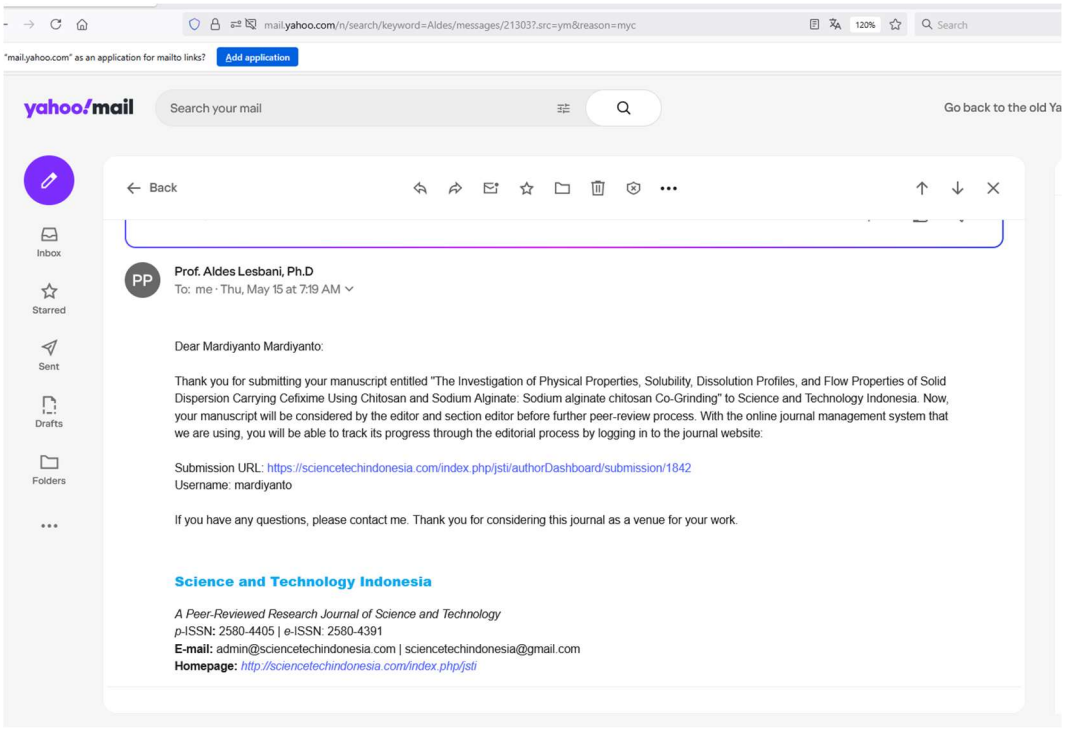
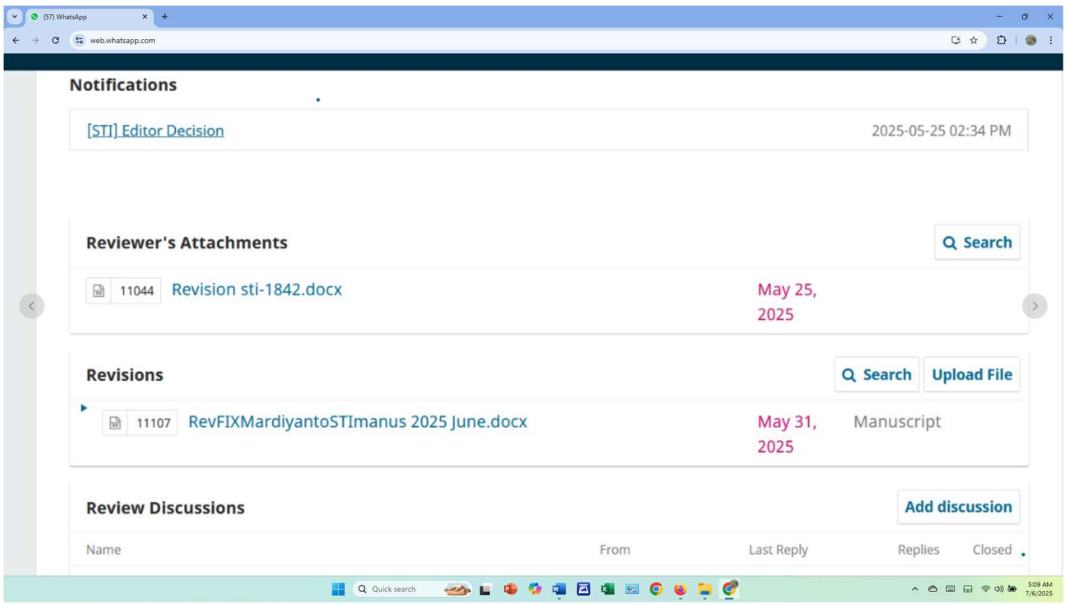




Manuskrip yang diperbaiki sesuai review adalah dihighlight warna kuning

[STI] Editor Decision

Prof. Aldes Lesbani
To: me · Sat, Jun 1, 2024 at 11:50 PM

Message Body

Dear Mardiyanto Mardiyanto:

Reviewers have now commented on your paper (attached below this email). You will see that they are advising that you must revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments can be read in your Author online interface. If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.

****>>>>Please be noted that you have up to **3 (three) weeks from now** to revise your manuscript, unless your manuscript will be considered as a new submitted manuscript. If you need additional time to complete your revision, please let us know by replying to this email and informing us of the date you expect to submit it. <<<<****

To submit a revision, please upload your revised manuscript documents to SCIENCE AND TECHNOLOGY INDONESIA online submission interface at (https://sciencetechindonesia.com) after you log in as Author. Important: Please indicate the revision as RED-highlighting the revision sentences or words within your revised manuscript.

The revised document files (three files) MUST include:
- One (1) file of Revision Note file in a table form with respect to Reviewers comments including the location of the revision on the revised manuscript.
- One (1) file of Revised Manuscript file according to Template-based format (MS Word file) (please **RED**-color highlighted texts in the revised sentences).
- One (1) file of Graphical Abstract file according to Guideline of Graphical Abstract
---
GUIDELINE TO UPLOAD REVISION: To upload your revised manuscript, please login to Science and Technology Indonesia journal submission interface (https://sciencetechindonesia.com) login using your user and password as usual. **Therefore, click on "Review" and upload to “revision box”**.
For second and continuing order of revision of manuscript, please just add your latest version file(s), do not delete the previous round of file(s) of manuscript.

IMPORTANT NOTE: A GRAPHICAL ABSTRACT of each article is mandatory for this journal. This graphic should capture the reader’s attention and, in conjunction with the manuscript title, should give the reader a quick visual impression of the essence of the manuscript without providing specific results.
Choosing/Creating a Graphical Abstract: The graphic should be simple, but informative; The use of color is encouraged; The graphic should uphold the standards of a scholarly, professional publication; The graphic must be entirely original, unpublished artwork created by one of the coauthors; The graphic should not include a photograph, drawing, or caricature of any person, living or deceased; Do not include postage stamps or currency from any country, or trademarked items (company logos, images, and products); Avoid choosing a

