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Research Paper

Formation of Hydroxyl-Amide Solid Dispersion Involving Azithromycin and Chitosan-Alginate Biopolymer to Increase the Dissolution Rate of Azithromycin

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Abstract
Research to increase the solubility of active pharmaceutical ingredients is usually conducted by reducing the particle size. This research is one side that used the solid dispersion systems to increase solubility, especially on macrolide antibiotics for which there is still little information. The co-grinding technique on azithromycin-chitosan-alginate was chosen to produce a solid dispersion system. The parameters observed were changes in crystal structure, FTIR spectral patterns, morphological changes, and dissolution profile changes. The results of this research showed a change in the pattern of X-diffraction of azithromycin, physical interaction between azithromycin and the polymer, changes in the image of surface of solid dispersions, the solubility of solid dispersions in simulated-intestinal-fluid (SIF) solutions, and an increase in the dissolution rate of azithromycin indicating that the co-grinding technique to produce solid dispersions can increase the solubility of azithromycin.

Keywords
Co-grinding, Solid-dispersion, Azithromycin, Chitosan, Alginate

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1. INTRODUCTION

The immunomodulatory properties of azithromycin are an important reason for its use against the inflammatory manifestations that cause interstitial lung disease. SARS-CoV-2 has been shown to exacerbate symptoms of lung inflammation and cause serious damage to the lung interstitial tissue. Azithromycin (Figure 1) is part of the class of macrolide-derived antibiotics and is one of the most important antibiotic compounds used in use to treat gram-positive bacteria (Myers and Clark, 2021; Echeverría Esnal et al., 2021).

Co-crystals can be utilized to change the crystalline phase of a drug compound into a soluble form. This effort is among the methods that have been taken by experts such as presenting nanoparticles, nanosuspensions, nano-emulsions, and others. Co-crystals were chosen because they are simpler to work with and do not require complex equipment to make nanoparticles. The novelty of this study is the character of large drug molecules that are insoluble crystals. The answer is being questioned by experts whether it can be changed into water-soluble properties with the co-crystal method (Sun et al., 2021; Nugrahani and Parwati, 2021).

Co-crystals can cause crystalline medicinal ingredients to lose their crystal structure to form soluble amorphs (Rekdal et al., 2018). Physical interactions in the form of hydrogen bonding from the carboxyl and amine functional groups of the drug substance with polymers having amide or ester functional groups. In the past decade, researchers have used many small molecule samples, namely piperine with polyhydroxy biopolymers, and among others, carboxylic acid drugs have been used with polyamide biopolymers (Ngilirabanga and Samsodien, 2021; Wu et al., 2020).

The most widely tried is the interaction of the carboxyl functional group of the drug substance with the amide of the polymer (Jiang et al., 2014; Bol'shakov et al., 2022; Brennan et al., 1998; Sharma et al., 2004). There is not much information regarding the interaction of the amine groups of medicinal ingredients with large molecular weights. (Bol'shakov et al., 2022; Brennan et al., 1998; Vangala et al., 2012).

Macrolides are large molecular weight antibiotics that have an amine group (Jednačak et al., 2020; Myers and Clark, 2021; Yuan et al., 2021; Mardiyanto et al., 2022a; Mardiyanto et al., 2022b) have low solubility in water (Echeverría Esnal et al., 2021; Jiang et al., 2014; Rajbhar et al., 2016; Vangala et al., 2012). Low solubility has an impact on low bioavailability Of the total discovery of new drug compounds, it is known that 70% have low solubility in water (Bhalani et al., 2022; Khatri

