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Solid Dispersion of Acetosal Using Polyvinyl Pyrrolidone (PVP) K-30 in Tablets with Direct Compressing Method

Khuswatun Khasanah[1], Desy Nawangsari[1*], Ikhwan Yuda Kusuma[1,2]

[1]Pharmacy Study Program, Faculty of Health, Harapan Bangsa University, Jl. Raden Patah No. 100, Purwokerto
[2]Institute of Clinical Pharmacy, Faculty of Pharmacy, University of Szeged, 6725 Szeged Szikra utca 8., Szeged, Hungary

[*]*Corresponding Author: desynawangsari@uhb.ac.id*

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Abstract

Acetosal is classified in the Biopharmaceutical Classification System (BCS) class II (low solubility, high permeability). Low solubility causes a decreased dissolution rate. Polyvinyl pyrrolidone (PVP) K-30 is an inert carrier easily soluble in water and can influence the solubility of a drug substance. Efforts to increase the solubility of acetosal make a solid dispersion system. This study aims to determine the effect of the solid dispersion system of acetosal: PVP K-30 on dissolution rate, the ratio of the solid dispersion with the best dissolution rate, and the physical properties of acetosal tablets formed in the dispersion system. Solid dispersions using the dissolving method with variations in the concentration of acetosal: PVP K-30 1:1, 1:3, and 1:5. The results of the dissolution test of acetosal in solid dispersion powder, i.e., PVP Formula 1:5, which has the highest dissolution percentage compared to formula 1:1 and 1:3 with the concentration this formula was 140.96 mg, dissolution percentage was 28.19±0,63% in 30 minutes. Statistical results by ANOVA test show a significant difference of 0.044 ($p<0.05$). The physical properties of tablets with a dispersion system show higher addition of PVP K-30. This result is related to slower disintegration time and lower friability.

Keywords: Acetosal, BCS, Solid dispersion, PVP K-30, Anova.

INTRODUCTION

Non-Steroid Anti-Inflammatory Drugs (NSAIDs) are a group of therapeutic drugs used for analgesics, antipyretics, and anti-inflammatories (Alkabodi et al., 2016). One of which is acetosal (acetylsalicylic acid) or often known as aspirin (Kuntari, Aprianto, Noor, & Baruji, 2017). Acetosal is a drug in the Biopharmaceutical Classification System (BCS) class II group (low solubility, high permeability) (Shanthala et al., 2021). Low solubility affects absorption because it causes a decreased dissolution rate (Noval & Rosyifa, 2021). Therefore, efforts must be made to increase the solubility of acetosal, which will improve the dissolution rate; the way to increase the solubility of acetosal is to create a solid dispersion system.

Solid dispersions are prepared by dissolving, melting, or combining two methods of one or more pharmaceutical compounds in an inert carrier or solid matrix (Zaini et al., 2017). The goal is to increase the bioavailability of low-solubility drug substances (Umar et al., 2014). Solid dispersion systems are based on the concept of a drug dispersed in an inert carrier or polymer, usually methylcellulose, polyethene glycol (PEG) 4000 (Kurnia et al., 2021), PEG 6000, and polyvinylpyrrolidone (PVP) (Mogal et al., 2012).

Formulation studies and evaluation of solid dispersions containing acetosal with polyethene glycol 6000 carriers showed increased solubility of the pure drug at F4 (1:4) with a dissolution rate of 95.94%, which was optimized at 90 minutes (Sahoo et al., 2017). In this study, the polyvinyl pyrrolidone (PVP) carrier was chosen because PVP is an inert carrier with easy solubility in water. With an increase in PVP levels, it is expected that the solubility of a drug substance in water will increase. Its dissolution rate will increase (Umar et al., 2014).

There are three methods for making tablets: wet granulation, dry granulation, and direct compression (Zaman & Sopyan, 2020). Direct compression is used for materials that cannot stand heat and humidity and have good compatibility and flow properties (Jayanti, 2020). In this study, acetosal is sensitive to heat and moisture (Hidayati et al., 2020). PVP is a versatile polymer with good flow properties and is hygroscopic but does not harden with time (Hidayati et al., 2020). The authors chose to use the direct compression

method because it suits the nature of the material used.

Based on the above background, the authors are interested in making solid dispersions with variations in the ratio of acetosal solid dispersions using PVP K-30 with the best dissolution rate. They can produce tablets that meet the physical properties requirements.

