FORMULATION AND EVALUATION OF AMOXICILLIN TRIHYDRATE FAST DISINTEGRATING TABLET (FDT) USING SODIUM STARCH GLYCOLATE (SSG) AS SUPER DISINTEGRANT

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ABSTRACT

This study was conducted to make a fast-disintegrating amoxicillin tablet formulation using a super disintegrant. Fast disintegrating tablets are tablets that quickly disintegrate after being placed in the mouth so that they can provide benefits for patients who have difficulty getting water or patients who have difficulty swallowing tablet drugs. Amoxicillin fast disintegrating tablet uses lactose monohydrate as filler, avicel pH 102 as binder, sodium starch glycolate as super disintegrant, stearic acid as lubricant, and aspartame as sweetener. The results of the granule evaluation showed that the fines produced from the particle distribution test were 4,56%. The tablet evaluation results showed that the tablets produced had a diameter of 0.6 ± 0,0 cm with a thickness of 0,4 ± 0,0 cm. The average weight of the tablets produced was 143,62 ± 3,04 mg. The hardness of the tablets obtained was 3,962 ± 0,5678 kg with an average tablet friability of 0,63 ± 0,0028%. Tablet dissolution results showed that within 30 minutes tablet 1 dissolved as much as 116,21% and tablet 2 dissolved as much as 116,38%. The results of the disintegration time test showed that the tablets disintegrated for 44,44 ± 15,3957 seconds and the wetting time test was pored for 20 seconds. All evaluations carried out have met the predetermined acceptance requirements. Therefore, this FDT amoxicillin preparation formulation is declared as an optimal and effective formulation for use.

Keywords: Amoxicillin trihydrate; Fast disintegrating tablet; Formulation; Sodium starch glycolate; Superdisintegrant

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INTRODUCTION

Antibiotics are the most widely used drugs in infections caused by bacteria (Depkes RI, 2014). One of the antibiotics that is widely used is amoxicillin. Amoxicillin is an analog of ampicillin. This broad-spectrum antibiotic is used to treat various infections in children, adults, pregnant and lactating women. Some of the diseases that are treated with amoxicillin include bacterial infections, sore throat, ear and sinus infections, and urinary tract infections (Tjay, T. H., & Rahardja, K. 2015).

Amoxicillin is a type of beta-lactam antibiotic with a broad spectrum because it can inhibit the growth or kill gram-positive and gram-negative bacteria (Black, 2004). The mechanism of action of amoxicillin is directly killing the bacteria by interfering with the last stage of cell wall synthesis or transpeptidase reaction, rupturing bacteria's cells, and inhibiting bacterial cell wall synthesis by binding one or more penicillin-protein bonds (Lowy, 1986). Penicillin is a first-line treatment with a broad spectrum of effectiveness and is free from toxic effects (Ovikariani et al., 2019).

Amoxicillin is generally tolerated by patients, especially pediatric and geriatric patients. It is established that amoxicillin is effective and safe for treating skin, soft tissue, respiratory tract, and genitourinary tract infections in pediatric patients as young as 12 weeks old with dosage adjustment. Amoxicillin is available in numerous forms, including immediate-release and extended-release tablets, chewable tablets, fast-

disintegrating tablets, and suspension. It can also be mixed and administered with a drink, so it is more convenient for patients who have trouble swallowing (Akhavan et al., 2023).

Fast Disintegrating Tablets (FDT) are tablets that are intended to be rapidly disintegrated in the mouth upon contact with saliva in less than 60 seconds or preferably less than 40 seconds (Kundu & Sahoo, 2008). The purpose of making fast-disintegrating tablets is to facilitate the administration of drugs in tablet form to pediatric and geriatric patients who tend to have difficulty swallowing drugs in solid dosage forms such as tablets. This fast-disintegrating tablet is designed to disintegrate quickly without chewing and without the need for drinking water and has a good taste in the mouth so that it can facilitate patients who have difficulty getting drinking water. FDT when placed in the mouth immediately dissolves and releases the active substance. Drugs that disintegrate faster will be absorbed faster and have a faster effect. The bioavailability of drugs in the form of FDTs is better than conventional tablets (Nurdianti et al., 2018).

