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Research Paper

Formulation and Evaluation of Azithromycin Dihydrate Solid Dispersion with Esther of Polyethylene Glycol-6000 and Stearic Acid Using A Co-Grinding Technique

Mardiyanto[1]*, Budi Untari[1], Ady Mara[2], Nauval Hady Prasetyo[1]

[1]*Department of Pharmacy, Faculty of Mathematics and Natural Science, Sriwijaya University, Ogan Ilir, 30662, Indonesia*
[2]*Department of Chemistry, Faculty of Mathematics and Natural Science, Sriwijaya University, Ogan Ilir, 30662, Indonesia*
***Corresponding author**: mardiyanto@mipa.unsri.ac.id*

Abstract
Azithromycin is a narrow-spectrum bacterial growth inhibitory antibiotic derived from macrolides with low dissolution in water. Several methods have been carried out to increase the dissolution of medicinal substances, one of which is solid dispersion. Solid dispersions are mixtures consisting of one or more active substances in an inert carrier. The purpose of this study was to determine the effect of formatting solid dispersions with PEG 6000 polymer and stearic acid on increasing the dissolution rate of azithromycin. The method of formatting solid dispersions uses the co-grinding method. Solid dispersion of azithromycin was prepared in four formulas with variations in the amount of PEG 6000. Tests carried out on solid dispersion samples of azithromycin were XRD, FTIR, SEM, solubility tests, and dissolution tests. Test results on azithromycin solid dispersions prepared by co-grinding showed that there was an effect of the amount of PEG 6000 on decreasing the intensity of azithromycin crystals, there was no chemical interaction between azithromycin and the carrier, differences in the morphology of pure azithromycin powder and solid dispersions, and an increase in the dissolution of solid dispersions in medium SIF.

Keywords
Azithromycin, Solid Dispersion, Dissolution, FTIR, XRD, SEM

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1. INTRODUCTION

Azithromycin, a macrolide-derived antibiotic compound is one of the most widely used antibiotic compounds in the world. Azithromycin is given orally to treat bronchial infections, skin infections, and inflammation of the tonsils (Parnham et al., 2014; Martingano et al., 2020; Blumenberg et al., 2020). Azithromycin (Figure 1) is known to have low solubility in water, therefore its absorption after oral administration is very low. This can affect its therapeutic effectiveness. Based on the system of classification for biopharmaceutical substances (BCS), azithromycin is included in the second class category, namely substances with low solubility and high permeability. The process of absorption of azithromycin in the body will be limited by its low dissolution rate, therefore the increase in the dissolution rate of this drug will be very significant (Kalepu and Nekkanti, 2015; Mardiyanto et al., 2022; Mardiyanto et al., 2021).

Azithromycin in the last two years has become popular because it is known to have the potential as a therapeutic agent for COVID-19 infection (Pani et al., 2020; Sultana et al., 2020). The effect of azithromycin as an antiviral has been demonstrated in vitro, although not all samples have been tested in vivo. Azithromycin is known to mediate exacerbations of airway disease, particularly asthma. Its effect was studied against viruses that cause respiratory tract infections such as rhinoviruses. Azithromycin inhibits rhinovirus replication and release in human bronchial epithelial cells. In various drug effectiveness tests against SARS-CoV2, azithromycin was found to be a target in bioinformatic screening investigations of pathways that could potentially be converted into pharmaceutically acceptable forms (Schwartz and Suskind, 2020; Gyselinck et al., 2021).

The use of polymers for medicinal products acceptable to the human body has advanced (Pokhrel, 2015; Ainurofiq et al., 2021). Polyethylene glycol (PEG) with a molecular weight of 6000 is a non-ionic, water-soluble natural polymer. PEG 6000 is the most widely used carrier as a solid dispersion carrier and is proven to provide an increase in dissolution rate in preparations. One of the advantages of using PEG 6000 as a carrier material is that it can change the drug particles to become more amorphous so that the rate of drug dissolution can be better. PEG in general has been widely used as a carrier

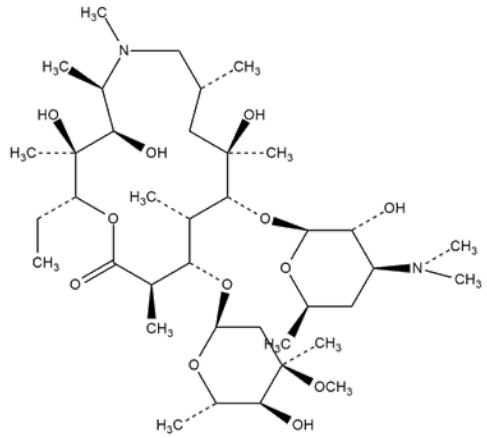

Figure 1. Molecular Structure of Azithromycin

for solid dispersion preparations. This is because PEG has a low melting point, fast freezing rate, ability to form solid solutions, and low toxicity. Solid dispersion with PEG 6000 carrier polymer has better storage stability when compared to 16 kDa chitosan, 30 kDa PVP, 11 kDa chitosan, and PEG 4000. The higher molecular weight of PEG 6000 results in a higher dissolution rate. This is because a higher viscosity can inhibit recrystallization (Li et al., 2015; Fu et al., 2014).