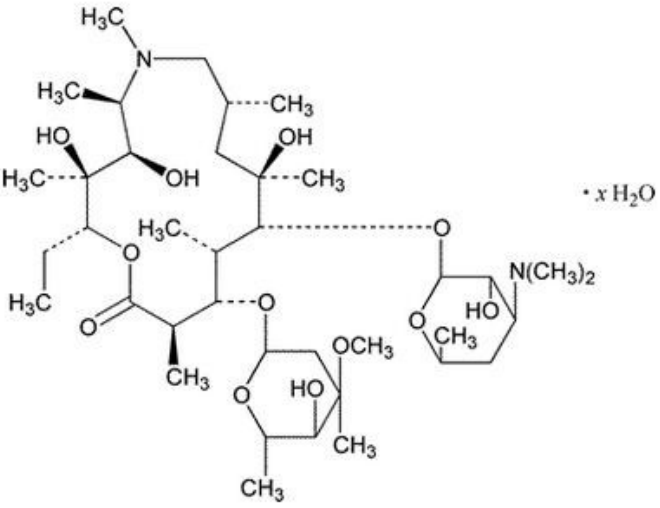

Figure 1. Azithromycin Chemical Structure

et al., 2022; Savjani et al., 2012).

2. EXPERIMENTAL SECTION

2.1 Materials

The materials used in this study were azithromycin dihydrate from Dexa Medica TBK, Chitosan and sodium alginate from Sigma-Aldrich®, KH_2PO_4, NaOH, and hydrochloric acid was obtained from Merck® KGaA, and water demineralized from Dira-Sonita®.

2.2 Procedure

2.2.1 Formula

The design of azithromycin carrier solid dispersion formulas consisted of 3 formulas as shown in Table 1. The three formulas used 100 mg of azithromycin based on preliminary research. The chitosan used was as much as 70 mg. Variations in the amount of ingredients in this study consisted of 80, 90, and 100 mg of sodium alginate which were given together with sodium alginate (Al Dulaimi et al., 2022; Lu et al., 2020; Wang et al., 2023).

Table 1. Three Formula of Solid-dispersion by Variation of Alginate Amount

Materials	Amount		
	F1	F2	F3
Azithromycin (mg)	100	100	100
Chitosan (mg)	70	70	70
Sodium alginate (mg)	80	90	100

2.2.2 Preparation Co-grinding

The co-grinding of azithromycin was created by the co-grinding method of chitosan and sodium alginate as a combination matrix using a ball-milling tool. Azithromycin solid dispersions were prepared in three formulas and all formulas were also prepared accurately. The weight of the ingredients for each formula was compared to the capacity of the grinding balls. The comparison of the weight of the mixture of ingredients and the capacity of the ball is 1:8. The composition of ingredients from each formula is milled in a miller machine for 20 minutes and the time interval is every 5 minutes. Products that have been finished from the milling process are stored in a climate of free vapor of water.

2.2.3 X-Ray Diffractogram

XRD analysis was performed using an XRD machine (Mini-Flex 600 from Rigaku®) on azithromycin samples, physics mixture, and azithromycin-chitosan-alginate solid dispersion formula. The operational parameters used are a voltage of 45kV, a generator current of 40 mA, a step scan of 10 seconds, and a scan of 2θ every 0.0080 (Al Dulaimi et al., 2022; Lu et al., 2020).

2.2.4 Fourier-Transform Infrared Spectroscopy

FTIR determination of functional group interactions using an FT-IR spectrophotometer (Thermo Scientific®). Infrared spectra collection was obtained by using three types of samples, namely azithromycin powder, chitosan, sodium alginate, physical mixture, and solid dispersion with a weight of 0.1 mg each. dispersed on the KBr plate and then the percent transmittance and wave number from 4000 to 500 cm^{-1} were measured (Garbacz and Wesolowski, 2020; Mardiyanto et al., 2022a).

2.2.5 Scanning Electron Microscopy

The morphology of the azithromycin solid dispersion product can be visualized using an SEM (JSM-6510A from JEOL®). Three samples were characterized by placing them on the SEM-holder (10 mm in diameter, 3 mm in height), then coating them with a layer of gold under vacuum (0.25 torr). Collection of Scanning Electron Microscope (SEM) images that scatter electron beams at 30 kV with magnifications of 500 times, 2500 times, and 5000 times (Jafari Ansaroudi et al., 2013; Khan et al., 2020; O'Malley et al., 2020).

