

Comparisons of physical properties and rates of rifampicin dissolution in Fixed Dose Combination (2FDC) tablet against rifampicin tablet

Normalitasari Ayu Damayanti¹, Widyasari Putranti*¹, Deasy Vanda Pertiwi¹

¹Department of Pharmacy, Faculty of Pharmacy, Universitas Ahmad Dahlan, Yogyakarta, Indonesia

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ABSTRACT

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*Corresponding author:

widyasari@pharm.uad.ac.id

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Background: The World Health Organization (WHO) has recommended using fixed dose combination (FDC) for tuberculosis treatments as it can improve patient compliance and prevent drug resistance. A combination of rifampicin and isoniazid can cause reductions in concentration of each drug because the rifampicin is labile and can not be mixed with all three other TB drugs

Objective: This study is aimed to understand effects of the combination of both physical properties and dissolutions of rifampin.

Methods: This laboratory study observed rifampicin tablets and combination tablets of rifampicin and isoniazid (2 FDC) by testing physical properties of the tablets and dissolution tests. Friability test was conducted by using friability tester, hardness test was by hardness tester, disintegration test was by disintegration tester and dissolution test was by dissolution tester type 1 (basket). Its data were analysed by Mann Whitney test. The data had value if $p < 0.05$ with CI 95%.

Results: This study found that each tablet of rifampicin and 2 FDC tablets respectively had averages of 0.25% and 0.14% of brittleness, 11.07 kg and 10.19 kg of hardness, 2 minutes 1 second and 10 minutes 9 seconds of disintegration time. Consequently, the generic rifampicin tablets were more fragile but harder and faster to crumble than the 2 FDC tablets, in which their mean values were DE_{45} 92.03% and 93.94%. Based on statistical test of Mann Whitney on the rifampicin tablets and 2 FDC, there were no significant differences of hardness test result and mean DE_{45} 0.076 ($p > 0.05$), while there were significant difference of fragile test result and disintegration time 0.015 ($p < 0.05$).

Conclusion: The combination of rifampicin and isoniazid in tablet 2 Fixed Dose Combination (2 FDC) had no effects on the dissolution rates of rifampicin, but they had effects on some parameters of physical property test of the tablets.

Latar Belakang: World Health Organization (WHO) telah merekomendasikan penggunaan Fixed Dose Combination (FDC) pada pengobatan TBC karena dapat meningkatkan kepatuhan pasien dan mencegah terjadinya resistensi obat. Rifampisin memiliki sifat labil dan tidak bisa dicampurkan dengan ketiga macam obat TBC lainnya. Adanya bentuk sediaan FDC dapat menyebabkan berkurangnya konsentrasi obat rifampisin.

Tujuan Penelitian: Mengetahui pengaruh bentuk FDC terhadap sifat fisik dan disolusi rifampisin.

Metode: Penelitian laboratoris ini dilakukan pada tablet rifampisin sediaan tunggal dengan tablet kombinasi yang berisi rifampisin dan isoniazid (2 FDC) dengan menguji sifat fisik tablet (uji kerapuhan, kekerasan, waktu hancur) dan uji disolusi (tipe 1). Data dianalisis dengan menggunakan uji Mann Whitney.

Data dinyatakan bermakna jika nilai $p < 0.05$ dengan confidence interval 95%.

Hasil: Tablet rifampisin dan tablet sediaan 2 FDC secara berturut-turut memiliki rata-rata kerapuhan 0.25% dan 0.14%, kekerasan 11.07 kg dan 10.19 kg, waktu hancur 2 menit 1 detik dan 10 menit 9 detik, sehingga tablet rifampisin sediaan tunggal lebih rapuh (0.25% vs 0.14%), lebih keras (11.07 kg vs 10.19 kg) dan lebih cepat hancur (121 detik vs 609 detik) dibandingkan dengan tablet 2 FDC. Kecepatan disolusi rifampisin sediaan tunggal lebih cepat dibandingkan tablet 2FDC (DE_{45} 92.03% vs 93.94%). Uji statistik Mann Whitney menunjukkan bahwa tidak ada perbedaan yang signifikan untuk uji kekerasan dan uji disolusi 0.076 ($p > 0.05$), namun terdapat perbedaan yang signifikan 0.015 ($p < 0.05$) untuk uji kerapuhan dan waktu hancur antara tablet rifampisin sediaan tunggal dibanding dengan sediaan 2 FDC.