Amoxicillin trihydrate has water solubility 1:400 and WHO also classifies amoxicillin 250 and 500 mg included in BCS class I (high solubility and permeability). Solubility and permeability studies show that amoxicillin with a dose of less than 875 mg falls into BCS class I, while 875 mg to 1000 mg falls into BCS class II, and a dose of more than 1000 mg falls into BCS class IV. (Widyasari et al., 2020).

In this research, we will make a fast-disintegrating tablet (FDT) formulation with amoxicillin trihydrate as the active ingredient. The excipients that will be used are lactose monohydrate as a filler, avicel pH 102 as a binder, sodium starch glycolate (SSG) as a super disintegrant, talc as a glidant, stearic acid as a lubricant, and aspartame as a sweetener. The preparation of amoxicillin fast disintegrating tablet (FDT) will be carried out using SSG at a concentration of 8%. The evaluation test that will be carried out on Amoxicillin FDT are organoleptic test, size uniformity test, weight uniformity test, hardness test, friability test, dissolution test, disintegration and wetting time test.

MATERIALS AND METHODS

a. Materials

Amoxicillin trihydrate, lactose monohydrate, avicel PH 102, talc, stearic acid, aspartame, sodium starch glycolate (SSG). All materials were obtained from the materials storage room in the Pharmaceutical Technology Laboratory, Faculty of Medicine, University of Pembangunan Nasional "Veteran" Jakarta. The ingredients used in the formulation shown in Table 1.

Table 1. Formulation of Amoxicillin Trihydrate FDT

Material	Function	Conc.
Amoxicillin trihydrate	API	30 mg
Lactose monohydrate	Filler	q.s
Avicel PH 102	Binder	60%
Talc	Glidant	2%
Stearic Acid	Lubricant	3%
Aspartame	Sweetener	0,2%
Sodium Starch Glycolate	Superdisintegrant	8%

b. Method

1. Tablet Formulation

The method used to manufacture the tablets was dry granulation method. Dry granulation does not involve heating, so it is more suitable for active ingredients that are not heat-resistant. In dry granulation, granulation is carried out by slugging, which is the manufacture of hard tablets which will then be re-milled (Shahidulla et al., 2019). The inner phase (amoxicillin, avicel pH 102, and lactose monohydrate) was put into the mortar and then crushed until homogeneous. Half of the outer phase (sodium starch glycolate, talc, and stearic acid) was put into the mortar, and then crushed until homogeneous. After that, the inner phase and half of the outer phase were compressed into slugs (hard tablets). In Process Control (IPC) of particle size distribution was performed using a sieve shaker. %Fines were calculated with the following formula:

$$\%\ fines\ = \frac{weight\ of\ fines\ (g)}{total\ granule\ weight\ (g)} \times 100\%$$

Terms: %fines less than 10%.

The sieving results were mixed with the remaining half of the outer phase and aspartame, then crushed until homogeneous. Then, tablets were compressed with a tablet press.

2. Tablet Evaluation

a) Organoleptic Test

The organoleptic test was done by visually observing the form, smell, and color of the tablets (Aisyah et al., 2023)

b) Size Uniformity Test

Ten tablets were taken and the diameter of the tablet thickness was measured using a ruler. Terms: tablet diameter is not more than three times and not less than 1⅓ tablet thickness (Depkes RI, 2014).

c) Weight Uniformity Test

Ten tablets were randomly taken and weighed at once and the average tablet weight was calculated. Then the tablet weights were weighed one by one. Calculated % deviation using the following formula:

$$\%Deviation = \frac{tablet\ weight - average\ weight}{average\ weight} \times 100\%$$

Terms: Less than 2 tablets deviated from column A and none deviated from column B (Depkes RI, 2020).