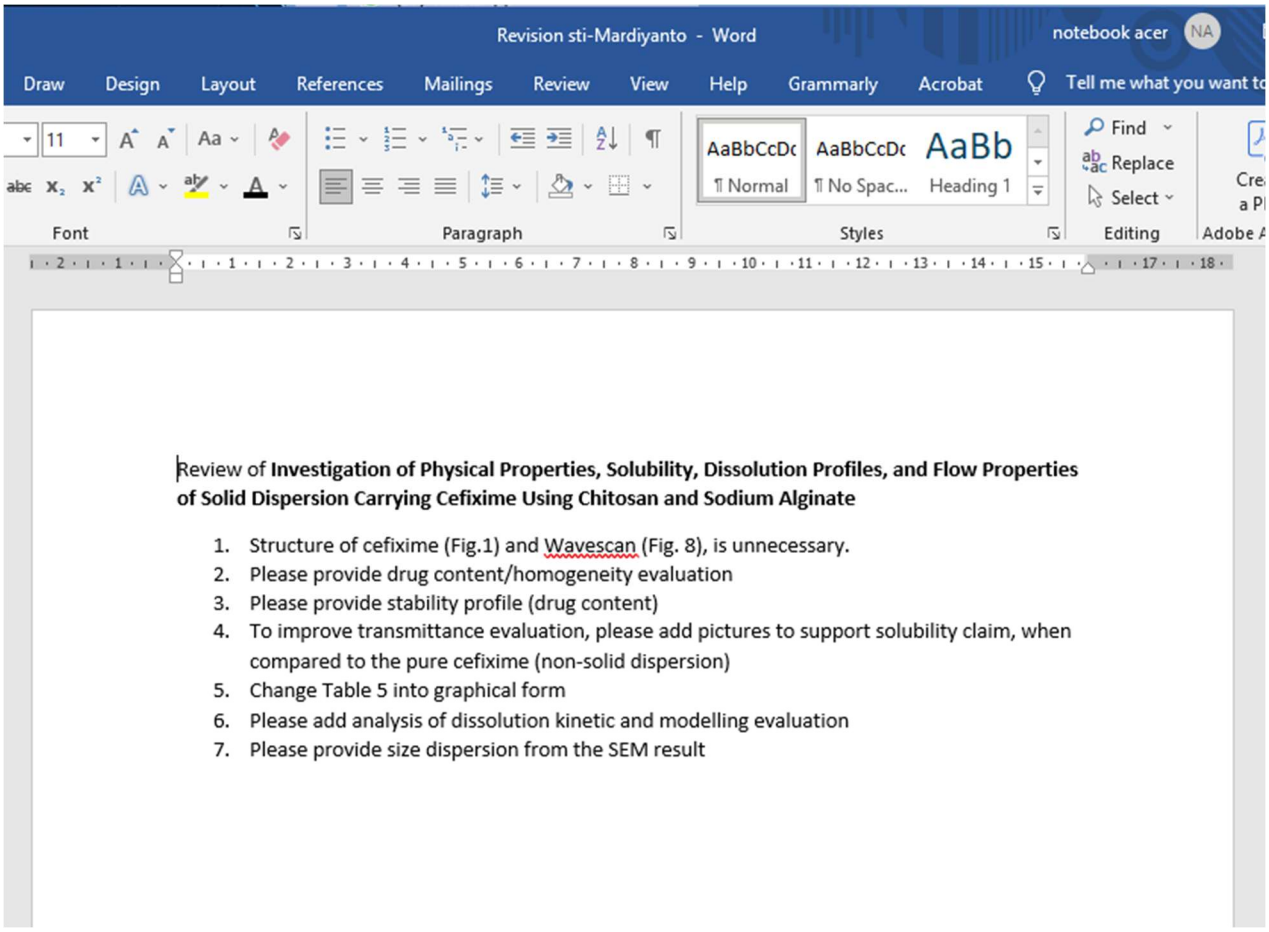
graphic that already appears within the text of the manuscript. Image size: please provide an image with a size of 500 × 800 pixels (height × width). Preferred file types: TIFF, JPG, PNG, PDF, or MS Office files.

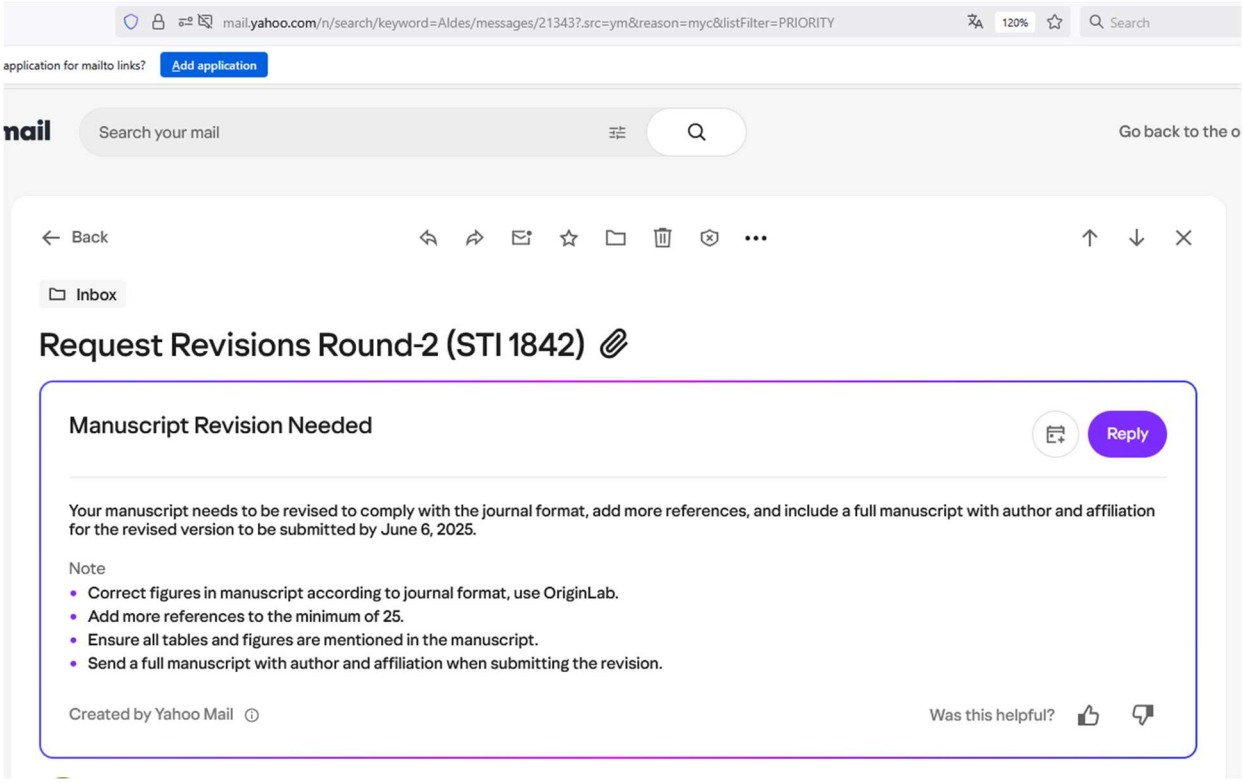
The Graphical Abstracts should be submitted as a separate file during the revised manuscript submission system or otherwise, it can be submitted by email to: sciencetechindonesia@gmail.com

Thank you for submitting to this journal.

Science and Technology Indonesia

A Peer-Reviewed Research Journal of Science and Technology
p-ISSN**:** 2580-4405 | *e*-ISSN: 2580-4391
E-mail: admin@sciencetechindonesia.com | sciencetechindonesia@gmail.com
Homepage: *http://sciencetechindonesia.com/index.php/jsti*





Investigation of Physical Properties, Solubility, Dissolution Profiles, and Flow Properties of Solid Dispersion Loading Cefixime Using Chitosan and Sodium Alginate

Mardiyanto[1*], Najma Annuria Fithri[1] , Shaum Shiyan[1] , and Fakhri D Satrio[1]

[1]Department of Pharmacy, Faculty of Mathematics and Natural Science, Sriwijaya University

[*]Corresponding Author: mardiyanto@mipa.unsri.ac.id

ABSTRACT

The co-grinding method has been used to produce solid dispersions that increase the solubility of drug substances by utilizing hydrophilic polymers. The purpose of this study was to evaluate the effect of chitosan and variations of sodium alginate as polymers on the dissolution rate of cefixime solid dispersion using the co-grinding technique. The cefixime solid dispersion formulation was made in three variations of sodium alginate formulas, namely 200 mg. 250 mg. and 300 mg. Sample characterization was carried out using XRD, FTIR, SEM, solubility testing, dissolution rate, and flow properties. The results showed that Formula 2 (F2) cefixime solid dispersion was the best formula because the degree of crystallinity decreased to 21.71%, and FTIR analysis showed the functional group interaction. Evaluation of cefixime solid dispersion showed changes in particle morphology. In addition, there was an increase in the transmittance percentage in SIF of 98.587 ± 0.019 and an increase in the dissolution rate of

cefixime of 83.61%, an increase in the flow rate of 6.3 ± 0.14 grams/second, an angle of repose of 26.4 ± 0.4°, a compressibility index of 16.3 ± 0.29%, and a Hausner ratio of 1.19 ± 0.35.