METHODOLOGY

Materials and Instrumentals

The research tools were an analytical balance (Mettler Toledo), evaporating cup, 60 mesh sieve, glassware, desiccator, tablet press machine, UV-VIS spectrophotometry, oven, moisture analyzer (BEL), callipers (Tricle Brand), stopwatch, hardness tester, friability tester (CS-II), disintegration tester (Biostellar), flowability tester (Bonnin), tapped density tester (TDT-2-H), thermometer, spatula, and stamper mortar. The materials used are Acetosal (p.a), Polyvinyl Pyrrolidone (PVP), Talcum, Mg Stearate, Avicel 102 (pharmaceutical grade), Sodium acetate trihydrate, glacial acetic acid, 96% alcohol, and Aquades.

Methods

Determination of the acetosal standard curve

A standard acetosal solution was prepared with various concentrations of 100 ppm, 150 ppm, 200 ppm, and 250 ppm, namely by weighing 200 mg of acetosal and sufficiently dissolving 96% ethanol. Acetate buffer solution pH 4.50 ± 0.05 to reach a volume of 100 mL (2000 ppm), and the standard solution was diluted to obtain 100, 150, 200, and 250 ppm concentrations. Absorption was observed with UV spectrophotometry at a wavelength of 277 nm. The use of UV spectrophotometry because it is simple, easy to work with, fast, accurate and only requires a small sample (Rustiah & Umriani, 2018).

Preparation of solid dispersions

Acetosal solid dispersion: Polyvinyl Pyrrolidone (PVP) K-30 was prepared in several comparisons, as shown in Table 1.

Table 1. Solid dispersion

Formula	Drug	Carrier	(drug: carrier) (g)
1	Acetosal	PVP K-30	1:1
2	Acetosal	PVP K-30	1:3
3	Acetosal	PVP K-30	1:5

Each ingredient weighed and acetosal dissolved using 96% ethanol and stir until the solution is clear. PVP K-30 was also dissolved in 96% ethanol and then added slowly into the acetal solution while stirring. The mixture is then evaporated and dried in an oven at 40-50 °C until dry. Store the solid in a desiccator for 24 hours. The resulting solid was scraped off, ground in a mortar, then sieved through a 60 mesh sieve, and stored in a desiccator for 24 hours before being evaluated. (Noval & Rosyifa, 2021).

Solid dispersion test

Moisture content test

Weigh 1 gram of solid dispersion sample using a moisture analyzer cup. Set the moisture analyzer at 50°C, close the moisture analyzer cover, wait a few minutes until the moisture content results appear, and record the results obtained. (Kumalasari, 2012; Rukmawati, Hartini, & Cahyani, 2017).

Solid dispersion dissolution test

The acetal solid dispersion dissolution test was carried out using the "rotating basket" method at 50 rpm. Mix 2.99 g of sodium acetate P trihydrate and 1.66 mL of glacial P acetate with water to make up to 1000 mL and pH 4.50 ± 0.05, adjusting the temperature to 37° ± 0.5°. Upon reaching temperature, a solid dispersion equivalent to 50 mg of acetal was added to the dissolution flask. Pipette up to 5 mL of the solution in the flask at 5, 10, 15, and 30 minutes. With each pipetting, the solution in the flask is replaced with the same volume of dissolution medium and pipetting at the same temperature (Depkes RI, 2020).

The absorbance of the liquid taken was measured at a maximum wavelength of 277 nm using a UV spectrophotometer. The results were calculated by determining the percentage of the drug released at a specific time. The requirement for determining the solubility test is the value of the active substance that will be dissolved within 30 minutes of not less than 80% (Ministry of Health RI, 2020).

Tablet production

Acetosal tablets are made by mixing the resulting solid dispersion powder with lubricant (Talkum), slip agent (Mg stearate), and filler (Avicel PH 102). The acetosal tablet formula in Table 2 will be produced using direct compression. Direct compression is used for materials that cannot stand heat and humidity and have good compatibility and flow properties (Jayanti, 2020).

Production mass evaluation

Flow rate

The 10 g of granules was put into the flowability tester and leveled, and the time it took to pass through

the funnel was recorded. The excellent flow rate category is 4-10 grams/second, and difficult if it is 1.6-4 seconds (Warnida et al., 2012).