Kesimpulan: Kombinasi rifampisin dan isoniazid dalam tablet 2 Fixed Dose Combination (2 FDC) tidak berpengaruh pada kekerasan dan disolusi obat rifampisin, akan tetapi berpengaruh pada kerapuhan dan waktu hancur obat tersebut.

INTRODUCTION

Tuberculosis (TB) is caused by Mycobacterium tuberculosis, a bacillus that can lie dormant in human bodies for a long time.¹ Lack of compliance of TB patients and other factors in their therapeutic process of treatments tend to make a number of organisms resistant to several anti-tuberculosis drugs. In that case, a multiple TB drug therapy is usually administered. Isoniazid, rifampicin, ethambutol, streptomycin, and pyrazinamide are its primary drugs or so-called "first-line" drugs because of their acceptable efficacy and degree of toxicity.² In certain cases, combinations of the drugs are administered to reduce or prevent emergence of bacterial resistance to TB treatment.

In 1990, TB prevalence rates in Indonesia were 443 per 100,000 populations. Based on a result of a TB prevalence survey in 2013, the prevalence of positive smear pulmonary TB aging 15 year old or more was 257 per 100,000 populations.³ In 2015, TB patients in Indonesia were targeted to decrease to 280 per 100,000 populations.

Anti-tuberculosis drugs with fixed-dose combination (Fixed-Dose Combination), or known as OATFDC / FDC drugs, are tablets that contain combinations of several types of anti-TB drugs with fixed doses. FDC 2 tablets are combination tablets between rifampicin and isoniazid, whereas tablets 4 FDC are combination tablets of rifampicin, isoniazid, pyrazinamide, and ethambutol. The 2 FDC tablets are used as TB therapy at an advanced stage, while the 4 FDC tablets are at an intensive stage.

The combination of Isoniazid and rifampicin can reduce concentration of both drugs.⁴ Reduced concentration of both drugs can result an inadequate dose of the TB therapy. Therefore, it is necessary to conduct a study to determine quality of the FDC tablets through physical testing. It is necessary because physical parameters of the tablets can affect rates of drug dissolution, which can also affect efficacy and bioavailability of the drug formula.⁵

METHODS

This study is a laboratory research. The data of this study were results of a physical property test of the tablet and a dissolution test. Both tests were conducted by a single dosage form of 450 mg of rifampicin tablet and rifampicin combination dosages of 2 FDC. Replication was done for 3 times in each test.

Physical test

The physical test of the tablets included test of fragility, hardness, and disintegration time. The fragility test was conducted by debiting 20 sample tablets. Then, they were weighed and put in the friability tester as they can be seen in figure 1 below (speed: 25 revolutions per minute for 4 minutes). After 100 turns, the tablet samples were evaluated by weighing. Samples used in this study were those that fitted to these requirements: not having a total shortage of more than 1%, cracking, splitting, or rupturing.⁶



Figure 1. Friability tester

The tablet hardness test was conducted by using a hardness tester. This test observed scales achieved when the tablets was broken or appropriately destroyed. The scale indicator on the hardness tester before testing must be in the zero position. The hardness test of each tablet was organized by turning the tester slowly until the table t was broken or appropriately destroyed.⁶

The disintegration time test was conducted by using a disintegration tester by inserting one tablet into six tubes from a basket. 37° ± 2° C water was used as a medium in this study. The data obtained from this test were initial

time achieved by samples that were damaged or did not follow the initial tablet shape using a disintegration tester.⁷

Dissolution test

The dissolution test of the tablets were conducted by using a dissolution tester as it can be seen in Figure 2 below. The dissolution medium used was 900 ml 0.1N hydrochloric acid. This solution was prepared by diluting 8.5 ml of concentrated hydrochloric acid with distilled water up to 1000 ml. This test used a type 1 stirrer (basket shape mixer) with a speed of 100 rpm for 45 minutes.⁷



Figure 2. Electrolab dissolution tester equipment

This test was done by inserting the tablets into a dissolution container containing a dissolution medium. If air bubbles appeared on the surface of the test preparation, they must be removed. The dissolution tester run at a speed of 100 rpm. At intervals of 5, 10, 15, 20, 25, 30, 35, 40, and 45 minutes, 0.5 ml of sample was taken inside the middle area between the dissolution media surface and the top of the basket. The sample was then put into a 25 ml measuring flask and was diluted with 0.1 N HCl to the line mark (aliquot solution). The volume of the conditioned medium was always fixed by adding a 0.1 ml HCl medium of 0.5 ml each time when a sample was taken. The uptake of the solution was measured at a wavelength of 475 nm (0.1 N HCl was used as a blank). The dissolution test above was on a single-dose rifampicin tablet and a 2FDC tablet.⁷