Keywords: Cefixime, dissolution, flow-properties, formulation, solid-dispersion

1. INTRODUCTION

The discovery of new antibiotics is a complicated endeavor. A lot of effort must be devoted. Not only the efficacy aspect that scientists attempt, but the economic aspect, which is obtained afterward, is often reconsidered if the selling price is lower than the price to find it. Finding antibiotics also considers the risk factor in the future, resistance often makes its existence in trade not long (Silver & Bostian, 1993)(Spellberg, 2014). This is different from ordinary drugs that are not related to resistance; therefore, the aspect of the discovery of new antibiotics is full of caution. Recently, an antibiotic that is three decades old can still be found, while bacteria that are resistant to it continue to increase. However, this antibiotic is still formulated into the most commonly found dosage form, such as capsule and tablet form, even though some of these antibiotics have low solubility in water (Lindenberg et al, 2014).

In general, it can be seen that the problem of solubility is not only found in the group of antibiotic drug ingredients, but also 70% of newly discovered drugs are classified as difficult to dissolve in water. The production of drug preparations certainly should not stop just because of solubility problems, and fortunately, some of these drugs, although their solubility is problematic, their permeability is quite good permeability. Nevertheless, the achievement should not stop striving for its good permeability, supported by good solubility, the efficacy of the drug compound will increase greatly (Shankar et al., 2017; Kalepu & Nekkanti, 2015).

The efficacy of a drug compound delivered orally is determined by its bioavailability. Bioavailability is influenced by solubility because, to overcome difficulties in absorption, the drug substance must be in a dissolved state. It is also known that the use of some additional ingredients in the formulation involves decreasing solubility. This is due to the physical and chemical interactions of the functional groups owned by the active compound properties with additional ingredients (De Simeis & Serra, 2021; Kumari et al., 2023).

Antibiotics are very specific and their targets are bacterial cells that also continue to modify themselves, and this is what makes antibiotics different from ordinary drug compounds. If ordinary drug compounds then problems do not arise because the target is not an organism that can modify itself. From the literature, it is known that if the concentration of an antibiotic in human blood plasma can be maintained to kill bacteria, then resistance can be prevented (Basak & Adhikari, 2012); Ajmal et al., 2023). Maintaining concentration is related to the success of antibiotics through the absorption process if given orally. Cefixime is a third-generation cephalosporin antibiotic used to treat urinary tract infections caused by *Escherichia coli, Staphylococcus saprophyticus, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Enterococcus spp*. Until now, dosage forms containing cefixime have been in the form of film-coated tablets, capsules, and dry suspensions.

Solid dispersion can increase the solubility of drug compounds. A technique often used to obtain solid dispersions is the co-grinding of drug compounds with hydrophilic polymers. This technique can increase the surface activation energy and damage the crystal lattice so that it can form an amorphous phase effectively. In this research, cefixime was co-grinded with hydrophilic polymers, namely a mixture of sodium-alginate and chitosan (Attia et al., 2021; Leuner & Dressman, 2000).

2. EXPERIMENTAL SECTION

2.1. Materials

Cefixime was obtained from Dexa Medica Pharm Co, LTD, sodium alginate, chitosan, citric acid (Sigma-Aldrich®), sodium phosphate, potassium dihydrogen phosphate, sodium hydroxide (Merc®), and aqua-bidest (Otsuka®).

2.2. Methods

2.2.1. Formulation

In this study. cefixime solid dispersion formulations were made in three formulas (F1. F2. and F3) shown in Table 1. Three cefixime solid dispersion formulas were made to obtain the best cefixime solid dispersion preparation that passed every solid dispersion system evaluation test. This formulation uses 50 mg cefixime and 200 mg chitosan. The variation in this study lies in the amount of sodium-alginate used of 200 mg, 250 mg, and 300 mg (Mardiyanto et al. 2023).

Variations in the amount of sodium-alginate were carried out to determine the best amount to improve the solubility of cefixime.

Table 1. Formula of F1, F2, and F3

Component	Amount (mg)		
	F1	F2	F3
Cefixime (mg)	50	50	50
Chitosan (mg)	200	200	200
Sodium-alginate (mg)	200	250	300

2.2.2 Formation of Solid-dispersion

A total of 2 grams of sodium-alginate and 2 grams of chitosan were prepared for the physical mixture and the solid dispersion carrier of 100 mg of cefixime. The physical mixture, namely without cefixime, was worked in a 12 cm diameter mortar with tumbling 7 times and a duration of 30 seconds. For co-grinding, the working conditions were adjusted according to the amount of the mixture. The co-grinding conditions (Planetary-Ball-Mill Miller®) were to regulate the type of ball, the duration of grinding, and the grinding time interval. The type of ball used was ball number 8, the grinding time was 5 minutes, and the time interval was 1 minute (Lali et al., 2022).

2.2.3 Measurement of Crystallinity Using XRD

X-ray diffractogram analysis was carried out using an X-ray diffraction meter (Rigaku MiniFlex-600) on cefixime samples, physical mixtures, and solid dispersion formula series. The operational voltage parameters used were 45kV, 40mA generator current, 9 seconds scan step time, and 0.0080 (2θ) scan step size (Mardiyanto et al., 2023).

2.2.4 Determination of Functional Group Interactions

Infrared spectra measurements were obtained using an FT-IR spectrophotometer (Thermo-Scientific®). Cefixime powder, chitosan, sodium alginate, manual mixture, and solid dispersion, each weighing 100 mg, were detected by infrared spectra by dispersing each substance on a KBr plate (Akelesh et al., 2015). Then the percent transmittance was measured from wave numbers 4000 to 200 cm^{-1}.

2.2.5 Determination of Crystal Morphology

The shape and characteristics of cefixime solid dispersion can be seen using a Scanning Electron Microscope (JSM-6510A JEOL®). The sample was placed on a SEM holder (diameter 10 mm, height 3 mm), then coated with a layer of gold under vacuum conditions (0.25 torr). Observation of Scanning Electron Microscope (SEM) images using a 30 kV electron beam with a magnification of 500 times, 2500 times, and 5000 times (Mardiyanto et al., 2023).

2.2.6 Solubility Testing

The solubility test was carried out using the transmittance percentage indicator. The solubility test began with the preparation of a 200 ppm concentrated stock solution using SGF, SIF, and distilled water as solvents. A total of 20 mg of sample was dissolved in a 100 ml measuring flask to produce a 200 ppm stock solution. Next, 1 ml of the stock solution was taken using a pipette, then 10 ml of each SGF, SIF, and distilled water were added, so that a solution with a final concentration of 20 ppm was obtained. The solution was then measured for optical density at a wavelength of 650 nm using a UV-Vis spectrophotometer (Tajmir & Roosta, 2020).

2.2.7 Dissolution Testing

In vitro dissolution testing using the dissolution tester DT-128 Erweka® of cefixime solid dispersion was carried out by testing cefixime, manual mixture, and cefixime solid dispersion in a dissolution tester apparatus (tool name) type I at 100 rpm in 900 ml of 0.05 M potassium phosphate buffer (pH 7.2). The test was maintained at a temperature of 37.0 ± 0.5 ^{0}C. The solution was taken 5 ml at certain time intervals of 5, 10, 15, 20, 30, 45 minutes, and replaced with the same volume of new medium (Attia et al., 2021).

2.2.8 Determination of Flow Properties

A total of 10 grams of powder was weighed and then put into the flowability tester funnel (GTL-B Erweka®). Then the bottom cover of the funnel was opened while the timer was running. The flow rate was expressed in grams/second. Measurement of the angle of repose (α), cone height (h), and radius (r) of the cone base of the formed granules was carried out after the powder flowed freely (Attia et al., 2021).

2.2.9 Stability Test

Quantification of cefixime level when tested for thermodynamic stability is necessary to predict dosage form storage, was conducted in this step. The selected solid dispersion formula,

physical mixture, and pure cefixime were placed in a temperature difference of 40 degrees Celsius in an oven (Oberhaus®) and a temperature of 8 degrees Celsius in a refrigerator (Toshiba®) for each warm and chill for each 24 hours. The cycle was repeated up to 6 times.