Stearic acid is a saturated fatty acid having 18 carbon atoms. Stearic acid has a much higher melting point than human body temperature. The higher melting point of stearic acid compared to human body temperature means that stearic acid can be used as a lipid matrix in nanoparticle formulations. Previous studies reported that the formation of Stearic acid is added to solid dispersion formulas as a lubricant. Lubricants are used to prevent the active substance from agglomerating and sticking to the grinding balls and to ensure that preparation of the preparation can occur with low friction between the solid dispersion preparations and the mold walls (Monteyne et al., 2016; Chen et al., 2023). Based on important information regarding azithromycin, PEG 6000, and stearic acid, a physical interaction study was carried out through the co-grinding technique.

2. EXPERIMENTAL SECTION

2.1 Materials

The materials used in this study were azithromycin dihydrate (Dexa Medica company), PEG 6000 polymer, stearic acid, KH_2PO_4, NaOH, and hydrochloric acid was obtained from (Merck KGaA), and water for injection was obtained from Otsuka.

2.2 Laboratory Work

2.2.1 Physical Mixture Preparation

Physical mixture preparation was carried out with good precision measurements. The physical mixture consists of azithromycin in the amount of 100 mg, 900 mg of polysorbate- 6000, and 200 mg of stearic acid. The mixture was obtained and mixed in a glass beaker for five minutes. Mixing was carried out using a stir bar homogeneously. The results of the physical mixture are weighed and stored in a container that is not damp and away from sunlight (Guo et al., 2014; Fitriani et al., 2016).

2.2.2 Preparation of Buffer and Antibiotics

The phosphate buffer of pH 6.0 was prepared by mixing NaOH and KH_2PO_4. Created two masses. Mass 1 was prepared by weighing 6.810g of KH_2PO_4 and dissolved in 300 mL of distilled water. Mass 2 was prepared by weighing 0.15 g of NaOH and dissolved in 300 mL. Mass 1 and mass 2 are mixed in a beaker glass and distilled water is added to 1000 mL. The solution that has been formed is checked for its pH with a pH meter until the pH shows pH 6.0. Azithromycin in phosphate buffer was analyzed using a UV spectrophotometer. The standard drug determination curve was prepared by adding azithromycin in the buffer to obtain the linearity >0.990. The graph obeys the quantification law in the appropriate range to be selected. The concentrations of standard solutions used in this study were 20, 30, 40, 50 and 60 ppm (Beynon and Beynon, 2018).

2.2.3 Formulation

The azithromycin solid dispersion formula and azithromycin physical mixtures are shown in Table 1. The azithromycin solid dispersion formulations in this study were made into four formulas (F1, F2, F3, and F4) and one physical mixture formula (PM) was made as a comparison. Four azithromycin formulas of solid dispersion (Guo et al., 2014; Fitriani et al., 2016) were made to get the best azithromycin solid dispersion that passed every solid dispersion system evaluation test. The solid dispersion formulation in this study is azithromycin as much as 100 mg. Variations in this study were the amount of PEG 6000 used, namely 300 mg, 500 mg, 700 mg, and 900 mg. PEG 6000 variation was carried out to determine the best amount of PEG 6000 in improving azithromycin solubility.

Table 1. The Formula of Solid Dispersion of Azithromycin

Substances	Ammount of Substances				
	F1	F2	F3	F4	PM1
Azithromycin (mg)	100	100	100	100	100
PEG 6000 (mg)	300	500	700	900	900
Stearic acid (mg)	200	200	200	200	200

2.2.4 Preparation of Solid Dispersion

The preparation of azithromycin solid dispersion was carried out by the co-grinding method (Guo et al., 2014; Fitriani et al., 2016). Each formula is weighed and its weight is compared with the weight of the grinding ball used. The ratio of dosage weight and ball weight used is 1:8. The mixture of each formula was milled in a planetary ball mill for 20 minutes and every 5 minutes for machine breaks so that grinding does not cause

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excess heat to the ground preparations. Preparations that have finished their grinding period are stored in a dry room and away from sunlight.