Determination of the amount of rifampicin in 2FDC tablet preparations was maintained by filtering an aliquot solution (10 ml of the first filtrate was discarded). After the aliquot solution was cold (let it stand for 10 minutes), as much as 5 ml of filtrate and 10 ml of phosphate buffer were put into a 50 ml measured flask. The mixture was then diluted with water up to its mark. The uptake of the solution was carried out at a wavelength of 475 nm (wavelength of

rifampicin).⁷

Result data analysis of the dissolution test for rifampicin and mixed tablets was conducted by using a dissolution efficiency (DE) method. The dissolution efficiency was a ratio of an area under the dissolution curve at a particular time to an area of a rectangle representing 100% of active substances dissolved at the same time. The data used in this test was the DE value at 45 minutes (DE_{45}).

Data analysis

The obtained data were analyzed by using the Mann Whitney test. The data were considered significant if the p-value <0.05 with a 95% confidence interval. All the data were analyzed by using statistical software. Data are presented as mean + standard deviation.

RESULTS

Table 1 demonstrated physical test results of tablets for both rifampicin preparations (2FDC and single). In determining their dissolution test levels, researchers used a standard curve equation with a concentration series of 20, 30, 40, 50, 60, and 70 mcg / ml at 475 nm was taken for rifampicin and 2FDC single preparations according to Table 2.

Table 1. Physical test results of the tablets

Preparation	Fragility test (%)	Hardness test (Kg)	Disintegration time test of tablet (Minute)
2 FDC tablet	0.14±0*	10.19±0.53	10.92±0.29*
Rifampicin tablet	0.25±0.11*	11.07±2.67	2.06±0.23*

Note: * p<0.05

Based on results of Q Total dissolution test (the total amount of rifampicin dissolved in the dissolution medium in each time) against rifampicin tablets and 2FDC (RifaNH) tablets can be plotted in a time (minute) of curve with Q total. This curve aimed to show solubility profiles of

the rifampicin in the dissolution medium when each time the samples were presented (Figure 3). Figure 4 presented the relationship between DE and time. DE_{45} values on rifampicin tablets and 2FDC tablets respectively have an average of 92.03 ± 9.61 and 93.94 ± 4.35 .

Table 2. Equation series of the rifampicin standard curve

Preparation	Equation
Single preparations of rifampicin	$Y=0.0093x + 0.0239$ R = 0.9998
2FDC preparation	$Y= 0.0116x -0.0198$ R = 0.9956

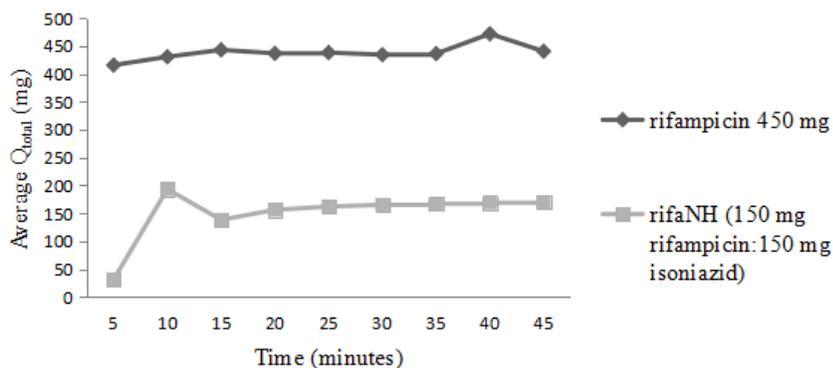


Figure 3. Relationship of the averages of Q total to time (minutes)

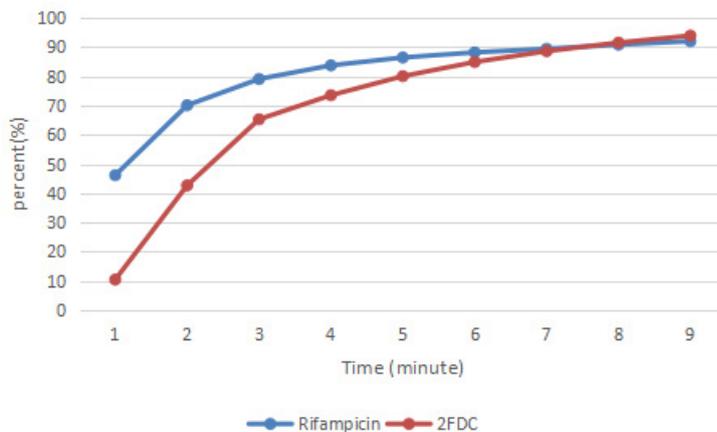


Figure 4 . Dissolution speed test profile (DE)

