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Aspirin Orally Disintegrating Tablet (ODT) Formulation With Sodium Starch Glycolate As Superdisintegrant

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ABSTRACT

Orally disintegrating tablets (ODT) are an alternative antiplatelet drug in the treatment of stroke which disintegrate quickly in less than 60 seconds.The research aimed to determine the effect the concentration of the sodium starch glycolate disintegrating agent on the physical properties and solubility of the aspirin (ODT) formulation and to determine the concentration of the sodium disintegrating agent glycolic starch. Aspirin ODT tablets are produced with sodium starch glycolate concentrations of 0%,10%,15% and 20%. Evaluation of ODT tablets includes weight uniformity, size uniformity, hardness, friability, tablet dissolution time and stability tests. Data were analyzed using one-way ANOVA. Results show the physical properties of tablets F1, F2, F3 and F4 including the tablet mass uniformity test showing ANOVA results (0.000), namely the test for uniformity of sizes between different diameters, the results (0.056) are no different in thickness. The difference is 0.086, the hardness test result is 0.000 so there is a difference, the friability test result is 0.125 there is a difference, and the solubility test result is 0.03 indicating there is a difference. The dissolution test produces F1(10.1%), F2(10.06%),F3(9.12%)and F4(9.3%). In the chemical stability test of the dissolution test,the dissolution percentage results experienced changes in stability on day 14, F1 (9.3%),F2(5.8%), 3 (12.6%), F4 (12.6%), stability 28 days F1(10.6%, F2(8.88%), F3(8.9%), F4(8.9%). Regarding physical stability, testing tablet weight uniformity, size uniformity, tablet hardness, friability tablets and the stability of the tablet dissolution time were obtained because the stability tests of 0.14 and 28 gave the same results.

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INTRODUCTION

According to WHO (Word Health Organization), stroke is a symptom of functional brain disorders that occurs suddenly with focal or global clinical signs and symptoms that can cause death within 24 hours or more (Permatasari, 2020). Stroke is also associated with significant economic problems that result in unbalanced intake and impact on imbalances in the health care system.

Based on 2018 Riskesdas data, the prevalence of stroke in Indonesia is 12.1 per 1,000 population, this figure is an increase compared to Riskesdas in 2013, which was 8.3%. The death rate due to stroke within 5 years, more than half of stroke patients aged > 45 years died (Nurhikmah et al., 2021). One of the therapies used for stroke patients is antiplatelet. Antiplatelets are drugs that are widely used to prevent platelet activation and aggregation, inhibiting the formation of arterial thrombus which can contribute to the development of myocardial infarction and stroke (Octariani et al., 2021). The use of antiplatelets is important for acute ischemic stroke, this therapy can reduce the incidence of recurrent stroke from 68% to 24% (Lukas and Pravita, 2020). Aspirin belongs to the Biopharmaceutical Classification System (BCS) class II (low solubility, high permeability) group (Indra et al., 2019). Orally Disintegrating Tablets (ODT) are preparations that disintegrate more quickly, with a disintegration time of less than 60 seconds when placed in the mouth and do not require additional water to swallow (Sa'adah, 2015). ODT preparations can disintegrate quickly in the oral cavity so that the drug can be absorbed through the oral cavity, pharynx and esophagus when saliva moves towards the digestive tract (Fu et al., 2004).

One of the super disintegrants that can be used in the formulation of ODT preparations is sodium starch glycolate (Hahm et al, 2008 in Karina., 2017). SSG is a super disintegrant which has an important role in increasing dissolution. SSG has swelling properties in the dissolution medium so that it can increase the porosity and wettability of the drug (Jones, 2008). In Indonesia, there are currently no ODT aspirin tablets available on the market. For this reason, aspirin is made in ODT preparations because it is to increase stroke patient compliance in taking the drug because it is difficult to swallow and to maintain therapeutic levels of the drug in the blood over an accelerated period of time. Based on this background description, it is necessary to research ODT aspirin preparations with SSG super disintegrant to see the drug dissolution profile.