Table 2. Acetosal tablet formula

Ingredients	F1	F2	F3	Description
Acetosal	80 mg	80 mg	80 mg	Active substance
PVP K-30	80 mg	240 mg	400 mg	Carrier
Talcum	2%	2%	2%	Lubricant
Mg Stearate	1%	1%	1%	Slip agent
Avicel PH 102	ad 500	ad 500	ad 500	Filler
Mass per tablet (mg)	500	500	500	

to produce 300 tablets (Source: (Sinaga et al., 2021)

Static angle evaluation

Evaluation of the angle of repose is the same as evaluating the flow rate. Still, here the powder is allowed to flow through the funnel, the height of the cone formed is measured, and the cone's diameter formed with a ruler is also measured (Khairunnisa et al., 2016). The angle of repose is calculated using the following Equation 1.

$$\Theta = \tan^{-1}(h/r) \quad (1)$$

Compressibility index

Put 50 mL of the pellet into a measuring cup (volume), place it on the tap density tester and turn on the tool for 5 minutes. Particle volume is measured after compaction and then weighed to determine the weight (w/v). The following Equation 2 (Nawangsari & Prabandari, 2021) calculates percent compressibility (Equation 2).

$$Compressibility\ index = \frac{\rho\ \text{tapped} - \rho\ \text{bulk}}{\rho\ \text{tapped}}\ x\ 100\% \quad (2)$$

Hausner ratio

The Hausner ratio is a number related to the flowability of the powder (Equatin 3), not an absolute value for a particular material, depending on the method used to determine it (Arulkumaran & Padmapreetha, 2014) (Equation 3).

$$Hausner\ ratio = \frac{\rho\ \text{tapped}}{\rho\ \text{bulk}}\ x\ 100\% \quad (3)$$

Tablet physical properties test

Organoleptic test

Observe the tablet's physical appearance, including its smell, color, and shape.

Mass uniformity test

Taken a total of 20 tablets and weigh each tablet. The average weight of each tablet was calculated and compared with the requirements for uniformity of tablet weight. Tablets are considered average weight if no more than two 300 mg tablets deviate from the average weight specified in Column A (5%) and no tablets deviate from Column B (10%) (MOH RI, 1995).

Size uniformity test

Taken a total of 10 tablets and measure the diameter and thickness of the tablets with a caliper. A good tablet has a diameter of not more than three times the size of the tablet and not less than 4/3 of the thickness of the tablet (Depkes RI, 1979).

Friability test

The number of tablets to be tested is 20, initially weighed with dust removal. The tablets are put into the friability tester, rotated for 100 rounds (4 minutes), and then sprinkled again. Tablets are said to be good if their friability does not exceed 1% (Depkes RI, 1979).

Tablet hardness test

Take a total of 10 tablets, place the tablets vertically on the hardness tester, then adjust the distance between the base and the spring bolt on the bottom to compress the tablets. Set the hardness scale to zero, then turn the lever until the tablet breaks. The number on the device's scale indicates the tablet's hardness in kg (Lachman, 1994). A good tablet has a hardness between 4-10 kg (Depkes RI, 1979).

Time trial destroyed

A total of 6 tablets were taken and put into each tube in the disintegrator. The tube is periodically raised and lowered in ~1000 mL of aquadest medium at a temperature between 36°C-38°C the medium. The disintegration time of the tablets was recorded. The tablet is declared disintegrated if there is no part of the gauze. Disintegration time is less than 15 minutes for uncoated tablets (MOH RI, 1979).

Dissolution test

The Acetal tablet dissolution test was carried out using a type 1 apparatus (basketball), and the dissolution medium was 500 mL of 0.05 M acetate buffer. This solution was prepared by mixing 2.99 g of sodium acetate P trihydrate and 1.66 ml of glacial P acetate with water until 1000 mL and pH 4.50 ± 0.05. Load the dissolution media into the container, set up the apparatus, and allow the dissolution medium to cool to 37º±0.5º. Put one tablet into the tool, remove air bubbles from the surface of the test formulation,

and immediately run the device at 50 rpm for 30 minutes (Depkes RI, 2020).

Sampling was performed at 5, 10, 15, 30, and 45 minutes; each 5.0 ml sample was replaced with 5.0 mL acetate buffer. Measure the absorbance of the resulting sample with a UV-Vis spectrophotometer at a wavelength of 277 nm ± 2 nm. The requirement for determining the dissolution test is that the value of the active substance dissolved is not less than 80% within 30 minutes (Ministry of Health RI, 2020).

Data analysis

The data obtained from each test were analyzed using the SPSS program using One Way Anova to find out the differences in each formula (Priyanto, 2013). One Way Anova test to see the results of each comparison of acetosal solid dispersions with PVP K-30.