2.2.6 Dissolution

Evaluation of the solubility of the solid dispersion product of azithromycin carrier was carried out by comparing the turbidity of the pure substance, the physical mixture, and the solid dispersion resulting from co-grinding in serial solutions for solubility tests. An excess of about 1 g of the drug was added to 10 ml of phosphate buffer (pH 6.8), HCl (pH 1.2), and distilled water. The sample was agitated at 100 rpm at 37°C for 15 minutes. The sample was then observed for turbidity at OD580. In-vitro dissolution testing of azithromycin solid dispersions was carried out by testing the dissolution results of co-grinding azithromycin with the matrix and compared with the physical mixture. The solid dispersion of azithromycin and the physical mixture were successively placed in a dissolution

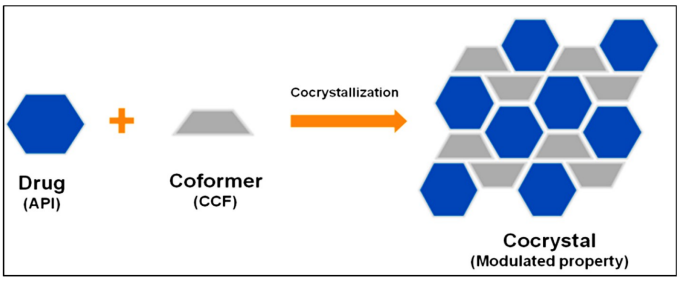

Figure 2. Formation of Co-crystal

tester with 100 rpm agitation in 900 ml of phosphate buffer (pH 6.0). The test was maintained at a temperature of 37.0 ± 0.5°C (USP, 2007). The dissolution test was carried out using 100 mg of pure azithromycin and an equivalent amount of each sample preparation. Aliquots of 5 ml were withdrawn at certain time intervals of 5, 10, 15, 20, 30, 45, and 60 minutes and replaced with the same volume of fresh medium without the appearance of bubbles, and the connection of the water circulation in the chamber and in the outer chamber was ensured to be constant. The collected samples were filtered using filter paper and analyzed with a UV Vis spectrophotometer to determine the amount of dissolved drug. This dissolution work was carried out in three iterations (Gaglioti et al., 2014; Kim and Ulrich, 2022).

3. RESULTS AND DISCUSSION

3.1 Preparation of Co-grinding Azithromycin

As an antibiotic compound, azithromycin is administered orally to treat infections and inflammation of the bronchi, skin, and tonsils. Despite its widespread use, there are still problems with using this drug, namely its low solubility in water. The low solubility in water causes this drug to be absorbed very poorly after oral administration, which affects its therapeutic effectiveness (Blumenberg et al., 2020; Echeverría Esnal et al., 2021).

Following the biopharmaceutical classification system, azithromycin belongs to group II, namely drugs with low solubility and high permeability. Azithromycin absorption events by the gastrointestinal tract will be hampered by the dissolution stage. Increasing the dissolution rate of drugs of this group will significantly increase the bioavailability in blood. Several technologies are known to be able to overcome the problem of low solubility of medicinal substances, one of which is by creating solid dispersion formulations. Solid dispersion technology has been widely used based on its advantages in dispersing the drug in the matrix and modifying the morphology of the drug substance from crystalline to amorphous form to increase solubility.

In these three decades, it is known that by adding complex compounds to substances that have low solubility and dissolution rates, absorption rates and bioavailability can be increased. Increasing the solubility as well as the dissolution rate is currently being developed, among other things, by seeking to make complex poorly soluble drug compounds in a cavity-shaped matrix (inclusion complex) where the inside of the cavity is hydrophobic and the outside is hydrophilic. This increase in the speed of dissolution of inclusion complexes can also be caused by a decrease in product crystallinity (Figure 2).

The definition of a solid dispersion follows the morphological pattern of a solid stack consisting of at least two distinct components, generally a hydrophilic matrix and a hydrophobic drug. The matrix used can be natural polymers such as polysaccharides and proteins because of their suitable biocompatibility and biodegradability for drug products. One of these matrices is chitosan which represents a group of polysaccharides that has also been used as a nanoparticle system to increase the dissolution properties and bioavailability of several drugs that are poorly soluble in water. Chitosan can function as a drug-release enhancer for drugs that are difficult to dissolve in water because it can improve the wetting process of drug ingredients that are difficult to dissolve in water (Kim and Ulrich, 2022; O'Malley et al., 2020).