2.2.5 Dissolution Test

Evaluations of the quality dosage form (part of 2.6, 2.7, 2.8, and 2.9) were conducted based on Ahuja et al. (2015) and Martin et al. (2020). In-vitro dissolution testing of azithromycin dispersion was carried out by testing azithromycin dihydrate, PEG 6000, physical mixture, and azithromycin solid dispersion in a dissolution tester at 100 rpm in 900 ml of buffer dissolution apparatus (Erweka DT-950). The test was maintained at a temperature of 37.0 ± 0.5 °C. The dissolution test was carried out using 100 mg of pure drug and an equivalent amount of the individual sample preparation. Aliquots of 5 ml were withdrawn at specified intervals of six ranges each 5 minutes with adding fresh medium of each range. The resulting sample was free particles and quantification by UV-Vis spectrophotometry.

2.2.6 X-Ray Diffraction (XRD)

The characterization of azithromycin solid dispersion was carried out by measuring azithromycin dihydrate, PEG 6000, stearic acid, azithromycin physical mixture, and azithromycin solid dispersion preparations using an X-ray diffraction meter machine (Rigaku MiniFlex-600). Measurements were made with copper tube anodes in intervals of 5 - 900 2θ-1. The operational parameters used are a voltage of 45 kV volts, a generator current of 40 mA, a scan step time of 9 seconds, and a scan step size of 0.0080 (2θ).

2.2.7 Fourier Transform Infrared (FTIR)

FTIR spectra of samples, polysorbate- 6000, stearic acid, physical mixture of azithromycin, and azithromycin solid dispersion were obtained by testing using an IR spectrophotometer (Thermo-Scientific®). About 0.1 mg of the sample was united in dry KBr and spectra were monitored in the wavenumber range of IR.

2.2.8 Solid Dispersion Morphology of Azithromycin

The other area of grinding powdered samples of azithromycin was determined using a scanning electron microscope (JEOL® JSM-6510A). Samples were placed on a sample disc carrier silica stub (15 mm, 5 mm height) and plated with gold under vacuum (0.25 Torr). The image was visualized by using a 30 kV beam of the electron.

3. RESULTS AND DISCUSSION

3.1 Preparation of Azithromycin Solid Dispersion Formula

The solid dispersion of azithromycin prepared using the co-grinding technique enhanced the dissolution of the dosage form (Martínez et al., 2022). This is because the co-grinding process will modify the solid properties of the drug compounds. Azithromycin crystalline solid will undergo transformation into an amorphous phase in the polymer chains. The co-grinding technique has an advantage when compared to other solubility-enhancing techniques because co-grinding technique is carried out in a simple and environmentally friendly manner because it does not require organic solvents (Chun et al., 2013).

Preparation of azithromycin solid dispersions using the co-grinding technique utilizes the principles of impact and attrition for particle size reduction that occurs when the ball falls from near the top of the hollow cylindrical shell. The azithromycin solid dispersion samples for each formula were put into a ball mill using ceramic-based balls, for twenty minutes of grinding time and every five minutes of rest during the grinding process.

The grinding time of each azithromycin solid dispersion sample was set for 20 minutes. Grinding the sample for 20 minutes has increased the particle distribution, this is due to the ball milling treatment for 20 minutes can reduce the particle size and increase the specific surface area of the sample. The grinding elements in a ball mill move at different speeds. Hence the kinetic energy between two or more elements varies greatly in the charge of the balls. These forces originate from the rotational motion of the balls and the movement of the particles in the mill and the contact zone of the balls colliding with each other during grinding. The total weighing amount of formula 1 was obtained as much as 0.6 g. Formula 2 was obtained as much as 0.8 g. Weighing in formula 3 obtained as much as 1 g, and weighing in formula 4 obtained as much as 1.2 g. The weight of each formula must be compared to the weight of the grinding ball in a ratio of 1:8. This is intended so that the grinding process can run well and minimize material damage due to the inappropriate number and weight of grinding balls. The grinding product was revealed in Figure 2.

Figure 2. Product of Co-crystal

Physical mixture azithromycin is prepared by weighing each ingredient according to a predetermined physical mixture formula. The material that has been weighed is mixed in a beaker glass and stirred homogeneously with a stirring rod for 5 minutes. Stirring with a stir bar aims to avoid too much mechanical friction that can damage the material. The completely

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mixed physical mixture was stored in a plastic clip and kept in a dry room.