METHOD

This research method is laboratory experimental research which includes testing the physical properties of tablets including weight uniformity, size uniformity, hardness, friability, tablet dissolution time and stability tests. The tools and materials needed are as follows:

1. Tools and Material
   a. Tools
      The tools used in this research are: analytical balance (Fulgid®), Erlenmeyer (Pyrex®), stopper, measuring flask (Pyrex®), printing machine (single-turn perforation), disintegration test, flow property tester, hardness tester, fragility tester, and dissolution UV-VIS spectrophotometer (BEL®).
   b. Material
      The ingredients used in this research were: aspirin, Sodium Glycolate, Apartam, Magnesium Stearate (Bratachem), Aerosil (Bratachem), Talc (Bratachem), Peppermint, Avicel PH 102, Mannitol (Merck), Disodium Phosphate (Na2HPO4), Potassium Thiocyanate (KSCN), sodium chloride (NaCl), monopotassium phosphate (KH2PO4), sodium bicarbonate (NaHCO3), potassium chloride (KCL), sodium acetate trihydrate P, acetic acid trihydrate P, ethanol 95%, and Aquadest.

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2. Tablets Manufacturing
The aspirin tablet production process is carried out using the direct pressing method. All ingredients are mixed separately, including aspirin, SSG, and aspartame, in a drum mixer for ± 3 minutes. Then add Avicel PH 102, Aerosil, Mint Flavor, and Mannitol, and stir for ± 3 minutes until the ingredients are evenly mixed. Mg, stearate, and talc are then added. These ingredients are stirred until homogeneous, ± 10 minutes. After this stage, an evaluation is carried out, which includes flow time, angle of repose, water content, and a compressibility test.

Table 1 Orally Disintegrating Tablet (ODT) dosage formula.

	Interval	F1 %	F2%	F3%	F4%	Utility
Aspirin (50mg)	75 mg-150 mg per hari	16,67	16,67	16,67	16,67	Active substance
Sodium starch glycolate	10% - 20%	-	10	15	20	Destroyer
Aspartam	0,5% - 0,75%	0,5	0,5	0,5	0,5	Sweetener
Mg stearat	0,25% - 5,0%	1,5	1,5	1,5	1,5	Lubricant
Aerosil	0% - 30%	0,5	0,5	0,5	0,5	Lubricant
Talk	1% - 10%	1	1	1	1	Lubricant
Mint flavour	0,05% - 10%	1	1	1	1	Taste
Avicel PH 102	20% - 90%	45	45	45	45	Fastening
Manitol	10% - 90%	33,38	23,83	18,83	13,83	Flavouring dan Filling
Tablet Weight (mg)		300	300	300	300	

3. Evaluation of physical properties
Flow time, Angle of repose, Moisture content and Compressibility tests are used to assess the physical characteristics of the mold mass. Closed test equipment is used to accommodate a mold mass weighing 25 grams after being weighed for the flow time test. After the funnel lid is opened, the printed mass flow time is recorded. (Appriliani & Oktaviannoor, 2021). Less than 10 seconds per 100 grams is considered a good

flow rate. The height and diameter of the flow time test results are then measured to determine the angle of repose. A break angle between 25-30º shows excellent results and easy flow (Aulton and Taylor, 2018). Water content is determined by weighing 100 grams of printed mass and placing it in an oven at 1050 for 15 minutes (Susanthi et al., 2010). Compressibility is determined using beat density by weighing 25 grams of mold mass and placing it in a 100 mL measuring cup after which 300 beats are made (Susanthi et al., 2010).

4. Evaluation of the physical properties of the tablet

   To ensure uniformity of weight, each tablet was carefully weighed and the average weight was determined. Tablet weight uniformity meets the requirements if the average tablet weight is 151 mg - 300 mg. The deviation in weight when weighed one by one must not be more than 2 tablets which deviate more than 7.5% and there is no single tablet whose weight deviates more than 15% from the average weight. the average (Ministry of Health of the Republic of Indonesia, 2013).

   Test size uniformity by measuring the thickness and diameter of the tablet. The diameter of each tablet is measured using a caliper, the diameter of the tablet is not more than 3 times and not less than 1 1/3 the thickness of the tablet (Sharimina and Dolih, 2018).