DISCUSSION

The WHO and the International Organization for Tuberculosis and Lung Disease (IUATLD) have recommended FDC containing Isoniazid and Rifampicin as one of TBC therapies.⁸ Isoniazid is a class I biopharmaceutical classification (BCS), a very soluble or very permeable drug, meanwhile rifampicin (RIF) belongs to a BCS class II drug with high permeability and low

solubility drug.⁹ Because of its low solubility, RIF (solubility 2.5 mg/ml, log p 1,086, pKa 4.96 ± 0.7) has bioavailability in FDC formulation and single doses.¹⁰ The low bioavailability of RIF is due to changes in crystal properties, interactions with excipients, degradation in the digestive tracts, variability in absorption and metabolism, and changes in pH that can interfere with the speed of rifampicin solubility.¹¹

FDC formulation will affect values of product of the bioavailability.⁵ Therefore, it is necessary to observe physical natures of the FDC formula as an initial screening to ensure effectiveness of the product. This study compared physical properties and dissolution tests on rifampicin compounds existing in combination preparations (FDC tablets) and singles (generics).

Results of the rifampicin fragility test showed that a single preparation had a more significant percentage of fragility than the 2FDC tablets ($p < 0.05$ with Mann Whitney test). The 2FDC tablets and generic rifampicin tablets in this study could reach the fragility testing requirements (total shortage of tablets $< 1\%$).⁶ The fragility test found that generic rifampicin preparations were more fragile than those in the FDC combination formula. It was because binders used were not homogeneously distributed in the tablets. Another cause of this condition was an error when the drug was manually compressed. On the other hand, this study could argue that the rifampicin FDC dosage formula was stronger than the single dosage formula.

This study for hardness test tablets also could demonstrate that there was no difference of the hardness between single-dose rifampicin tablets and 2FDC combination preparations ($p > 0.05$). The hardness test in this study still fulfilled the research requirements even though the hardness of the tablets used was higher than 10 kg (a requirement of a reasonable tablet hardness testing was 4-10 kg). It was because requirements of disintegration time and dissolution in this study still reached their standard criteria. The rigidity of the single rifampicin tablet used in this study was due to the drug used as a film-coated dosage formula.

The result of disintegration time test 2FDC and rifampicin tablets reached the reasonable disintegration time testing requirements, which were no more than 15 minutes.⁷ The limit value on non-coated tablets and non-enteric coated tablets, i.e. no less than 16 of the 18 tablets tested, must be destroyed entirely.⁷ Statistical test results on rifampicin tablets and 2FDC tablets reported that there were significant differences in the two

dosage formulas of rifampicin ($p < 0.05$). The statistical test could demonstrate an effect of the combination of isoniazid and rifampicin in 2FDC tablets on the disintegration time of the tablets.

Based on results of figure 3 (Q total versus time) of rifampicin tablets and rifampicin and isoniazid mixture (2FDC) tablets showed the higher the dissolution time was, the more dissolved rifampicin increased. The Indonesian pharmacopoeia monograph IV stated that the concentration of 75% solute for rifampicin was indicated at 45 minutes. The results of this study are appropriate to what The Indonesian pharmacopoeia monograph IV argued because, at 45 minutes, the concentration obtained was more than 75%.

In the dissolution efficiency test (DE_{45}), it found that there was a difference between a single-dose rifampicin tablet and rifampicin-INH (2FDC) tablets on each replication. However, the results of statistical tests showed that there was no significant difference in mean DE_{45} values in the two tablets ($p > 0.05$). The results indicated there was no effect of the combination of Isoniazid and rifampicin in 2 Fixed-Dose Combination (2FDC) tablets on the rate of dissolved rifampicin drugs.

CONCLUSION

The combination of rifampicin and Isoniazid in 2 Fixed-Dose Combination tablets (2 FDC) does not affect the hardness and dissolution of the rifampicin drug, but it affect the fragility and disintegration time of the drug.

CONFLICT OF INTEREST

None of the authors have declared any conflict of interest.

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