3.2 Quantification of Azithromycin Dihydrate

Azithromycin dihydrate was analyzed using UV-Vis spectrophotometry. UV-Vis spectrophotometric analysis consisted of two stages, namely scanning the maximum wavelength of azithromycin and determining the calibration curve. A mixture of azithromycin with phosphate buffer pH 6.0 was used as a solution parent stock, and phosphate buffer pH 6.0 were used as blanks in the analysis of azithromycin using UV-Vis spectrophotometry. The maximum wavelength of azithromycin was scanned on a UV spectrometer (200-400 nm) using a standard solution to determine λmax. UV-Vis spectrophotometric analysis of azithromycin in phosphate buffer solvent obtained λmax at 205 nm. λmax azithromycin in phosphoric acid and 1N NaOH at pH 6.0 showed a maximum wave peak at 210 nm.

Determination of the azithromycin calibration curve using 5 concentration ranges, namely 20; 30; 40; 50; and 60 ppm. Determination of the standard curve of azithromycin dihydrate will obtain the required linearity in azithromycin analysis. Linearity is used to obtain test results that are directly proportional to the concentration of the analyte within a certain range. Generally, linearity is known as the variance of the slope of the regression line. The linearity obtained from the standard curve can be used to calculate the percent release from the dissolution rate of azithromycin.

Based on the tests that have been carried out, the linearity of azithromycin was 0.993. These results indicate that the linearity of azithromycin obtained is acceptable. The acceptance criterion of linearity is that the correlation coefficient (R2) is not less than 0.990 for line analysis using the least squares method. In addition, the relative standard deviation (RSD) should not be greater than 5.0% at all standard concentrations.

3.3 Dissolution Test

The dissolution test was carried out using a type II dissolution tester. The test was carried out in a phosphate buffer medium (pH 6.0). Azithromycin has a major problem, namely, it is very poor solubility in biological fluids resulting in poor bioavailability after oral administration. So that various techniques are applied, one of which is solid dispersion. Through dissolution testing, it can be seen that the increase in solubility of azithromycin solid dispersions is compared to that of pure azithromycin. Tests were carried out on pure azithromycin samples, physical mixtures, and the best azithromycin solid dispersion formula, namely formula 4.

Based on the results of the average percent release of azithro mycin solid dispersion, it was found that in the 5th minute, the solid dispersion dissolved 167.17%. This shows that within 5 minutes there were 62.138 mg of ground powder which had dissolved in SIF phosphate buffer pH 6.0. The average percent release of solid dispersions in the last minute was 202.91%, which means that there were 83,328 mg of solid dispersions that dissolved. and the solubility properties of azithromycin. The Percent DE of solid dispersion was 427.03% for 45 minutes.

The average percent release of pure azithromycin at 5 and 45 minutes was 13.6% and 16.1%, respectively. This shows that in the 5th minute, the sample of azithromycin dissolved as much as 5.181 mg, and in the 45th minute as much as 5.918 mg. It is known that the percent release of pure azithromycin is smaller when compared to azithromycin solid dispersion. This could be because pure azithromycin has a larger particle size compared to azithromycin solid dispersion. The percent DE value of pure azithromycin was obtained by as much as 32.66% for 45 minutes. All the results were revealed in Figure 3.

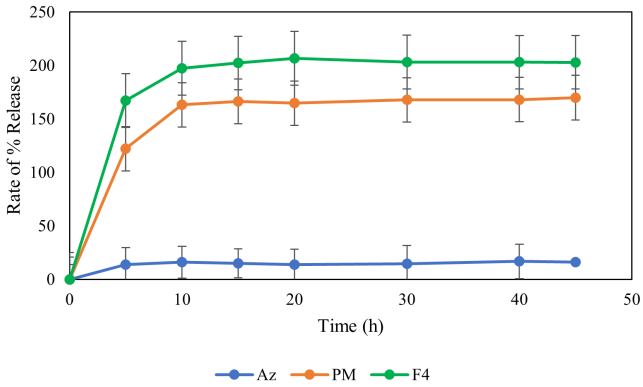

Figure 3. Dissolution Profiles of Pure Substances (Az), Physical Mixture (PM), and Solid Dispersion (F4)

Based on the results of dissolution calculations, it can be concluded that azithromycin solid dispersion preparations can increase the low solubility of azithromycin in physiological fluids. The ground powder method, applying a hydrophilic polymer such as polysorbate-6000 can be obtained as the relevant technique to increase the solubility of azithromycin. The released percent and DE percent data from the dissolution tests that have been analyzed will then be analyzed statistically using ANOVA and independent t-test, to see the significant difference between these parameters to the solid dispersion of azithromycin and pure azithromycin.