A natural polymer that can be mixed chemically and physically with chitosan is sodium alginate. Sodium alginate in the pharmaceutical field has been used in the formation of hydrogel products. Sodium alginate is also known as a natural ingredient in the development of pharmaceutical particles for drug delivery systems (Untari et al., 2019).

The co-grinding method is related to the formation of solid dispersions of drug ingredients that are poorly soluble in water using a ball mill by mixing polymers and drug ingredients using a planetary ball mill instrument. Solid dispersions using the co-grinding technique have the advantage of being able to change the crystal structure of the drug into a water-soluble structure or even remove the crystal structure and make it amorphous, easy to work with, affordable cost, and without using organic solvents so it is friendly to the environment.

3.2 Results of XRD

The azithromycin diffractogram shows a crystalline solid due to the presence of a characteristic and sharp interference peak with a high degree of crystallinity, with the peak at 2θ at an angle of 9.79° with an intensity of 4822. Compared to the physical mixture which has a maximum crystalline intensity of 607.62 at 2θ at an angle of 20.02°. These results indicate that the physical mixture has experienced a decrease in the crystal lattice to become more amorphous. The results of the XRD test on sample of the azithromycin solid dispersion formula was compared with the results of the XRD test on pure azithromycin and the physical mixture. No visible diffraction peaks in the physics mixture samples and the azithromycin solid dispersion samples at 2θ angle of 9.79° which is the maximum peak of azithromycin have not seen any diffraction peaks. However, the physics mixture has an intensity of 590.12. The solid dispersion samples in formula 1 (F1) at that angle have a crystal intensity of 469.25 (Figure 3). Even though there is not a diffraction peak for a mixture of physics and solid dispersion

samples.

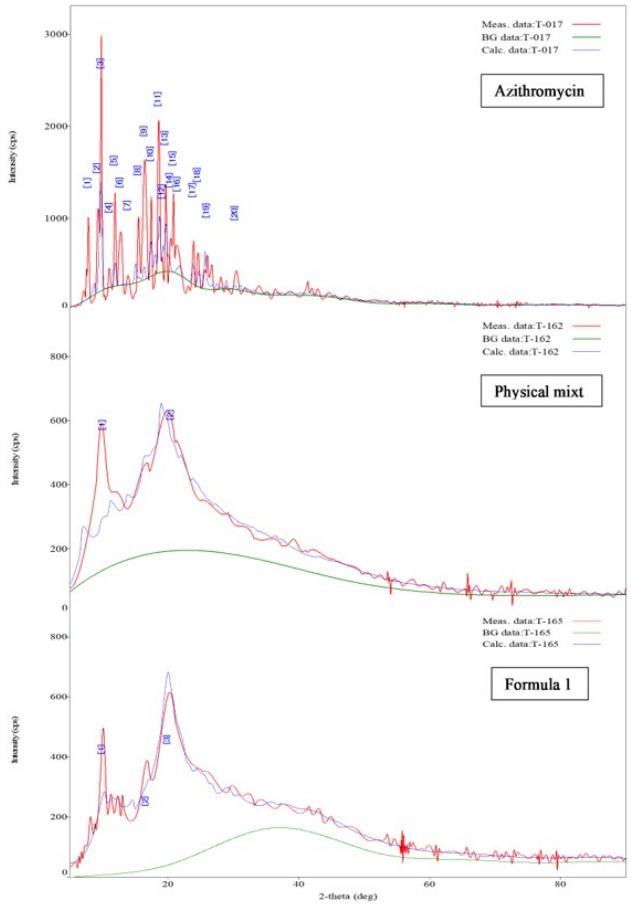

Figure 3. The Diffractogram of Azithromycin Solid Dispersion

3.3 Results of FTIR

The hydroxyl absorption bands in the solid dispersion samples of azithromycin F1, F2, and F3 (Figure 4) were marked with peak numbers at 3484.19; 3450.08; and 3458.95 cm^{-1}. Changes in wavenumber bands in the wavenumber region of 3100–3400 cm^{-1} in the solid dispersion system of azithromycin-chitosan and sodium alginate indicate the occurrence of deformation of the OH group in azithromycin due to the formation of hydrogen bonds between azithromycin and chitosan polymer and sodium alginate. Despite this, there is no substantial shift in the position of the functional group on the azithromycin molecule. Observations at wave numbers 2000-1500 cm^{-1} produced spectra with different intensities in the samples of azithromycin, chitosan, sodium alginate, physical mixture, and the three azithromycin solid dispersion formulas. 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 of chitosan showed a peak at 1643.91 cm^{-1} (C=O strain). The spectrum for sodium alginate has a peak at 1607.75 cm^{-1} (C=O strain). The results of the FTIR spectrum on the physical mixture and each azithromycin