Table 2. Weight Uniformity Test Requirements
(Source: Depkes RI, 2014)

Average Weight of Tablet (mg)	A	B
≤ 25 mg	15%	30%
26-150 mg	10%	20%
151-300 mg	7,5%	15%
> 300 mg	5%	10%

d) Hardness Test

This test uses a device called a Hardness Tester. Ten tablets were taken and placed horizontally on the hardness tester, then recorded at what pressure the tablets broke (Depkes RI, 2014).

e) Friability Test

Ten tablets were cleaned from dust and then weighed (a) and put into the Friability Tester at 25 rpm for 4 minutes. Then the tablets were removed and cleaned from dust, then weighed again (b). The difference in tablet weight before and after treatment was calculated with the following equation:

$$F = \frac{a-b}{a} \times 100\%$$

Terms: 0,5%-1% (Depkes RI,2014)

f) Dissolution Test

1) Preparation of amoxicillin standard curve

100 mg of amoxicillin were weighed and dissolved with CO_2-free water in a 100 ml volumetric flask. The solution was pipetted 0,1 ml; 0,2 ml; 0,3 ml; 0,4 ml; and 0,5 ml of each, put into a 10,0 ml

volumetric flask, and diluted with CO_2-free water to obtain a series of amoxicillin solutions with concentrations of 10, 30, 50, 70, and 100 ppm. The absorbance was measured by UV-Vis spectrophotometer at the maximum wavelength of amoxicillin (247 nm). A curve was made between concentration and absorbance, then the linearity value R and the equation of the regression line were determined.

2) Dissolution test

The dissolution test was done using a paddle-type dissolution tester. The 900 ml of CO_2-free water medium was put into the dissolution flask, using dissolution apparatus type-2 for the paddle, and set at 75 rpm for 45 minutes. Weighed tablets were put into the dissolution flask. The test temperature was maintained at 37 ± 0,5°C. Samples were taken at 0, 5, 15, 30, and 45 minutes as much as 10 ml. The samples taken were replaced with new dissolution media with the same amount so that the volume of dissolution media was maintained. The absorbance of the sample was measured by UV-Vis spectrophotometer at the maximum wavelength of amoxicillin (247 nm) (Ardiningtyas, 2012). The dissolution test of amoxicillin tablets must meet the requirements of the Indonesian Pharmacopoeia VI edition, which has a %dissolved amoxicillin of not less than 75% within 30 minutes (Depkes RI, 2020).

g) Disintegration and Wetting Time Test

The disintegration time is the time required for the tablet to soften and disintegrate. 10 ml of room temperature water was added to a petri dish with a diameter of 10 cm, then the tablet was placed and the disintegration time was recorded. The measurements were carried out ten times and the mean value was calculated (Ashish & Ajay, 2017).

Wetting time is the time taken for water to reach the top surface. The spherical filter paper was placed in a petri dish with a diameter of 10 cm. 10 ml of methylene blue was added, then the tablet was placed on the wet filter paper (Watora et al., 2018).

RESULT

Particle Size Distribution Test

Results of the particle size distribution test shown in Table 3.

Table 3. Particle Size Distribution Test Results

Mesh Size (mm)	Weight (g)
0,850	0,51 g
0,425	1,8 g
0,150	7,14 g
0,106	5,02 g
0,075	5,24 g
0,053	6,61 g
0,038	9,27 g
Pan	1,7 g
Total	37,29 g
%fines	4,56%

Based on the data in table 3, it can be seen that the results of the particle size distribution test produced mean values for %fines was 4,56%.

Organoleptic Test

Results of the organoleptic test shown in Figure 1 and Table 4. Based on the data in Table 4, it can be seen that the results of the organoleptic test were white, sweet, and odourless tablets without capping, laminating, cracking, and crumbling.