Statistical analysis was performed to compare three or more means. The main assumption in applying ANOVA analysis is that the response must follow the normal distribution. The variance of the response is constant and independent and randomly distributed. Based on the results of azithromycin solid dispersion ANOVA analysis, it is known that the largest average percent dissolution release occurs in the 20th minute. The significance value in the ANOVA analysis shows a value of 0.00. This explains that the average percent release of the three samples is significantly different. Independent t-test analysis was performed to determine the significance of the two samples, namely solid dispersion with pure azithromycin and solid dispersion with the physical mixture.

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Independent t-test ANOVA analysis was performed using SPSS. The average yield of percent release between pure azithromycin and azithromycin solid dispersion obtained a significance value of 0.00. This shows that there is a difference in the percentage of release between the solid dispersion and pure azithromycin. According to statistical significance value of less than 0.05 means there is a significant difference in the sample, but if it is more than 0.05 then there is no difference between the two samples. Percent DE analysis using an independent t-test obtained a significance value of 0.00.

Independent t-test analysis of the percent release and percent DE of solid dispersions with physical mixtures shows a significant value of 0.00. The results of the independent t-test showed that the solubility values of the solid dispersions and physical mixtures obtained were different. This could be because the azithromycin solid dispersion has undergone a transformation of the crystallinity of the drug to become amorphous and has experienced a reduction in particle size so that the surface area of the solid dispersion increases.

3.4 X-Ray Diffraction (XRD) Test

X-ray diffraction is used to view single-crystal or polycrystalline materials. Most X-ray diffraction tests work based on the reflection geometry of the sample being tested. The results of the XRD test are generally in the form of a diffractogram, where the y-axis is expressed as the intensity and the x-axis shows the angle of the scan. Based on the observations of the XRD results of the six samples tested, it is known that each sample shows a different diffractogram pattern. This shows that the milled solid dispersion of azithromycin causes a change in the shape of the particle geometry. So the reflection geometry that is plotted on the XRD diffractogram can be different.

Based on the results of the XRD test, it was found that the pure azithromycin dihydrate sample had a maximum crystalline intensity of 4822 at an angle of 2θ of 9.790, while the physical mixture sample had a maximum crystalline intensity of 1164 at an angle of 2θ of 19.080. XRD profile analysis on azithromycin showed that the crystal peaks were located at an angle of 2θ = 9.58-9.980. While the amorphous phase in the XRD data is indicated bythere is a peak at an angle of 2θ of 190-350. So it can be seen that the azithromycin data obtained have shown the intensity at the crystal peak, and the physical mixture has shown a peak at the amorphous phase.

The results of the XRD test (Figure 4 and Figure 5) on each sample of the azithromycin solid dispersion formula were compared with the results of the XRD test on the physical mixture. Formula 1 is known to have a maximum crystal intensity of 1562 at an angle of 2θ of 23.410, formula 2 shows a maximum crystal intensity of 828 at an angle of 2θ of 19.040, formula 3 has a maximum crystal intensity of 1882 at an angle of 2θ of 23.180, and formula 4 has a maximum crystal intensity namely 636 at an angle of 2θ of 19.040. Through the results of XRD analysis and comparison with the physical mixture, it is known that formula 4 fulfills the requirements, this refers to the decrease in sample crystal intensity. Based on the results of the XRD analysis, it can be seen that the four solid dispersion samples of azithromycin have shown a change in the phase of the particles from crystalline to amorphous. This is known based on the maximum peak angle of 2θ for each sample which is in the suitable range.