RESULTS AND DISCUSSION

Determination of the acetosal standard curve

According to Pharmacopoeia Edition VI, the maximum wavelength of acetosal is 265 nm; based on the measurements, it was found to be 277 nm. These results show a significant (electrochromic) wavelength shift, likely due to polar solvents. This leads to a higher free electron transition and, thus, more excellent absorption at that wavelength (Hanwar et al., 2017).

Acetal concentration series with acetate buffer levels of 100, 150, 200, and 250 ppm. Measurement of the concentration at a wavelength of 277 nm produces the equation y = 0.0022 (x) + 0.0794 with a correlation coefficient of r = 0.9999. The correlation coefficient represents the linear relationship between the concentration (x) and the resulting absorption (y). The resulting correlation coefficient is close to 1, which meets the acceptance criteria for a correlation coefficient of 0.999 (Handoyo et al., 2020).

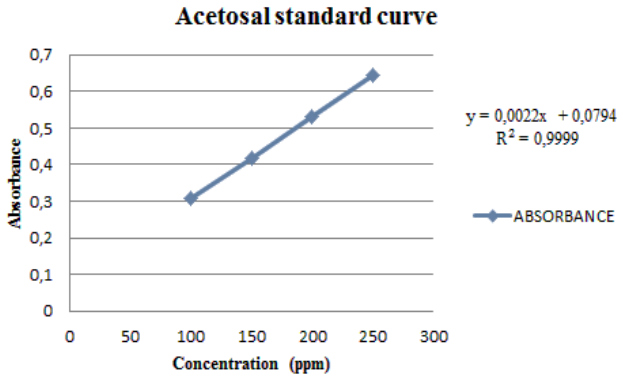

Figure 1. Acetosal standard curve

Solid dispersion production

The method used in manufacturing acetosal solid dispersions: PVP K-30, in this study, is the dissolution method. This is due to the nature of the active acetosal material, which is not resistant to high heating (Putra, 2011), so the dissolution method is suitable for manufacturing acetosal solid dispersions. The process of making acetosal solid dispersions in this study is included in classifying eutectic mixtures by mixing two compounds that have been dissolved well in liquid form (Bhut et a., 2012).

The purpose of forming solid dispersions is to help increase the solubility and dissolution of drugs that are difficult to dissolve in water (Zahara et al., 2020), as well as from comparisons to obtain the optimal combination that can increase the highest acetosal solubility. Solid dispersions were prepared by the dissolution method using 96% ethanol as a solvent because acetosal is soluble in ethanol (Depkes RI, 2020).

Acetosal of 1500 mg was dissolved in 30 ml of 96% ethanol until dissolved and clear, and 4500 mg of PVP K-30 was dissolved in 45 mL of 96% ethanol until dissolved and clear. After each material is dissolved and clear, slowly pour the PVP K-30 solution into the acetal solution while stirring until homogeneous. The mixture is then evaporated and dried in an oven at 40-50 °C until dry. The purpose of the oven is to remove the solvent, and the choice of temperature is also very influential because it will affect the quality of the particles produced in solid dispersions (Das et al., 2013).

The formed precipitate is scraped, crushed, and sieved to obtain smaller particles to obtain a solid dispersion powder (Noval & Rosyifa, 2021). The obtained powder was stored in a desiccator for 24 hours. The purpose of storage in a desiccator is to maximize the solvent evaporation process and as a place for cooling after leaving the oven (Engelen et al., 2018).

Solid dispersion evaluation

Moisture content test

Assessment of water content aims to determine the water content of solid dispersion powders, which can interfere with effectiveness because they can affect microbial growth and formulation stability (Ameliana et al., 2018). A water content test was carried out to ensure the quality of the resulting powder (Usman et al., 2020). Acetal solid dispersion: The results of measuring the water content in PVP K-30 are shown in Table 3.

The highest percentage of water content is in the 1:5 Formula. This follows the literature (Noval &

Rosyifa, 2021). The high rate of water content in the 1:5 Formula The high water content in the 1:5 formula is said to be due to the highest concentration of PVP K-30. PVP K-30 is a material with a hydrophilic polymer composition that can absorb ambient moisture, so the more significant the attention added to PVP K-30, the greater the ability to absorb moisture from the surrounding environment, increasing the percentage of water content (Arifin et al., 2019); Noval & Rosyifa, 2021).