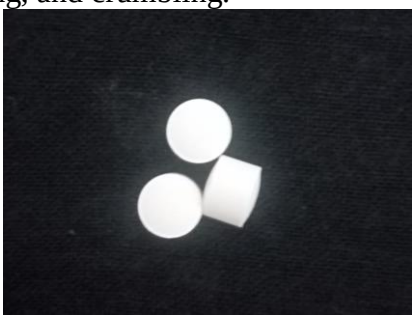

Figure 1. Amoxicillin Fast Disintegrating Tablets

Table 4. Organoleptic Test Results

Parameter	Result
Colour	White
Flavour	Sweet
Smell	Odorless
Surface	No capping, laminating, cracking, and crumbling

Table 5. Evaluation Test Result

Tablet Evaluation	Result	Requirement
Hardness Tester (kg)	3,962 ± 0,5678	3-5
Friability Test (%)	0,63±0,0 028	≤ 1
Size Uniformity Test (cm) a. Diameter b. Thick	 0,6 ± 0,0 0,4 ± 0,0	3 x Thick ≥ D ≥ 1/ x Thick
Weight Uniformity Test (mg)	143,62 ± 3,04	Column A < 10 % Column B < 20%
Disintegration Test (second)	44,44 ± 15,3957	≤ 3 minutes
Wetting Time (second)	17	-

Based on the evaluation test results in Table 5, it can be seen that the amoxicillin FDT tablets meet the requirements of all evaluation test

Dissolution Test

Results of the dissolution test shown in Table 6.

Table 6. Tablet 1 Dissolution Test Results

Tablet	Minutes	Abs	C	% Dissolution	Log % Dissolution
1	0	0,3053	20,7	62,1	1,793
	5	0,3531	32,36	97,77	1,990
	15	0,3702	36,53	111,33	2,046
	30	0,3752	37,75	116,21	2,065
	45	0,4056	45,17	139,73	2,145
2	0	0,3043	20,4	61,2	1,786
	5	0,3536	32,4	97,88	1,990
	15	0,3705	36,60	111,56	2,047
	30	0,3754	37,8	116,38	2,065
	45	0,4080	45,75	141,49	2,150

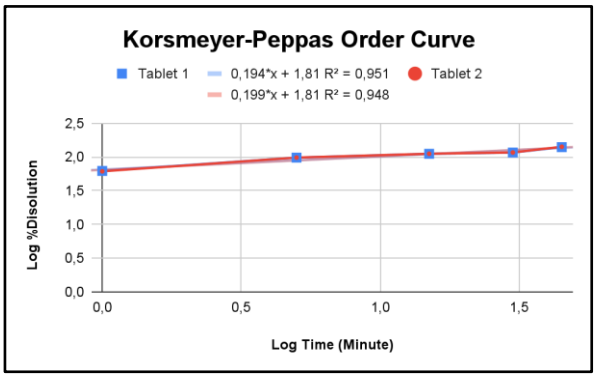

Figure 2. Korsmeyer-Peppas Order Curve Tablet 1 and 2

Table 7. Comparison of Reaction Order Curve

Order	R^2 Value	
	Tablet 1	**Tablet 2**
Zero order	0,822	0,824
First order	0,731	0,73
Higuchi order	0,95	0,947
Korsmeyer-Peppas order	0,951	0,948

Based on the R^2 value in Table 7, it can be seen that the drug release in amoxicillin FDT followed Korsemeyer Peppas order.

DISCUSSION

Particle Size Distribution Test

The particle size distribution test is one of the tests for granule evaluation. This test is carried out by sieving the granule using a sieve shaker. The sieve is assembled from the largest mesh number to the smallest mesh number and the sieving process is carried out with an amplitude of 25 for 10 minutes. A granule is said to have a good particle size distribution if the amount of fines is no more than 10% (Putri et al., 2019). Based on the results of the research conducted, the %fines value was obtained at 4,56%, so it can be concluded that the granules used have a good particle size distribution.

Organoleptic Test

The organoleptic test, or sensory test, is a testing method that uses human senses as the main tool to measure product acceptance. This test assessed tablets based on their colour, taste, smell, and shape (Gusnadi et al., 2021). Based on the organoleptic test, our tablets were white, had a sweet taste, and were odourless. The surface of our tablets did not experience capping, laminating, cracking, or crumbling.