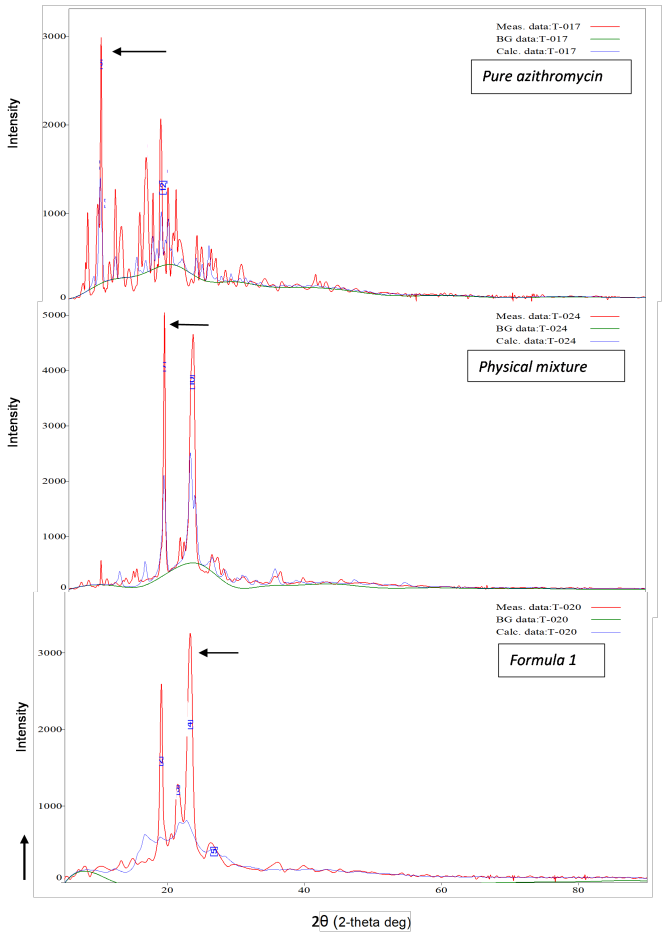

Figure 4. XRD Analysis of Pure Substance, Physical Mixture, and Optimum Formula

Based on a comparison with the results of the XRD physical mixture, the results of the XRD analysis in formulas 2 and 4 showed a decrease in crystal intensity, while formulas 1 and 3 showed an increase in crystal intensity.

The decrease in crystal intensity in formulas 2 and 4 is due to the milling process which reduces the level of crystal regularity. Treatment of the sample using the milling technique not only changes the phase formed, but the sample experiences a decrease in diffraction intensity which can decrease the crystallinity index or level of crystal regularity.

Formulas 1 and 3 experienced an increase in maximum crystal intensity. This could be because, after the milling process, formulas 1 and 3 changed back from the amorphous to crystalline phases. The crystallization process of formulas 1 and 3 can occur during the sample storage period. Amorphous

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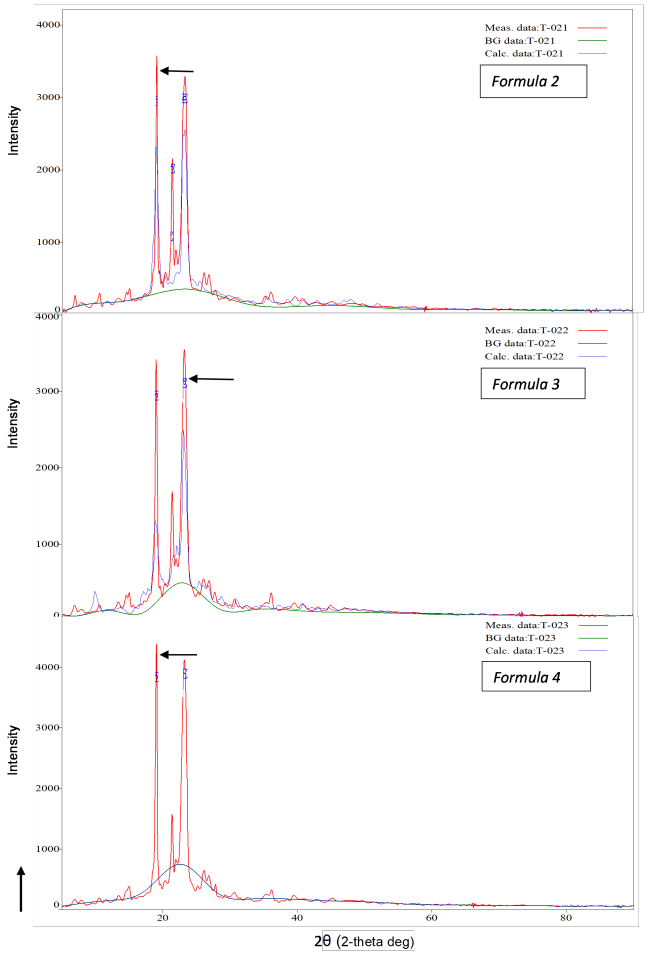

Figure 5. XRD Analysis of Formula Preparation

solids have high energy and mobility, but this also makes amorphous solids physically unstable. Amorphous particles during operation or storage tend to return to a metastable crystal.

The crystallization process can occur in each sample. This is because mechanical activation can cause incomplete disruption leaving crystal regions or high energy points which leads to recrystallization over time or thermal degradation of the milled sample. The amorphous phase in formulas 2 and 4 can last longer due to better sample storage, besides that the concentration of the polymer also affects the increase in the glass transition temperature (Tg). The relationship between Tg and mechanical properties in large quantities greatly affects the polymer used. Most polymer-carriers have a high Tg temperature, thereby increasing the Tg of amorphous drugs.

Analysis using XRD showed that each sample changed to the amorphous phase. The difference in maximum crystal intensity between formulas 2 and 4 is due to the different concentrations of PEG 6000 used. This shows that PEG 6000 affects the phase change of the particle of azithromycin solid dispersion. However, the change in particle phase is not the only parameter of increasing azithromycin solubility.