3. RESULTS AND DISCUSSION

3.1 Formation of Solid Dispersions Containing Cefixime

The increase of cefixime solubility was carried out through a solid dispersion method using a co-grinding technique (the grinding results can be seen in Figure 1). In this process, cefixime was dispersed with a carrier material in the form of a combination of chitosan and various concentrations of sodium alginate. This method has been recognized to determine the most effective proportion of sodium alginate in changing the crystalline phase to amorphous to increase the solubility and dissolution rate of drugs, intended to support the efficiency of its absorption in the body (Adamo et al, 2015)(Mardiyanto et al., 2022).

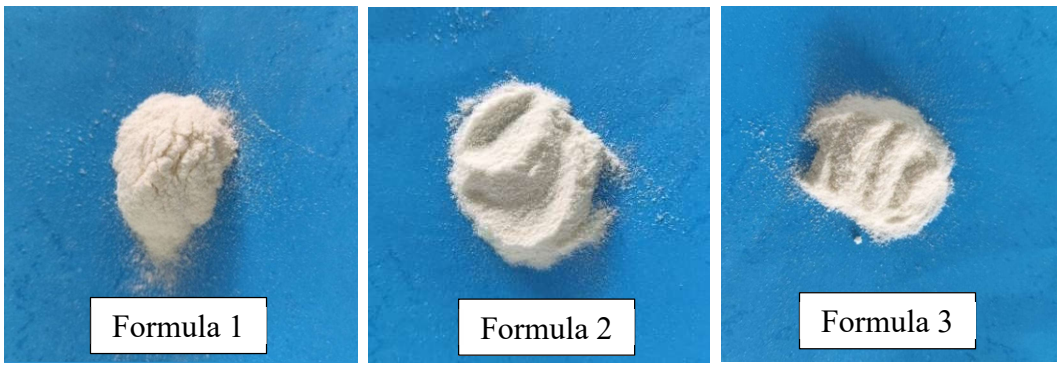


Figure 1. The product of formula co-grinding

Cefixime solid dispersion was formed based on the formula that has been determined according to Table 1. In this process, the ratio of powder mass to ball mass, or known as ball to powder ratio (BPR), was 8:1. The BPR value plays an important role in determining the effectiveness of mechanical energy transferred to the powder during grinding, as well as the pressure applied to the powder particles.

An illustrative image of the position of cefixime and the two polymers surrounding it can be seen in Figure 2.

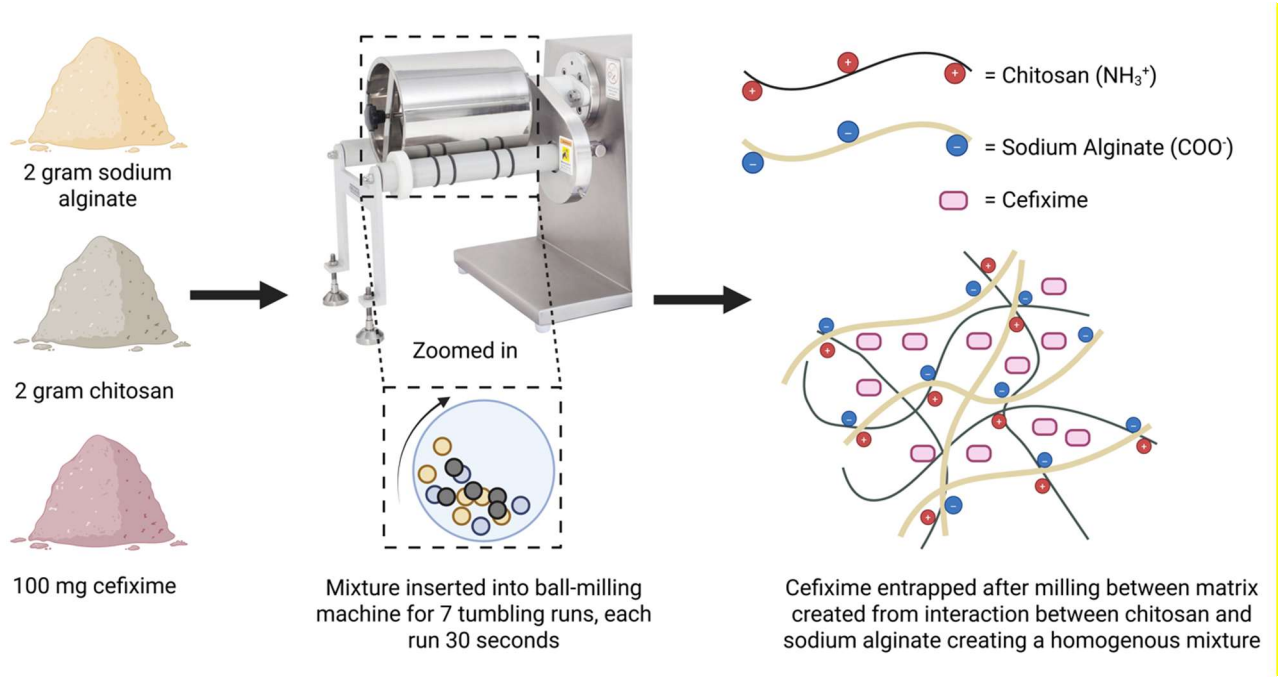
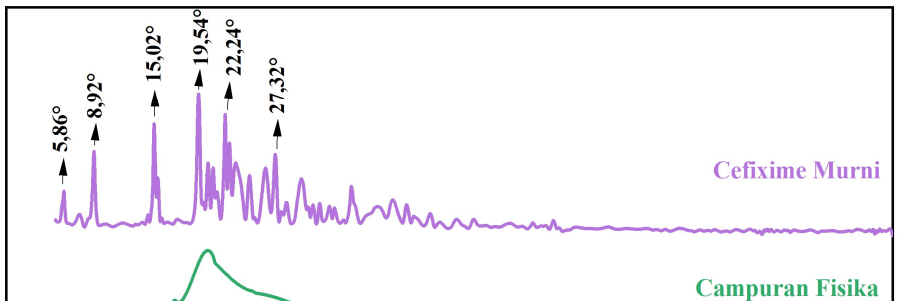


Figure 2. Illustration of preparation cefixime solid dispersion

3.2 Measurement of Crystallinity

Cefixime has a specific diffraction peak at the angle of 5.751°. 8.859°. 14.969°. 19.512°. 22.152°. and 27.274°. Based on the diffractogram (Figure 3) of pure cefixime, the specific diffraction peak, which revealed the difference value of 2θ, i.e 5.86°. 8.92°. 15.02°. 19.54°. 22.24°. and 27.32°. The difference is caused by the changes in molecule distance (Table 2).



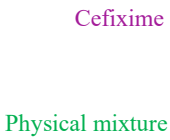


Figure 3. Diffractogram of solid dispersion, physical mixture, and cefixime

Table 2. Specific Angle of Solid Dispersion, Physical Mixture, and Cefixime

Samples	Intensity (cps)					
	5.86°	8.92°	15.02°	19.54°	22.24°	27.32°
Cefixime	396.452	819.973	1010.433	1489.721	1043.401	843.253
PM	253.331	388.493	470.912	929.739	838.344	584.131
Formula 1	178.653	262.219	384.106	783.296	765.471	580.514
Formula 2	222.827	300.462	397.769	692.460	642.151	536.533
Formula 3	186.514	266.123	375.904	726.825	706.588	534.483

The disappearance of this characteristic peak indicates a possible decrease in the degree of crystallinity. The absence of a characteristic peak indicates a decrease in the degree of crystallinity and the formation of an amorphous phase in the solid dispersion system. This change is usually caused by the interaction between the active ingredient and the polymer in the solid dispersion system, which disrupts the regular arrangement of molecules in the crystal structure (Wu et al., 2020). The maximum crystal intensity of pure cefixime reached 1489.721 at an angle of 19.54°. While the manual mixture. Formula 1, Formula 2, and Formula 3 of each were recorded with an intensity of 929.739. 783.296. 692.460. and 726.825. From these results. Formula 2 showed the greatest decrease in crystal intensity compared to the others. The

widening of the diffraction peak, accompanied by a decrease in intensity, can indicate a change in the crystal structure. It leads to the formation of a new phase and causes the crystal structure to become more amorphous (Urakov et al., 2021)(O'Malley et al., 2021).