Size Uniformity Test

The size uniformity test is carried out using a vernier measuring tool. This test was carried out on 10 tablets. Size uniformity parameters were calculated by measuring the diameter and thickness of the tablets tested first and then comparing them. The requirements for a good tablet are the diameter is not more than 3 times the thickness of the tablet and not less than 1,3 times the thickness of the tablet (Depkes RI, 2014). As for the results of measuring the uniformity of size on 10 tablets, the average diameter value was 0,6 cm. Previously we had also calculated the thickness of the tablet, and the result was 0,4 cm so based on the good condition of the tablet it was known that all the tablet samples tested met the requirements contained in the compendial. It can be stated that the process of making tablets produces tablets that have uniform sizes.

Weight Uniformity Test

The weight uniformity test was carried out using an analytical balance. This test was carried out using 10 tablets. The requirement for uniformity in tablet weight as stated in the Farmakope Indonesia V (2014) for tablets with an average weight of 26-150 mg is that not more than 2 tablets have a deviation greater than 10% and not more than 1 tablet has a deviation greater than 20%. The results of the weight uniformity test carried out on 10 test tablets obtained an average deviation value of 2%. None of the tablets had a deviation of more than 10%. The lowest and highest

deviation values obtained were respectively 0.2% and 3,3%. Based on this, it can be stated that the tablets produced have a uniform tablet weight.

Hardness Test

The tablet hardness test was conducted using a hardness tester. This test was carried out using 10 tablets. The hardness requirement for a good fast disintegrating tablet is 3-5 kg (Putranti et al., 2021). Hardness is a measure of tablet resistance to mechanical impact that can occur during the production, packing, distribution, and rough treatment by consumers. Based on the results of the research that has been done, it can be seen that all tablets meet the requirements of tablet hardness, so it can be concluded that the tablets produced have good hardness. The tablet hardness test is a parameter that describes Factors that influence tablet hardness include: granulation method, compression pressure, granule hardness and type and quantity of binder (Buang, 2022).

Friability Test

Friability is a parameter to measure the resistance of tablet surfaces to friction during packaging and shipping. Measurement of friability is done using a device called a friability tester. Its working principle is to calculate the weight lost from a number of tablets after being rotated in a friability tester for a certain time. In this process, the device is rotated at a speed of 25 revolutions per minute for 4 minutes. The friability test measures the weight loss due to abrasion on the tablet surface. The higher the friability percentage, the more tablet mass is lost. High friability affects the level of active substance remaining in the tablet. In tablets with small weights and low active substance concentrations, mass loss due to friability can affect the remaining active substance levels in the tablet (Gopalan and Gozali, 2018).

The F value is considered qualified if it is less than 1%. If the F value is more than 1%, the tablet can be improved by increasing or increasing its hardness (Putra et al, 2021). Based on the results of the research that has been done, the friability test results of 10 tablets are 0,63%±0.0028 so it can be concluded that the tablets produced meet the requirements of good friability.

Dissolution and Release Test

The dissolution test is a method used in developing new drug formulations, monitoring drug product quality, and predicting in vivo drug performance (Susanti, 2019). The dissolution test aims to predict the correlation of drug bioavailability in vivo. In the dissolution test of the FDT amoxicillin preparation, 2 tablets were used with 900 mL of water as the media. For the dissolution test tool, a type 2 dissolution tool (paddle) is used with a rotation speed of 75 rpm within 30 minutes at a temperature of 37ºC ± 2ºC (FI VI, 2020). The requirements for the dissolution of amoxicillin in FDT preparations according to the literature referred to generic amoxicillin tablets, with no less than 75% of the amount stated on the label must be dissolved within 30 minutes (FI VI, 2020). Based on the dissolution data obtained, at the 30th minute, tablet 1 had dissolved 116,21% and tablet 2 had dissolved 116,38%. Thus, it can be concluded that the amoxicillin FDT tablet dissolution test has met the requirements.