3.5 Fourier Transform Infrared (FTIR)

The chemical interaction study of azithromycin solid dispersions was carried out using FTIR instruments. Infrared spectroscopy in this experiment is intended to determine whether there are changes or certain interactions between the carrier substance and azithromycin. The absorption spectrum of the sample is recorded on the wave numbers 4000-200 cm^{-1}. FTIR analysis was performed on pure azithromycin dihydrate, PEG 6000, stearic acid, physical mixture, and azithromycin solid dispersion formulas (F1, F2, F3, and F4) were revealed in Figure 6.

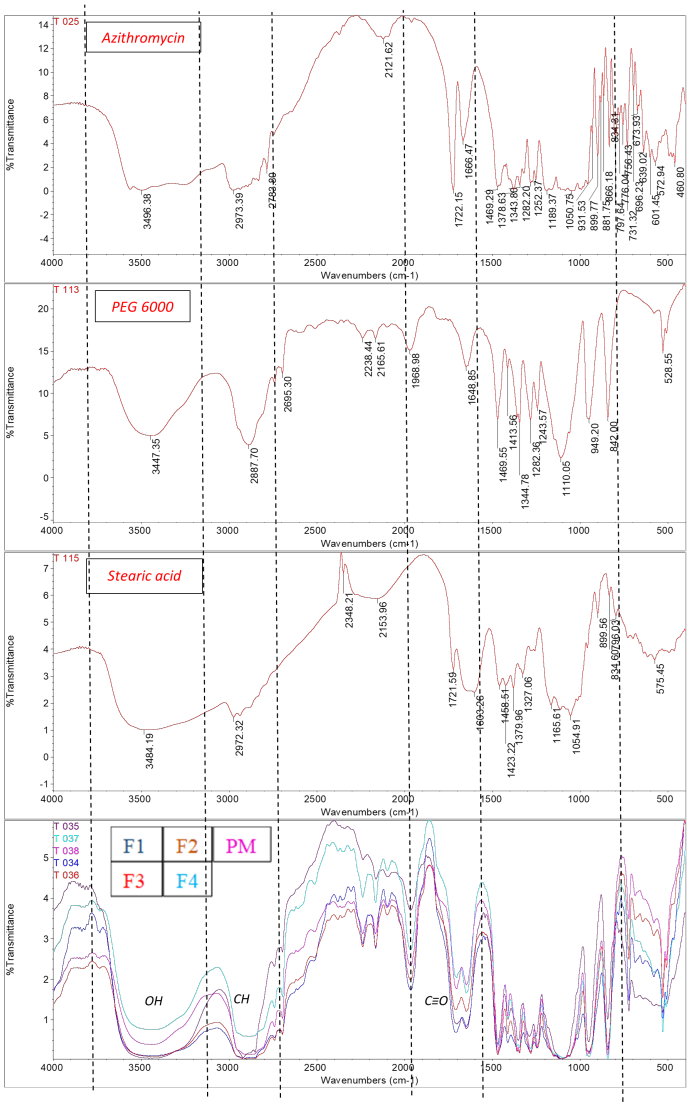

Figure 6. Results of FTIR Measurements

The FTIR spectrum of pure azithromycin in the single bond absorption region (2500-4000 cm^{-1}) is known to contain a hydroxyl group (-OH) marked with a peak at 3496.38 cm^{-1}. Whereas in PEG 6000 and stearic acid, it is known that

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the hydroxyl groups are present at the peaks of 3447.35 and 3484.19 cm^{-1}. FTIR results on the physical mixture hydroxyl absorption band shifted towards 3449.05 cm^{-1}. The results of FTIR analysis in the single bond region are by the literature. The molecular spectrum of azithromycin and the chemical structure of PEG show OH stretching at 3495.60 and 3560.68 cm^{-1}. The hydroxyl absorption bands in the solid dispersion samples of azithromycin F1, F2, F3, and F4 are marked with peak numbers at 3459.33, 3455.78, 3447.89, and 3432.12 cm^{-1}, respectively.

The FTIR spectrum of pure azithromycin in the double bond region (1500-2000 cm^{-1}) shows a peak number at 1722.25 cm^{-1} (C=O strain). The spectrum on PEG 6000 shows peaks at 1968.98 cm^{-1} (C-H strain) and 1648.85 cm^{-1} (C=C strain). The spectrum of stearic acid has a peak at 1721.59 cm^{-1} (strain C=O). The FTIR spectrum results for the physical mixture and each solid dispersion sample of azithromycin showed lower peaks at 1722.25 and 1721.59 cm^{-1} but showed identical peaks at 1648.85 cm^{-1}.