3.3 Determination of Molecular Interaction of Functional Group

FTIR analysis was performed to identify specific functional groups and the possibility of the formation of new functional groups in each sample (Han et al., 2017). In Table 3, it was stated the wave number of functional groups. In addition, the analysis aims to observe the interaction between cefixime with a combination of chitosan and sodium alginate. Through measurements using infrared spectroscopy. Information can be obtained regarding the presence of chemical interactions and the formation of new functional groups in the tested samples (Lali et al., 2022). Based on the results of the FTIR spectrum (Figure 4 and 5), pure cefixime has a typical IR absorption at 3303.27 cm^{-1} (N-H stretching). 1774.51 cm^{-1} (C=O stretching). 1543.59 cm^{-1} (C-C stretching). 1338.14 cm^{-1} (N-O stretching). 1226.16 cm^{-1} (C-O stretching). Cefixime has a characteristic IR absorption peak in the wave number around 3300 cm^{-1}, 1772 cm^{-1}, 1543 cm^{-1}. 1338 cm^{-1}. and 12223 cm^{-1}. The wavenumber around 1772 (C=O stretching) is a typical peak of the β-lactam ring. The main functional group in β-lactam antibiotics, such as cefixime which interacted to hydroxy and amine of chitosan and hydroxyl and carboxylate of alginate (Figure 6).

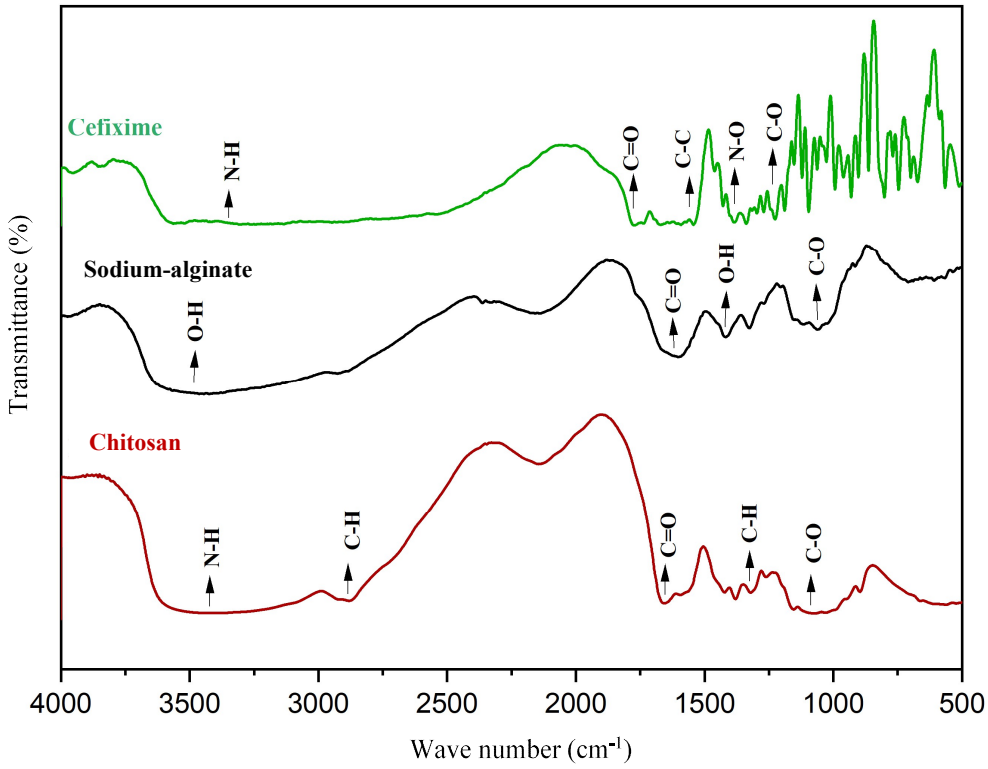


Figure 4. Spectra IR of cefixime, Na-alginate, and chitosan

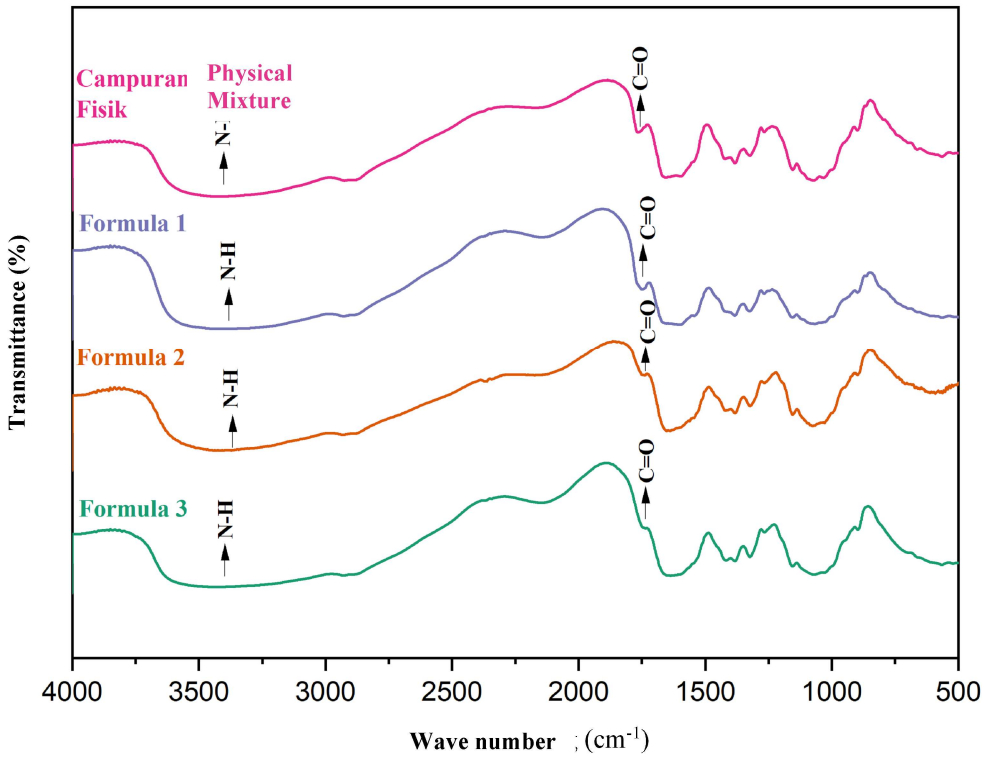


Figure 5. Comparison IR spectra of the solid dispersion to the physical mixture

Table 3. Specific Wave Number Of Functional Group

Functional Group	Wave-length						
	Cefixime	Sodium-alginat	Chitosan	CF	F1	F2	F3
N-H	3303.27	-	3427.11	3425.67	3421.78	3402.93	3428.43
C=O	1774.51	1654.90	1603.90	1768.49	1750.04	1749.19	1731.83
O-H	1338.14	1326.24	1379.42	1383.59	1383.03	1382.61	1382.09
C-O	1226.16	1062.11	1076.54	1063.92	1065.89	1075.51	1071.06