Determination of the reaction order is carried out by plotting a curve, with the x-axis being time, and the y-axis being concentration (zero-order curve) and log concentration (first-order curve). The second-order release curve was not determined, this is because the second-order curve involves 2 molecules that react and collide with each other (Martin, 2008). In this study, only one molecule is used, namely amoxicillin, so it is impossible to fulfill the second-order curve. Then, look for the straightest line from the curve obtained, by looking at the highest R value.

Based on tablet order curves 1 and 2, it can be seen that the release of amoxicillin FDT meets the Korsmeyer Peppas curve. This can be seen from the highest R value between zero order, first order and the Higuchi curve with an R value of 0.951 for tablet 1 and 0.948 for tablet 2.

The Korsmeyer–Peppas model was basically developed to describe the kinetics of drug release from a polymer matrix. This model explains the release mechanism based on Fickian and non-Fickian equations by looking at the value of n (release exponent) (Costa dan Sousa Lobo, 2001). If the value of n<5 then the release of the active substance occurs based on a Fickian diffusion mechanism and if the value 0.5<n<1 it means that the release mechanism of the active substance occurs based on non-Fickian diffusion. (Andrie et al., 2022).

The n value obtained is 0.951 for tablet 1 and 0.948 for tablet 2. Both have n values between 0.5-1. This shows that amoxicillin FDT is included in Non-Fickian transport, namely the release of the drug is controlled by a combination of diffusion and erosion.

Table 8. Interpretation of diffusional release mechanisms from polymeric films.

Release exponent (n)	Drug transport mechanism
<0,5	Fickian diffusion
0,5<n<1	Non-Fickian transport
1	Zero order release
>1	Super case II transport

Table 9. Interpretation of diffusional release mechanisms from polymeric films (Source : Jayanudin et al., 2016)

Exponential Diffusion (n)			Release Mechanism
Thin Film	Cylindrical Sample	Ball Sample	
0,5	0,45	0,43	Fickian diffusion
0,5<n<1	0,45<n<0,89	0,43<n<0,85	Non Fickian
1	0,89	0,85	Case II Transport

Disintegration and Wetting Time Test

Figure 7. Disintegration Time Test.

The disintegration time is the time required for the tablet to soften and disintegrate. The disintegration time test is carried out by placing the tablet in a Petri dish containing 10 ml of water at room temperature which represents saliva in the oral cavity (Ashish & Ajay, 2017). According to British Pharmacopoeia (2008), the requirement for the disintegration time of fast-disintegrating tablets is no more than 3 minutes. Based on the results of the research that has been done, the results of the destruction time test were obtained for 44,44 ± 15,3957 seconds, so it can be concluded that the tablets produced meet the requirements of a good destruction time.

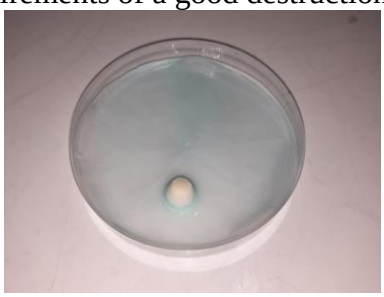

Figure 8. Wetting Time Test

Wetting time is the time required for the solvent to wet the tablet surface. The wetting time test was carried out by placing the tablet in a Petri dish containing 10 ml of methylene blue covered with filter paper (Watora et al., 2018). Based on the results of the research conducted, the wetting time test results were obtained for 17 seconds. There are no specific requirements for the wetting time of fast-disintegrating tablets, but it can be concluded that the tablets produced have a good ability to absorb water, thus accelerating the tablet disintegration time.

CONCLUSION

In this study, generic amoxicillin tablets have been developed into fast-disintegrating tablets using 8% of SSG as a super disintegrant. Various tablet evaluations have been conducted, such as particle size distribution test, size and weight uniformity test, hardness test, friability test, and dissolution test. All evaluations carried out have met the predetermined acceptance requirements. Therefore, this FDT amoxicillin dosage formulation is declared as an optimal and effective formulation for use. Further tests can be conducted, such as a drug stability test to determine whether any incompatibility was observed during packaging as well as the stability of the drug and excipients used.

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