Table 3. Water content determination

Formula	Initial mass (g)	Final mass (g)	%
1:1	1.074	1.069	0.35
1:3	1.001	0.986	0.75
1:5	1	0.993	0.97

The water content values obtained from 3 Acetosal solid dispersion formulas: PVP K-30 did not meet the water content requirements with the resulting range of 0.3-0.9%. Based on the journal states that the percentage of good water content is in the field of 2-5% (Devi et al., 2018; Noval & Rosyifa, 2021). This could be due to the powder taking too long the drying time, lower water content, reduced flow time and angle of repose, better weight uniformity, and reduced brittleness (Kusumawati, 2012).

Solid dispersion dissolution test

Dissolution tests were carried out for each acetal solid dispersion powder formulation: PVP K-30 with acetate buffer pH 4.5±0.05 at 50 rpm for 30 minutes. Measure the absorbance of the solution at a wavelength of 277 nm using a spectrophotometer. The results of the percentage of dissolved solid dispersions are shown in Table 4.

Table 4. Percentage of dissolution of solid dispersion powders

Time (minute)	% Formula		
	1:1	1:3	1:5
5	5.85±0.09	13.51±0.59	17.71±0.60
10	8.92±0.03	18.05±0.75	21.97±0.31
15	11.64±0.30	22.47±0.48	25.16±0.40
30	18.34±0.14	24.85±0.21	28.19±0.63
45	24.97±0.55	29.66±0.87	32.20±0.16

The results of the dissolution of each formula showed an increase in the percent dissolution in each formula, and the highest dissolution value was in Formula 1:5 minutes to 45 of 32.22 ± 0.16%. This result shows that in the solid dispersion system, there is an increase in the dissolution rate (Umar et al., 2014). These results follow the literature, which states that the greater the PVP K-30 concentrations added to the active substance, the higher the dissolution rate produced (Noval & Rosyifa, 2021; Zaini et al., 2017).

The requirement for determining the dissolution test is that no less than 80% of the substance is dissolved within 30 minutes (Ministry of Health RI, 2020). The study results in Table 4 show that the highest percentage of dissolution does not meet the requirements. The low percentage can be caused by several factors, namely, in the process of making solid dispersions between the active substances acetosal and PVP K-30, they are not mixed homogeneously (Noval & Rosyifa, 2021).

Dissolution test of acetosal solid dispersion powder: PVP K-30 statistically, the one-way anova test showed a significant difference in the dissolution rate due to the addition of PVP K-30 in the formula for making solid dispersion systems of 0.044 ($p<0$, 05).

Mass production evaluation

Flow rate

Evaluation of the flow rate is intended to determine the nature of the flow of the printed mass seen from the flow of the printed mass falling from the funnel. The results of the flow test are shown in Table 5.

Table 5. Print mass flow rate

Formula	Flow rate average (g/s)	Category
1:1	6.27±0.14	Good
1:3	6.90±0.54	Good
1:5	8.80±1.84	Good

The print mass flow rate results from 3 Formulas fall into the good flow rate category. The data follows the literature, which states that a good flow rate is 4-10 g/s and challenging if it is 1.6-4 seconds for 10 grams of powder (Warnida et al., 2012). Based on the One Way ANOVA statistical test, the print mass flow rate test showed a significant difference of 0.008 ($p <0.05$).

The 1:1 formula has the best flow rate of 6.27 ± 0.14 g/s. This is because the 1:1 formula has more advice PH 102 fillers than the 1:3 and 1:5 formulas. Avicel PH 102 has a large particle size and is easy to flow, so it can improve the flow properties of the printed mass (Sulaiman & Sulaiman, 2020).

Static angle

The angle of repose can be a determinant of powder flowability (Nawangsari, 2019), and the evaluation of the angle of repose aims to determine the flow characteristics of print quality as seen from the angle formed by all the powder that passes through it (Fudholi, 2013). The results of the angle of the repose test are shown in Table 6.

Table 6. Product mass static angle

Formula	Static angle average (°)	Category
1:1	29.95±1.30	Very good
1:3	24.7±0	Very good
1:5	26.56±0	Very good

The angle of repose of the 3 Formulas is in the very good category with a range of 25-30° (Fudholi, 2013). The angle of repose is proportional to the flow rate. The smaller or faster the flow time, the smaller the repose angle that is formed, which means that the cohesion quality of the print is getting smaller, and the fluidity is getting better. (Puspadina et al., 2021). Based on research data on the angle of repose, Formula 1: 3 has the smallest and best angles of repose. Statistical analysis using One Way Anova showed that the angle of repose test of the printed mass had a significant difference of 0.000 ($p < 0.05$).

Compressibility index

Compressibility testing aims to determine whether the properties of a material allow it to form a stable and solid mass under pressure (Akbar et al., 2019). The compressibility index is affected by density, particle size, and shape, and the lower the bulk density obtained, the better the flowability (Sirisha et al., 2012). The compressibility index results are shown in Table 7.