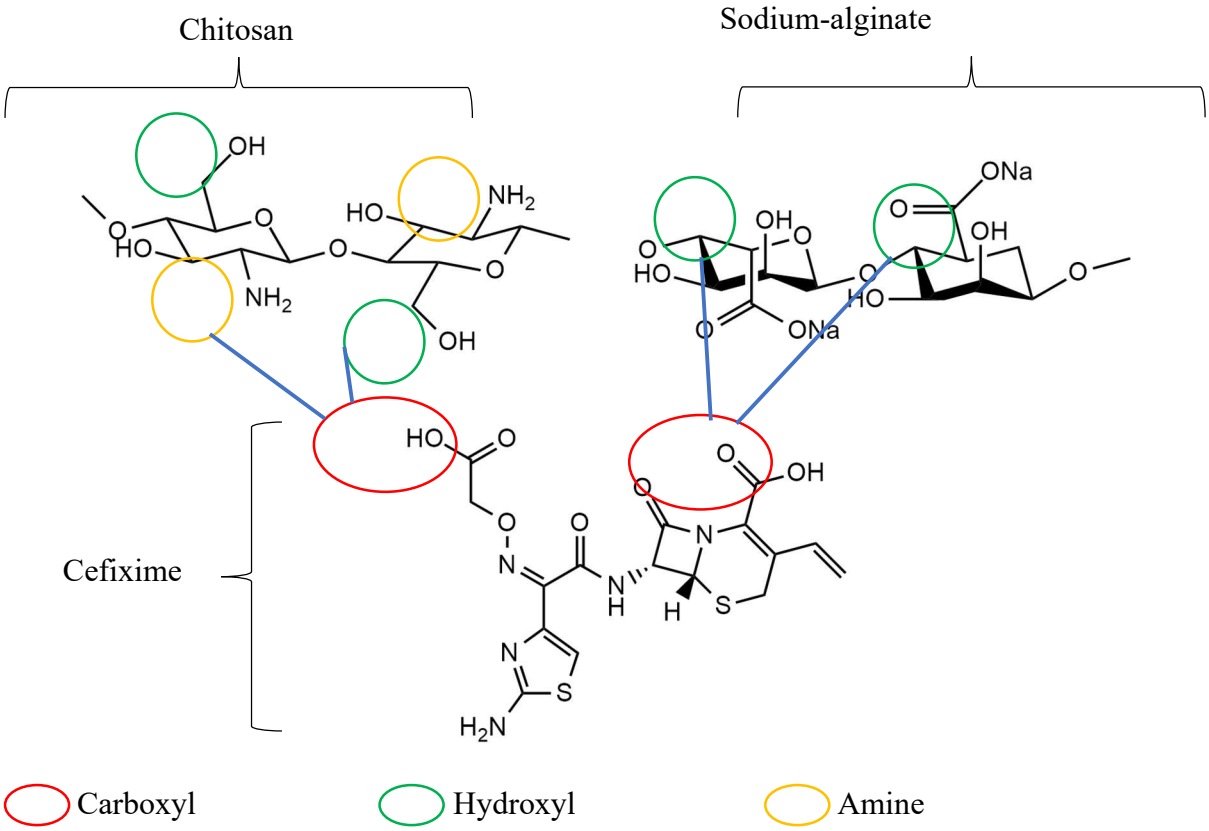


Figure 6. Interaction functional group

3.4 Determination of Solid Dispersion Solubility

Cefixime was analyzed using the UV-Vis spectrophotometry method, which involves two main stages, i.e, scanning to determine the maximum wavelength of cefixime and the preparation of a calibration curve. In this process, the stock solution consists of a mixture of cefixime with a pH 7.2 phosphate buffer, while the pH 7.2 phosphate buffer is also used as a blank in UV-Vis spectrophotometry measurements. The maximum wavelength of cefixime in phosphate buffer is 288 nm.

Solubility testing based on percent transmittance is carried out to measure the clarity of samples in various solvents. namely: SGF (Simulated Gastric Fluid). SIF (Simulated Intestinal Fluid) and aquadest. This test aims to determine the extent to which particles in a solid dispersion can

transmit light at a certain wavelength. Thus, providing an overview of the level of transparency or clarity of the solution. By using a UV-Vis spectrophotometer. The percent transmittance value (%T) is measured as an indicator of clarity. Higher results indicate that the particles have dissolved in the solvent medium. The transmittance percentage reflects the level of solution clarity. Lower transmittance values indicate higher turbidity. In the Figure 7, the transmittance values for pure cefixime, manual mixture, and Formula 2 are in the range of 90.3–98.587%. Percent transmittance values approaching 100% indicate that the particles have dissolved in a medium approaching the clarity of aquadest. The pictures to support solubility claim was presented in Figure 8.

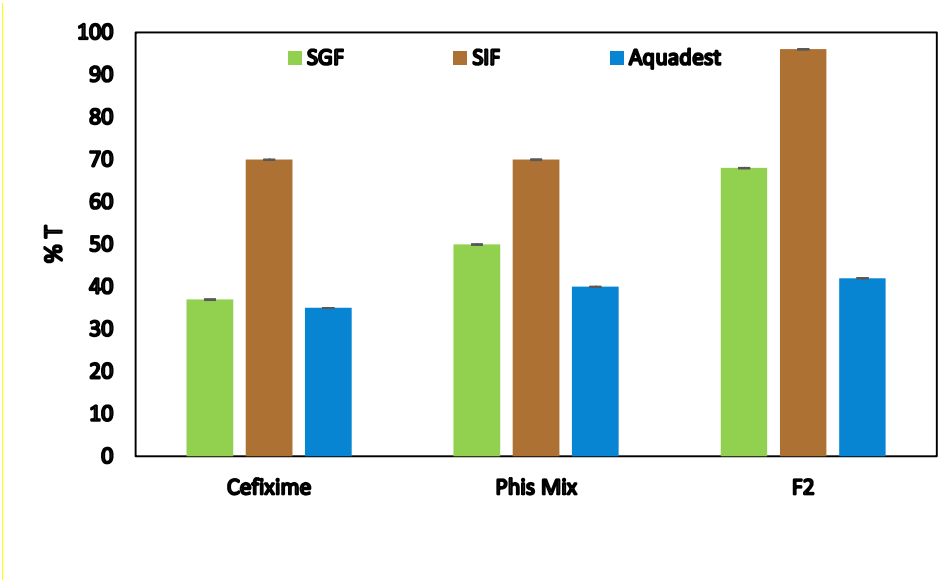


Figure 7. The %Transmittance of solid-dispersion, physical mixture, and cefixime

Cefixime has sufficient solubility in SIF medium but is low in SGF. The test results showed consistency with the reference. Where the percent transmittance of pure cefixime is. Physical mixture and formula 2 were higher in the SIF solution than SGF. Among the three samples. Formula 2 has the highest transmittance value. which is 98.587%. The transmittance value

above 90% indicates the clarity of the solution which indicates optimal particle dispersion. This indicates that the particles are perfectly dispersed and the solution becomes clear. The surface area of the particles increases. Increased surface area interfacial tension. which contributes to faster drug release and absorption in the digestive tract (Tajmir & Roosta, 2020).

Figure 8. The comparison of clarity; solid dispersion, physical mixture, and cefixime

3.5 Dissolution Profile of Solid Dispersion

The drug content of solid dispersion has an impact to the dissolution profile, therefore the determination was conducted to F1, F2, and F3 (three formula) solid dispersion. F2 was selected (Table 4) to the dissolution. Based on the results of the dissolution test, the solid dispersion formula has the highest dissolution percentage compared to pure cefixime and manual mixture samples. At the 45th minute, the pure cefixime sample has a dissolution percentage of 51.59%, the physical mixture of 70.07%, and the solid dispersion (Formula 2) of 83.61%. The results of the analysis of the drug release mechanism in solid dispersions showed an R^2 value approaching 1 and located in the range of 0.45-0.89 which indicated the Korsmeyer-Peppas; a non-Fickian transport model. The results in Figure 9 indicate that the method of forming solid dispersions using the co-grinding technique could increase the release ability of the active substance cefixime. Pure cefixime showed the lowest dissolution

percentage in the dissolution test. This is due to the absence of polymers that act as a carrier matrix to help release the active substance. In addition, pure cefixime has a very regular crystal structure and a high degree of crystallinity. This crystal structure affects the ability of molecules to separate and interact with solvents (Kim & Ulrich, 2022). Particles with a very regular and dense crystal structure tend to be more difficult to dissolve in solvents (Khantri et al., 2022).