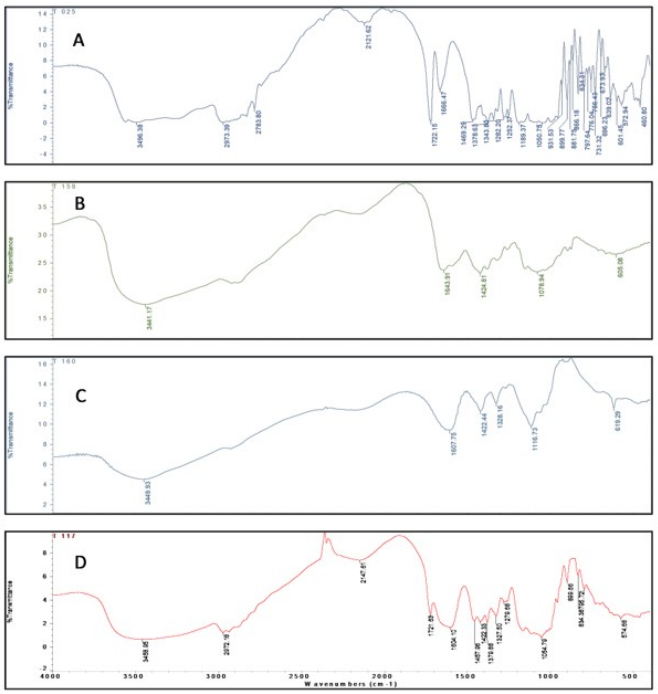

Figure 4. Comparison of FTIR Spectra of Material and product of Solid-dispersion (A. azithromycin; B. Formula I; C. Formula II; D. Formula III)

solid dispersion sample showed lower peaks at 1722.25 cm^{-1}, but displayed identical peaks with a peak of 1607.75 cm^{-1}.

3.4 Results of SEM

The morphology of azithromycin solid dispersion was determined by looking at the surface of the sample using an SEM (Scanning Electron Microscopy) tool. The purpose of this analysis is to see the polymorphism, texture, and surface morphology of each sample. The results of the SEM were then used to compare the morphology of the samples between pure azithromycin, a physical mixture, and the best formula resulting from the azithromycin solid dispersion system in this case was formula 3 of azithromycin solid dispersion. Observation of sample morphology using SEM was carried out by taking 5000x magnification images at the same location point for each sample. SEM results of pure azithromycin powder (Figure 5) with 5000x magnification. The morphology of azithromycin can be seen in that azithromycin has a cubic shape with a smooth surface. This form indicates that pure azithromycin powder has a crystal structure. These results are based on previous studies that pure azithromycin powder looks like a solid block crystal with a clean surface. The morphology of the azithromycin physical mixture sample shows that the structure of the azithromycin physical mixture is irregular, but the azithromycin crystal form can still be identified by the crystal beam shape in the picture. Simple stirring using a spatula makes azithromycin not completely dispersed in chi-

