou, 2006).

In batch 1 and batch 2 shows that the value of β between 0.75-1, this means that rifampicin tablets with a mixture of starch and lactose mixture that undergo a combined mechanism which shows that to release the active substance tablets requires more than one type of release mechanism.

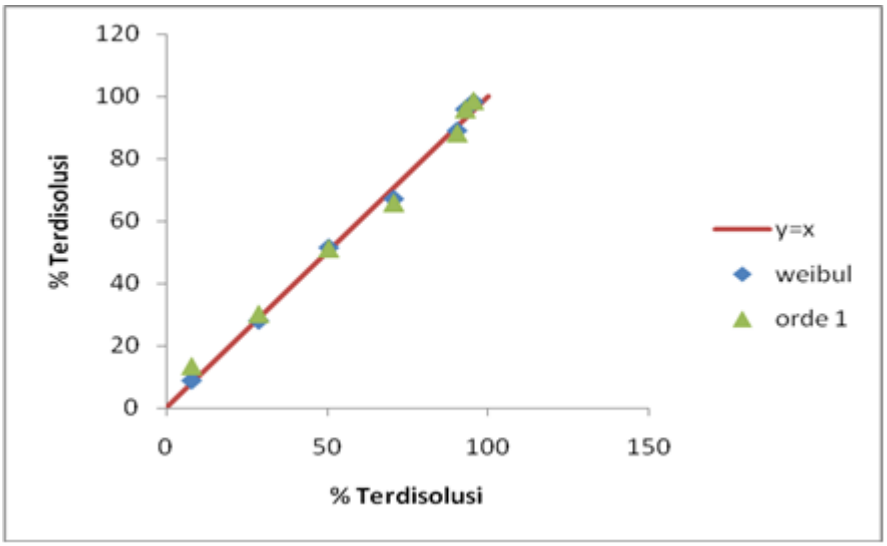

Figure 3: Comparison of visual release kinetics of batch 1.

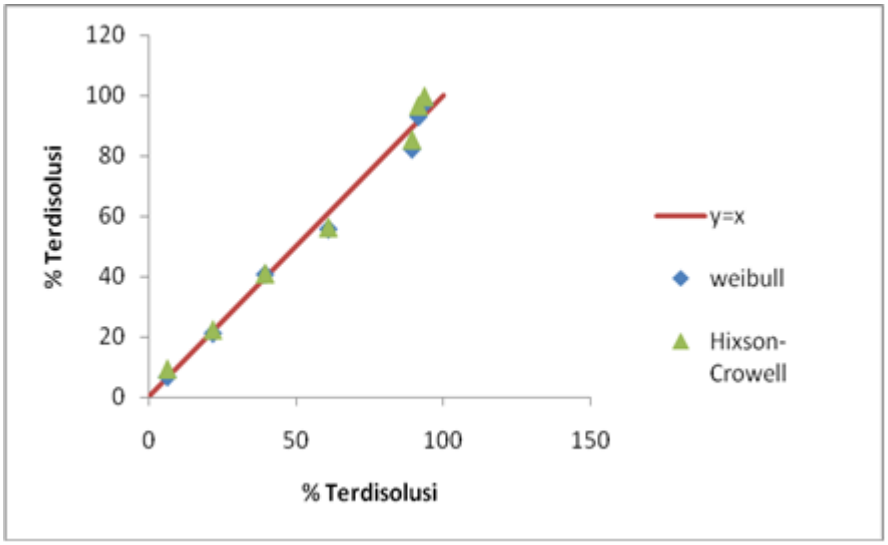

Figure 4: Comparison of visual release kinetics of batch 2.

CONCLUSION

The rifampicin tablet with a mixture of starch and lactose has good physical character and dissolution results of the tablet test show that the dissolution profile follows the Weibul release kinetics based on the results of the analysis using DDSolver software and has met the requirements of the tablet according to Pharmacopeia Edition V.

SUGGESTION

Further research needs to be done on the stability of rifampicin by temperature, humidity, pH and light factors.

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