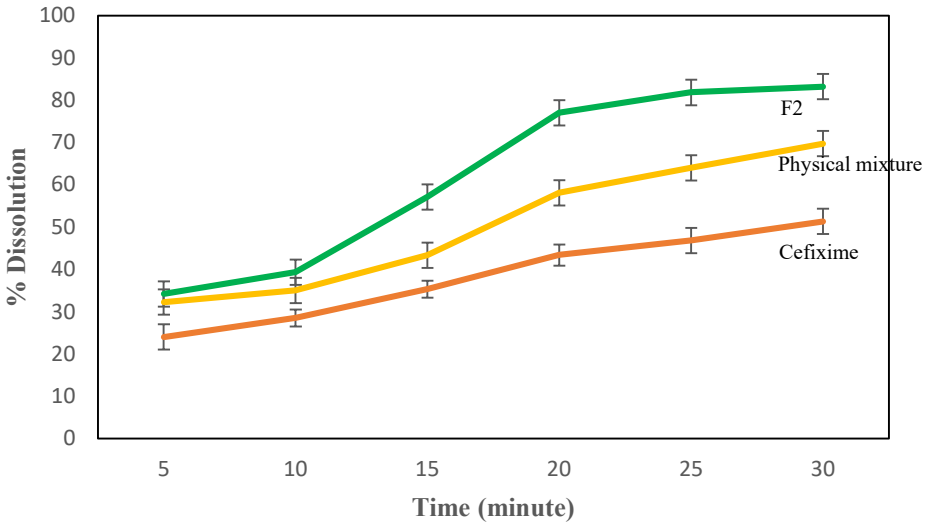


Figure 9. Dissolution profiles of pure cefixime, physical mixture, and solid dispersion

3.6 Morphology of Solid-dispersion

Observation of the surface morphology of a sample can be done using a Scanning Electron Microscope (SEM). SEM is used to study the morphology of powder and the structure of the sample after becoming a solid dispersion (Wu et al., 2020)(Khan et al., 2020). SEM analysis was carried out on pure cefixime samples, physical mixture, and the best formula (F2). During SEM testing, images were taken by focusing on a certain point on the object using a magnification of 1000 times. The SEM test results in Figure 10 was showed that the pure cefixime sample has a crystal morphology with a rod shape. Pure cefixime is in the form of a rod crystal with a rough surface. The analyzed samples showed variations in crystal size with a diverse distribution. Observations via SEM also revealed that some crystals were larger while others were smaller. Based on the *ImageJ* processing, the average size of powder was 310 ± 14 µm.

Table 4. The drug content of F1. F2, and F3

Samples	% Drug Content ± SD	%CV
F1	72 ± 5.32	7.38
F2	94 ± 3.12	3.31
F3	81 ± 6.29	7.76

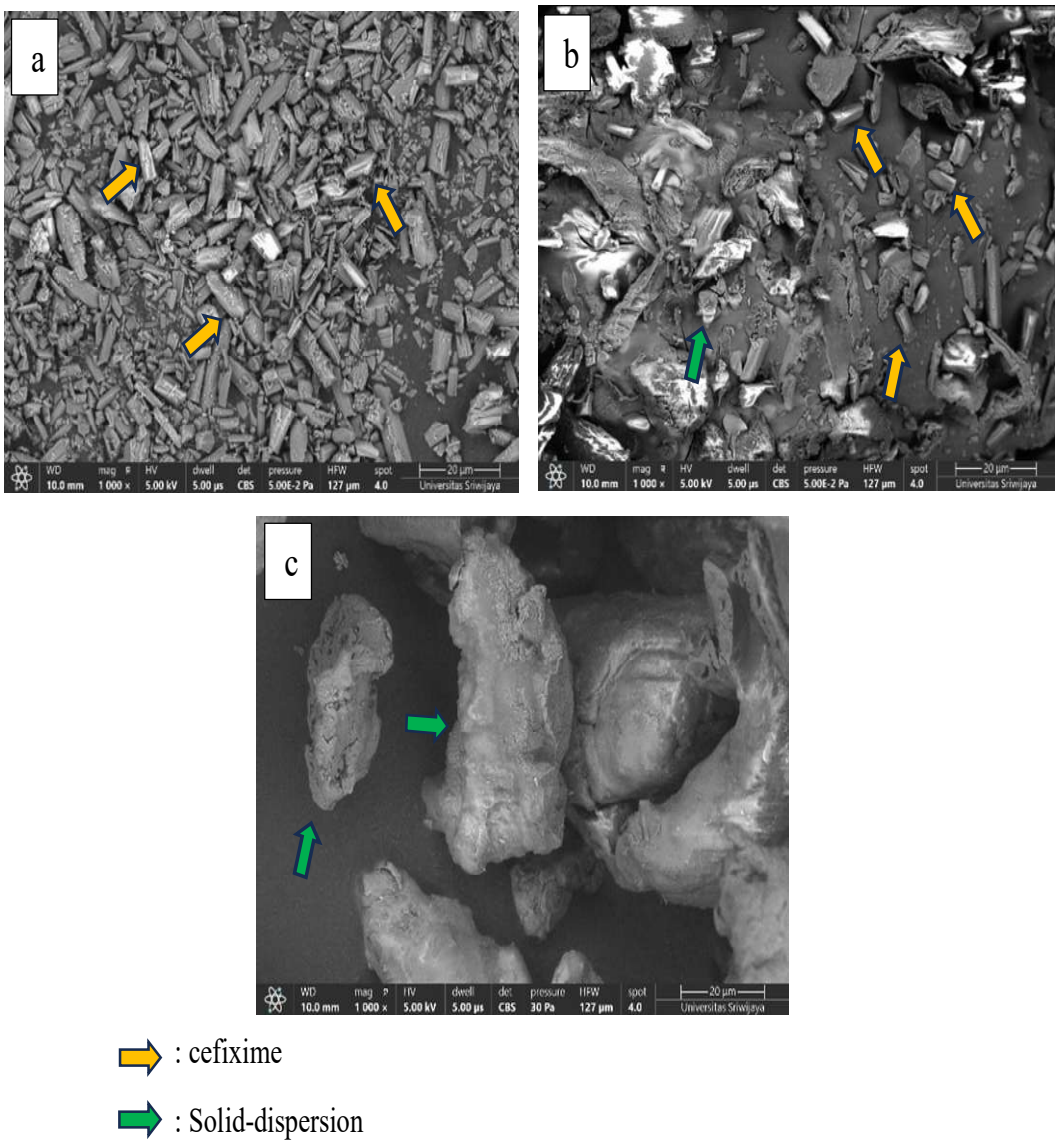


Figure 10. The morphology of solid dispersion compared to physical interaction and pure cefixime.

3.7 Determination of Solid-dispersion Flow Properties

Flow properties characteristics are intended to identify the characteristics of powder flow, which is an important parameter in ensuring the consistency of filling the compression space during the tablet and capsule manufacturing process (Rekdal et al., 2018)(Akelesh et al., 2015). In this study, testing was carried out on pure cefixime samples, physical mixture, and F2 solid dispersions were selected as the best formula. Flow properties testing carried out in this study includes four parameters: flow rate testing, angle of repose, compressibility index, and Hausner ratio. The results were presented in Table 5.

Table 5. The Flow Properties of Solid-dispersion, Physical Mixture, and Cefixime

Samples	Flow Rate ± SD	Angle of Repose ± SD	Compressibility Index ± SD	Hausner Rasio ± SD
Cefixime	3.6016 ± 0.0269	31.4951 ± 0.3876	27.2787 ± 0.4961	1.3752 ± 0.6822
Physical mixture	5.1464 ± 0.0665	29.6304 ± 0.3599	23.07853 ± 1.0189	1.3000 ± 0.3051
Solid-dispersion	6.3046 ± 0.1400	26.4598 ± 0.4027	16.3672 ± 0.2976	1.1957 ± 0.3559

3.8. Stability of Drug Content

The results of the quantification of cefixime in samples stored at different temperatures would be affected theoretically because antibiotics are generally known to be less stable. The results obtained as %decreasing levels (Table 6), that was generally an insignificant decrease in the third cycle. Solid dispersions (F2) and physical mixtures are more stable in the fifth cycle with a decrease in levels that was not higher than pure cefixime ($p \leq 0.05$).