Table 7. Compressibility index

Formula	Compressibility index (%)	Category
1:1	10.78±1.06	Very good
1:3	8±2	Very good
1:5	7.99±2	Very good

The results of the compressibility index of the three formulas obtained a percentage of <10%, so it can be said that the test results are included in the very good compressibility index category (Arulkumaran & Padmapreetha, 2014). This also follows the literature stating that generally, a compressibility index value of 5-15% indicates excellent flow properties (Begum et al., 2019; Elmubarak et al., 2021).

Statistical analysis using One Way Anova showed no significant difference of 0.160 ($p>0.05$). I followed Duncan's follow-up test and obtained a substantial result of 0.109 ($P> 0.05$). Based on the research data, it can be said that increasing the concentration of PVP K-30 in the formula affects the compressibility index. The smaller the percentage, the better the compressibility index; from the data, it is known that which has the smallest percentage is Formula 1: 5 of 7.99 ± 2.

Hausner ratio

The Hausner ratio test was performed by comparing the tapping density (ρ tapped) with bulk density (ρ bulk). Print quality requirements can flow properly if the Hausner ratio is less than 1.25 (Nawangsari, 2019). The Hausner ratio results obtained are shown in Table 8.

Table 8. Hausner ratio

Formula	Hausner ratio (%)	Category
1: 1	1.11±0.01	Very good
1 : 3	1.08±0.23	Very good
1: 5	1,08±0,23	Very good

Result in Table 8. The formula is in the very good category (range 1.00 ± 1.11) (Arulkumaran & Padmapreetha, 2014). This follows the Hausner Ratio literature, which is lower than (<1.25), indicating a better flow rate (Begum et al., 2019). The greater the addition of PVP K-30 to the formula in this study, the smaller the % Hausner ratio; the smaller the Hausner ratio, the better (Arulkumaran & Padmapreetha, 2014; Sudi, 2016).

Research data obtained the smallest percentage in Formula 1:3 and 1:5. The Hausner ratio relationship is directly proportional to the compressibility index (Kuncoro et al., 2015). Statistical analysis using One Way Anova showed no significant difference of 0.179 ($p>0.05$). Followed by Duncan's follow-up test, a significance result of 0.121 ($p> 0.05$) was obtained.

Tablet physical properties test

Organoleptic test

Sensory or sensory assessment is a method of analyzing physical characteristics using the human senses to measure texture, appearance, aroma, or odor and is then accepted by consumers. A good vision tablet must have a uniform color and be free of impurities (Nugrahani et al., 2021).

Based on the results of testing the acetosal dispersion tablets, it was observed that the physical appearance of all the tablets produced was no capping, cracking, picking, or other characteristics indicating tablet damage (Purba et al., 2018).

Figure 2. Acetosal dispersion tablets

Mass uniformity test

Weight uniformity aims to determine formulation uniformity, ensuring that each tablet contains several drugs or active ingredients and that the dosage is precise and uniform (Syamsia et al., 2017). Suppose no more than two tablets weighing 300 mg deviate from the measured value in column A (5%) from the average weight, and no more than one tablet deviates from column B (10%). In that case, the tablets are said to be uniform to the average body weight Average (MOH RI, 1995). The results of the weight uniformity test are shown in Table 9.

Table 9. Mass uniformity test

Formula	Mass (mg)
1: 1	509.06±1.23
1: 3	509.31±1.13
1: 5	510.91±1.50

The results of the weight uniformity test follow the literature because there are no tablets in column A test (5%) that deviate from the average weight by more than two tablets, nor is there one tablet that deviates from the average weight in column B (10%) (MOH RI, 1995). This also follows the literature, which states that the weight uniformity is good; that is, no tablets come out of columns A and B (Imtihani et al., 2021). Based on the One Way Anova statistical test, there was no significant difference in weight uniformity of 0.208 ($p>0.05$). Duncan's follow-up test was conducted to obtain significant results of 0.114 ($p>0.05$).

Size uniformity test

Size uniformity ensures that the tablets are of uniform thickness and diameter. Tablet size and shape can be assessed and controlled by measuring tablet size. The dimension that affects the process is the thickness (Syukri, 2018; Iskandar, 2019). The results of the dimensional uniformity test are shown in Table 10.