The range of the fingerprint region on the FTIR spectrum is in the range of 600-1500 cm^{-1}. The peak numbers of pure azithromycin in the fingerprint region (Table 2) are 1469.29 cm^{-1} (C-H strain), 1282.20 cm^{-1} (C-N strain), and 1105.75 (C-O strain). The spectrum on PEG 6000 shows peaks of 1469.55 (C-H strain) and 1413.56 cm^{-1} (O-H strain). Stearic acid shows a peak number at 1458.51 cm^{-1} (C-H strain). Based on the analysis of the physical mixture spectrum and solid dispersion samples, it is known that each peak only experiences a change in intensity at wave number. This can be caused by the mechanical forces in the milling process causing a shift in the intensity of the wave number. Based on the results obtained from the FTIR analysis of the solid dispersion of azithromycin, it can be seen that there is no new peak formed as a result of mixing azithromycin with other carriers. This indicated that there is no chemical interaction arising from the results of mixing azithromycin with PEG 6000 and stearic acid.

Table 2. The Formula of Solid Dispersion of Azithromycin

Wave Number (cm^{-1})	Functional Group
3550 – 3200	O-H (hydrogen bond)
2000 – 1650	C-H (aromatic)
1740 – 1720	C=O
1469 – 1450	C-H
1420 – 1330	O-H
1342 – 1266	C-N

3.6 Solid Dispersion Morphology of Azithromycin

Morphological testing of azithromycin solid dispersions was carried out using a scanning electron microscope (SEM) instrument and the results were revealed in Figure 7. Morphological testing of this research was conducted to see the topographical characterization of the azithromycin solid dispersion that had been prepared. SEM analysis was carried out on pure azithromycin samples, physical mixture, and the best formula in the study, namely formula 4. SEM testing was carried out by taking pictures at one location with magnifications of 2,500× and 5,000×.

Based on SEM results on pure azithromycin, it was found that the morphology of pure azithromycin particles had a crystal structure with sharp edges.). Pure azithromycin crystals are cuboidal with sharp edges, whereas SEM solid dispersions of azithromycin show the presence of irregular particles with several microscopic gaps. Azithromycin particles are coarse, mostly cubic with smooth surfaces. Therefore it can be seen that the morphology of the azithromycin crystals obtained is following the literature and previous studies (Sabnis et al., 2022).

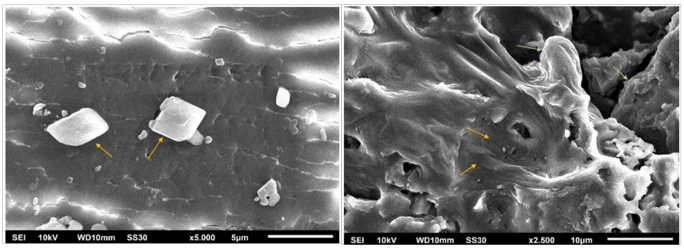

Figure 7. Results of SEM Measurement of Azithromycin (Left) and Co-crystal Product (Right)

SEM morphology of the physical mixture samples showed an irregular structure indicating the mixing between pure azithromycin and the carrier used. However, in the SEM physical mixture morphological images, azithromycin crystal structure can still be found. This indicates that the azithromycin molecule is not completely dispersed in the physical mixture carrier substance. Through physical mixing, the crystal size of azithromycin can be reduced, but because the mixing is not through grinding the azithromycin crystals cannot be completely dispersed in the carrier.

The SEM morphology of solid dispersion shows an irregular particle structure with several microscopic gaps. This shows that in formula 4 the particles have changed into amorphous forms and the azithromycin molecules are dispersed in the solid dispersion carrier matrix. Azithromycin crystals are mostly distributed on the surface of the ground powder. The SEM results obtained were comparable to the results of the XRD test, where it was known that the highest crystallization intensity was found in pure azithromycin and solid dispersions had the lowest crystalline intensity because they had changed to the amorphous phase (Sadia Pervez and Muhammad, 2021).

Regarding the particle morphology images obtained, it is known that grinding in solid dispersion has reduced the crystal size of azithromycin and distributed it in the carrier. Azithromycin crystals that have been in the form of an amorphous phase have experienced an increase in the dissolution

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rate, caused by a decrease in crystallinity. Dissolution testing is required to determine the level of dissolution in azithromycin solid dispersions.

4. CONCLUSION

Based on the results of the research that has been done, the following conclusions can be drawn: The effect of PEG 6000 and stearic acid as carriers can increase the amorphous phase of the powder, as well as increase the solubility and dissolution rate of azithromycin solid dispersions.

5. ACKNOWLEDGMENT

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