Table 6. The %Decreasing Levels of Cefixime During Stability Test

Samples	%Decreasing CI	%Decreasing CII	%Decreasing CIII	%Decreasing CIV	%Decreasing CV	%Decreasing CVI
Cefixime	2.056	2.320	2.814	5.431	10.302	23.391
Phys. mixture	1.328	0.043	0.061	1.824	4.205	8.348
F2	0.012	0.018	0.038	1.157	3.461	5.024

*c= cycles

4. CONCLUSION

Based on the results, it was known that F2 cefixime solid dispersion was the best formula because the degree of crystallinity decreased to 21.71%, and FTIR analysis showed no new peaks. Evaluation of cefixime solid dispersion showed changes in particle morphology. In addition, there was an increase in the transmittance percentage in SIF of 98.587 ± 0.019 and an increase in the dissolution rate of cefixime of 83.61%, an increase in the flow rate of 6.3 ± 0.14 grams/second, an angle of repose of 26.4 ± 0.4°, a compressibility index of 16.3 ± 0.29%, and a Hausner ratio of 1.19 ± 0.35.

ACKNOWLEDGMENT

This study was conducted with the support of PNBP Sriwijaya University funding for Kompetitif schematic research in the current year 2025. The gratitude is also toward PT Dexa Medica, which provided cefixime.

REFERENCES

Adamo Fini, José R. Moyano, Juan M. Ginés, José I. Perez-Martinez, A. M. R. (2015). Diclofenac salts, II. Solid dispersions in PEG6000 and Gelucire 50/13,. *European Journal of Pharmaceutics and Biopharmaceutics, 60*(1), 99-111. https://doi.org/10.1016/j.ejpb.2004.11.005.

Ajmal, M., Zamir, A., Rehman, A. ur, Imran, I., Saeed, H., Majeed, A., Aziz, M., Alqahtani, F., & Rasool, M. F. (2023). Clinical pharmacokinetics of cefixime: a systematic review. In *Xenobiotica* (Vol. 53, Issue 3). https://doi.org/10.1080/00498254.2023.2217265

Akelesh, T., Johnson, S., Chander, J. U., Samantha, S., & Venkatanarayanan, R. (2015). Formulation and evaluation of floating tablets of cefixime trihydrate using chitosan. *Research Journal of Pharmacy and Technology*, *8*(11). https://doi.org/10.5958/0974-360X.2015.00268.1

Attia, M. S., Hasan, A. A., Ghazy, F. E. S., & Gomaa, E. (2021). Solid dispersion as a technical solution to boost the dissolution rate and bioavailability of poorly water-soluble drugs. In *Indian Journal of Pharmaceutical Education and Research* (Vol. 55, Issue 2). https://doi.org/10.5530/ijper.55.2s.103

Basak, P., & Adhikari, B. (2012). Effect of the solubility of antibiotics on their release from degradable polyurethane. *Materials Science and Engineering C*, *32*(8). https://doi.org/10.1016/j.msec.2012.07.002

De Simeis, D., & Serra, S. (2021). Actinomycetes: A never-ending source of bioactive compounds—an overview on antibiotics production. In *Antibiotics* (Vol. 10, Issue 5).

https://doi.org/10.3390/antibiotics10050483
Kalepu, S., & Nekkanti, V. (2015). Insoluble drug delivery strategies: Review of recent advances and business prospects. In *Acta Pharmaceutica Sinica B* (Vol. 5, Issue 5). https://doi.org/10.1016/j.apsb.2015.07.003
Khan, F. M., Ahmad, M., & Idrees, H. A. (2020). Simvastatin-nicotinamide co-crystals: Formation, pharmaceutical characterization and in vivo profile. *Drug Design, Development and Therapy*, *14*. https://doi.org/10.2147/DDDT.S270742
Khantri, H., Hussain, M. S., & Tyagi, S. (2022). Solubility Enhancement Techniques: An Overview. *World Journal of Pharmaceutical Research*, *11*(5).
Kim, J., & Ulrich, J. (2022). Dissolution and Growth Kinetics and the Rate-Controlling Step in Transformation of Amorphous to Crystalline Phase Using Antisolvent Crystallization. *Industrial and Engineering Chemistry Research*, *61*(39). https://doi.org/10.1021/acs.iecr.2c02135
Kumari, L., Choudhari, Y., Patel, P., Gupta, G. Das, Singh, D., Rosenholm, J. M., Bansal, K. K., & Kurmi, B. Das. (2023). Advancement in Solubilization Approaches: A Step towards Bioavailability Enhancement of Poorly Soluble Drugs. In *Life* (Vol. 13, Issue 5). https://doi.org/10.3390/life13051099
Lali, S. P., Sher, M., Hussain, M. A., Hassan, F., Naeem-Ul-hassan, M., Ahmed, M., & Bukhari, S. N. A. (2022). Solid Dispersion Preparation of a Macrolide Drug Using Natural and Synthetic Polymers to Enhance its Solubility and Bioavailability: A Pharmacokinetics Application. *Latin American Journal of Pharmacy*, *41*(3).
Leuner, C., & Dressman, J. (2000). Improving drug solubility for oral delivery using solid dispersions. In *European Journal of Pharmaceutics and Biopharmaceutics* (Vol. 50, Issue 1). https://doi.org/10.1016/S0939-6411(00)00076-X
Lindenberg, M., Kopp, S. & Dressman, J. . (2014). Classification of orally administered drugs on the world health organization model list of essential medicines according to the biopharmaceutics classification system. *European Journal of Pharmaceutics and Biopharmaceutics*, *58*(1), 265 – 278. https;//doi.org/10.210.98-f23-kMB.1.
Mardiyanto, Untari B., Fithri A. N., Mara A., Aprianto A.A., N. G. A. (2022). The Enhancement Solubility and Stability of Erythromycin Formatted in Solid Lipid Nanoparticles by Utilizing PVA as Stabilizer. *Science and Technology Indonesia*, *7*(2), 195–201. https://doi.org/doi.org/10.26554/sti.2022.7.2.195-201
Mardiyanto, Untari, B., Mara, A., & Prasetyo, N. H. (2023). Formulation and Evaluation of Azithromycin Dihydrate Solid Dispersion with Esther of Polyethylene Glycol-6000 and Stearic Acid Using A Co-Grinding Technique. *Science and Technology Indonesia*, *8*(2). https://doi.org/10.26554/sti.2023.8.2.312-320
O'Malley, C., McArdle, P., & Erxleben, A. (2021). *Crystallization from the Gas Phase: Morphology Control, Co-Crystal and Salt Formation*. MDPI Proc. Int Pharmaceutics, 78(1), 23-29. https://doi.org/10.3390/iecp2020-08797
Rekdal, M., Pai, A., Choudhari, R., & Sathyanarayana, M. B. (2018). Applications of co-crystals in pharmaceutical drugs. In *Systematic Reviews in Pharmacy* (Vol. 9, Issue 1). https://doi.org/10.5530/srp.2018.1.11
Shankar, P. R., Piryani, R. M., & Piryani, S. (2017). The state of the world's antibiotics 2015. *Journal of Chitwan Medical College*, *6*(4). https://doi.org/10.3126/jcmc.v6i4.16721
Silver, L. L., & Bostian, K. A. (1993). Discovery and development of new antibiotics: The problem of antibiotic resistance. In *Antimicrobial Agents and Chemotherapy* (Vol. 37, Issue 3). https://doi.org/10.1128/AAC.37.3.377
Spellberg, B. (2014). The future of antibiotics. In *Critical Care* (Vol. 18, Issue 3). https://doi.org/10.1186/cc13948
Tajmir, F., & Roosta, A. (2020). Solubility of cefixime in aqueous mixtures of deep eutectic

solvents from experimental study and modeling. *Journal of Molecular Liquids*, *303*. https://doi.org/10.1016/j.molliq.2020.112636

Urakov, A. L., Urakova, N. A., & Reshetnikov, A. P. (2021). Physical–chemical properties of antibiotic drugs: What we miss in our research. In *Japanese Dental Science Review* (Vol. 57). https://doi.org/10.1016/j.jdsr.2021.08.005

Wu, X., Wang, Y., Xue, J., Liu, J., Qin, J., Hong, Z., & Du, Y. (2020). Solid phase drug-drug pharmaceutical co-crystal formed between pyrazinamide and diflunisal: Structural characterization based on terahertz/Raman spectroscopy combining with DFT calculation. *Spectrochimica Acta - Part A: Molecular and Biomolecular Spectroscopy*, *234*. https://doi.org/10.1016/j.saa.2020.118265