The size uniformity test based on table 10 follows the literature, which states that the requirements for a good tablet size uniformity test are that the diameter is not more than three times the thickness of the tablet and not less than 4/3 of the tablet thickness (MOH RI, 1979). It is also appropriate in the literature that good size uniformity must meet the requirements, namely $4/3T < D < 3T$. T is the thickness of the tablet, and D is the diameter of the tablet (Imtihani et al., 2021). The One Way Anova statistical test shows a significant difference in size uniformity of 0.002 ($p <0.05$).

Table 10. Size uniformity test

Formula	Diameter (cm)	Thickness (cm)
1:1	1.30±2.34	0.462±0.012
1:3	1.30±2.34	0.469±0.010
1:5	1.30±2.34	0.444±0.007

Friability test

Friability is a parameter used to measure a tablet surface's resistance to friction. The principle of friability testing is to determine the weight loss of several tablets after being rotated in the fritter for a certain period (Gopalan & Gozali, 2018). Friability testing relates to weight loss due to tablet surface abrasion (Benni & Susanti, 2019). The results of the dimensional uniformity test are shown in Table 11.

Table 11. Friability test

Formula	%
1:1	1.25±0.73
1:3	0.19±0.19
1:5	0.14±0.10

The results showed that the friability test of Formula 1: 1 lost more than 1% of the initial weight of the tablet. This indicates that the results do not follow the literature, which states that a good tablet must have a friability of <1% (Depkes RI, 1979). According to USP, a tablet friability value of <1% is considered acceptable for most pharmaceutical tablets (Elmubarak et al., 2021). High friability affects the concentration or content of the active substance contained in the tablet, and the greater the percentage of friability, the greater the mass loss of the tablet (Gopalan & Gozali, 2018).

The friability of tablets is affected by the powder size of each ingredient and the number of refined grains (Voight et al., 1995). The higher the number of fine granules, the tablet is more brittle (Apriani &

Arisanti, 2016). Based on the One Way Anova statistical test, there was a significant difference in the tablet friability of 0.038 ($p<0.05$).

The friability test of dispersion tablets found that increasing the concentration of PVP K-30 could reduce the value of tablet friability; the smaller the % tablet friability value, the better (Wijayanti et al., 2015). Based on research data, Formula 1: 5 has the smallest fragility value, so it can be said that Formula 1:5 has the best friability test compared to Formula 1:1.

Tablet hardness test

Tablet hardness is one of the important requirements for tablets. Factors that affect tablet hardness are compression pressure and the nature of the material being compressed (Banne et al., 2020). Tablet hardness is also affected by particle size and the presence of refined grains (Apriani & Arisanti, 2016). The results of the hardness test are shown in Table 12.

Table 12. Hardness test

Formula	Hardness (kg)
1:1	4.23±0.15
1:3	5.9±0.1
1:5	6.33±0.23

The requirement for a good tablet is to have a hardness between 4-10 kg (Depkes RI, 1979). Based on the data in Table 11, it is known that tablets from 3 Formulas meet the requirements for good tablet hardness, which has a range of 4-8 kg. This also follows the literature, which states that the tablet hardness requirement is 4-8kg (Imtihani et al., 2021). Based on the One Way Anova statistical test, it shows that there is a significant difference in the violence of 0.000 ($p <0.05$). Based on hardness test research data, it was found that increasing the concentration of PVP K-30 in the formula could affect tablet hardness. The more significant the increase in the concentration of PVP K-30, the harder the resulting tablet.

Time trial destroyed

The disintegration time test determines the time it takes for the tablet to disintegrate in the body so that the active substance is absorbed in the digestive tract until it dissolves. The active substance reaches the target cell (Rahmat et al., 2019). The results of the disintegration time test are shown in Table 13.

Based on the data in Table 13, it is known that the higher the ratio of the acetosal solid dispersion formula: PVP K-30, the greater the amount of PVP K-30 contained therein. One of the other functions of PVP K-30, apart from being a polymer, is as a binder (Sheskey et al., 2017).

Table 13. Time trial destroyed

Formula	Time (minute)
1:1	3.75±1.37
1:3	16.98±1.33
1:5	19.5±0.50

The One Way Anova statistical test showed a significant difference in the disintegration time of 0.000 ($p<0.05$). Based on the results of the research data, it is known that increasing the concentration of PVP K-30 in the formula affects the disintegration time test. The higher the concentration of PVP K-30, the longer the disintegration time will allow the tablet to dissolve for a long time, and from research data which has the best disintegration time is Formula 1:1.