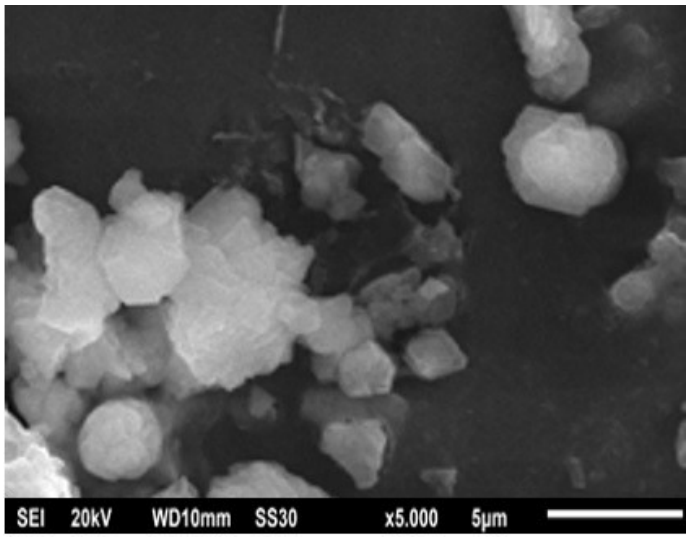

Figure 5. SEM of Azithromycin Crystal

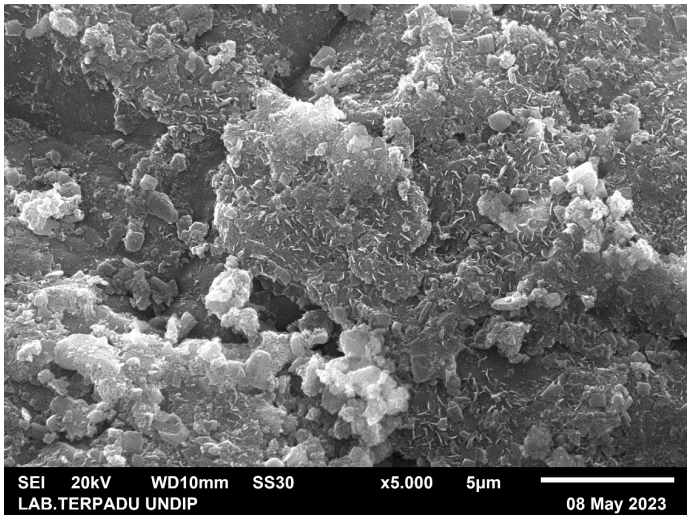

Figure 6. SEM of Solid-dispersion Containing Azithromycin

tosan and sodium alginate as a carrier. As a result, the sample is not completely mixed (Figure 6) so the crystal structure of azithromycin can still be found even though the size has been reduced.

3.5 Results of Dissolution

The dissolution test in the form of % release in this study used a type II dissolution tool (Erweka DT-950) with standard conditions (100 rpm speed and 37°C). Azithromycin used as an active pharmaceutical ingredient has poor solubility in body fluids, resulting in low absorption after oral administration, which may affect its therapeutic effect. The rate of absorption and bioavailability of drugs that are poorly soluble in water is often controlled by the rate of drug dissolution in the gastrointestinal tract. The medium used as a representative of gastrointestinal fluids uses 900 mL of phosphate buffer solution with a pH of

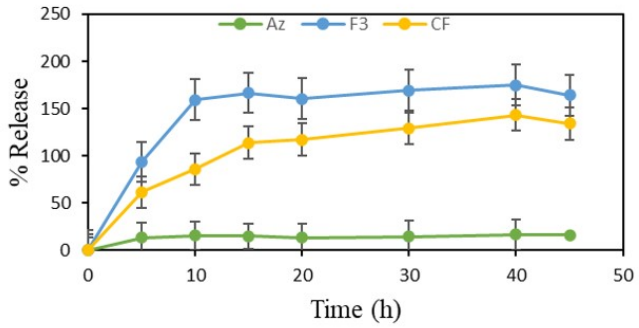

Figure 7. Profile of Dissolution Rate of Azithromycin Solid-dispersion

6.0. This test aims to determine the increase in the dissolution rate of the azithromycin solid dispersion system, compared to a physical mixture and pure azithromycin. The dissolution test used formula 3 as the best formula in the azithromycin solid dispersion system in this study (Figure 7).

4. CONCLUSION

The results of this study showed a change in the pattern of X-diffraction of azithromycin, physical interaction between azithromycin and the polymer, changes in the image of surface of solid dispersions, the solubility of solid dispersions in simulated-intestinal-fluid (SIF) solutions, and an increase in the dissolution rate of azithromycin indicating that the co-grinding technique to produce solid dispersions can increase the solubility of azithromycin.

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