Disintegration time in the 1:1 formula is the best because the 1:1 formula contains more advice PH 102 fillers compared to the 1:3 and 1:5 Formulas. Adding more Avicel PH 102 will affect pressure compaction, increasing water penetration into the tablet and speeding up the disintegration time of the tablet (Thorens et al., 2014).

Dissolution test

The dissolution test aims to determine how much active substance is dissolved and has a therapeutic effect on the body (Sari, 2018). The results of the dissolution percentage of acetosal solid dispersion tablets can be seen in table 14. The graph of the percentage of dissolution of dispersion tablets can be seen in Figure 3.

Based on the results of tablet dissolution testing of 3 acetosal solid dispersion formulas: PVP K-30, the percentage results for each formula have increased. This result indicates that increasing variations in the concentration of PVP K-30 in tablet preparations made with the dispersion system can increase the solubility of the active substance.

Table 14. Tablet dissolution dispersion percentage

Time (minute)	% Formula		
	1: 1	1: 3	1: 5
5	36.15±0.16	39.46±1.40	60.76±1.07
10	39.08±1.13	46.14±0.70	64.93±3.22
15	47.12±0.86	49.97±2.58	82.16±1.34
30	51.32±3.06	83.68±1.24	116.16±3.61
45	61.71±0.86	98.55±1.89	143.53±1.45

The results in Table 14 follow the literature, which states that the requirement for determining the dissolution test for acetosal tablets is that the substance dissolves at less than 80% within 30 minutes (MOH RI, 2020). The low percentage of Formula 1: 1 is because it contains a smaller ratio of PVP K-30 compared to Formula 1: 3 and 1: 5. Based on the literature, it is stated that the addition of PVP K-30 given shows an increase in the percentage of dissolved substances (Noval & Rosyifa, 2021).

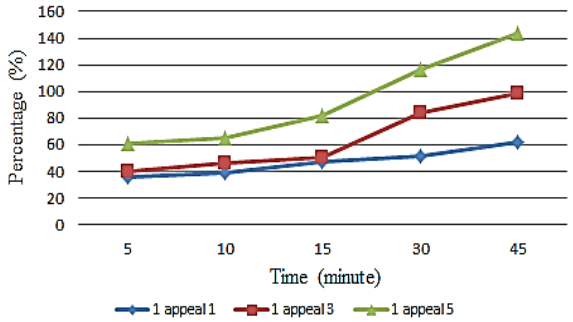

Figure 3. Tablet dissolution percentage graph

One way Anova statistical test showed the dissolution test of acetosal solid dispersion tablets: PVP K-30 obtained a significant value of 0.116 ($p>0.05$). Then continued with the Duncan test got effective results of 0.050 ($p<0.05$), which indicated that the dispersion system solid with the addition of PVP K-30 in the formula affected the dissolution rate ($p<0.05$). The increase in the dissolution percentage of acetosal solid dispersion tablets compared to solid dispersion powders was due to the assistance of other tablet-forming components, one of which was a filler. The filler material used in this study was Avicel PH 102. Avicel is a tablet filler that is very compressible and can function as a disintegrant in a dry state (Sung et al., 2012).

Avicel also has a high degree of porosity and is hydrophilic. It encourages the swelling and disintegration of tablets by contributing to water penetration into the tablet and then destroying hydrogen bonds (Thoorens et al., 2014). Destruction of hydrogen bonds occurs when Avicel PH 102 comes in contact with liquid. Then the fluid will break the hydrogen bonds that bind Avicel PH 102 particles, thereby contributing to increased absorption (Aisiyah et al., 2019).

Based on the evaluation of acetosal dispersion tablets using the direct compression method, overall, the higher the addition of PVP K-30 affects the slow disintegration time and decreases the friability value. This result contrasts the study of atorvastatin potassium solid dispersion tablets with the addition of PVP K-30, which increases the disintegration time and reduces the friability value (Gozali et al., 2015).

CONCLUSION

The dissolution test of acetosal solid dispersion powder: PVP within 30 minutes showed that Formula 1:5 had the highest dissolution percentage of 28.75% compared to Formula 1:1 of 18.34% and 1:3 of 24.85%.. The dissolution test of solid dispersion powders did not meet the Pharmacopoeial standard criteria, based on the results obtained at 30 minutes, the comparison of acetosal dispersion with PVP K-30, which had the highest dissolution rate, Formula 1:5. Based on the research results of testing the physical properties of tablets made in the dispersion system, it was found that the higher the addition of PVP K-30. The slower the disintegration time and lowered the friability value. Therefore the tablets in each formula did not meet the requirements yet.

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