   Hardness test is used to test tablet hardness. The hardness test was carried out by taking 10 tablets from the existing sample. Each tablet was then tested for hardness using a Hardness Tester and the average value ± SD was calculated (USP, 2009). The friability test is carried out to determine the tablet's resistance to mechanical stress due to shock and abrasion during the packaging and transportation process. The test was carried out by cleaning twenty tablets and then weighing them before being put into the friability test equipment. The tool is then operated for four minutes or one hundred times to complete the test. The fragility value is expressed as the percentage of weight lost, which cannot be more than 1% (Hyunh-Ba, 2008).

   The solubility time test is the amount of time needed for a tablet of a certain size to completely dissolve in a certain volume of saliva. The requirement for a good dissolution time is <5 minutes (Noval et al., 2021). The aim is to provide a guarantee that the tablet is capable of dissolving in a certain quantity and speed (Trio, 2016).

   Dissolution test by making a series of solutions and determining the maximum wavelength. Series solutions were made with concentrations of 50, 60, 70, 80 and 90 ppm. The dissolution test is the process of dissolving the medicinal substance in the preparation into the medium. Aspirin tablet dissolution test using a type 1 (Basket) apparatus with a dissolution medium of 500 ml of 0.05 M acetate buffer, which was made by mixing 2.99 g of sodium acetate trihydrate P and 1.66 ml of glacial acetic acid P with water to 1000 ml and pH 4.50 ± 0.05. The dissolution media is put into a container, the device is installed, and the dissolution media is allowed to reach a temperature of 370 ± 0.50. Insert 1 tablet into the tool, remove air bubbles from the surface of the test preparation and immediately run the tool at a speed of 50 rpm for 30 minutes. Samples were taken in the area midway between the surface of the dissolution media and the top of the rotating basket. At 5, 10, 15, and 30 minutes, the absorption was measured using a UV-vis spectrophotometer at a wavelength of 268 nm. Every time a 5.0 ml sample is taken, it is replaced with 5.0 ml of acetate buffer solution. Samples obtained from dissolution testing results at 5, 10, 15 and 30 minutes were then measured at a wavelength of 268 nm.

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The levels obtained were calculated using linear regression equations and standard curves. The requirement for determining this dissolution test is that the value of the active substance dissolved is not less than 80% within 30 minutes (Ministry of Health of the Republic of Indonesia, 2020).

The tablet stability test was carried out for 4 weeks. Tests were carried out on days 0, 14 and 28 to determine the stability of the tablets during storage and at a temperature of 40 ± 2oC. The stability test of asirin ODT with sodium starch glycolate was carried out chemically and physically (Bhagya, 2018). Physical stability tests are carried out using organoleptic tests (color, shape and odor) (Jayanthi, 2020). In addition, tablet weight uniformity tests, tablet friability tests, tablet hardness tests and solubility time tests were carried out.

5. Analysis

The data analysis used is One-way ANOVA analysis. One-way ANOVA analysis was carried out to determine whether the resulting responses were significant between formulas. The test criteria are based on significance, namely if <0.05 then it can be said that there is a significant difference in the formula used (Priyatno, 2013).

RESULT

1. Results and Discussio

2.1 Evaluation of Aspirin Imprint Mass

The goal of flow time testing is to achieve flow consistency and thereby ensure that each tablet has the same or nearly the same powder mass. (Auton and Taylor, 2018). From the flow time test, it was obtained 4.95 ± 0.51 gram/s, 5.03 ± 0.12 gram/s, 5.57 ± 0.04 gram/s, and 5.77 ± 0 for F1, F2, F3, and F4, 08. Based on the literature, the test results are in the good category, namely, the flow rate is in the good range of 4–10 grams per second (Lachman et al., 2008). The purpose of the angle of repose test is to determine the flow time. The angle of repose is a property of internal friction and particle cohesion, so it can describe the flow rate (Auton and Taylor, 2018). The backrest angle test results obtained for F1, F2, F3, and F4 were 28.36 ± 0.45º, 27.28 ± 1.19º, 28.5 ± 0.92º, and 26.41 ± 0.70. Test results show that the printed mass has a very good angle of repose, namely between 25 and 30º (Auton and Taylor, 2018).

Table 2. Results of printing mass evaluation

Uji	F1	F2	F3	F4	p-value
Waktu Alir (gram/s)	4,95 ± 0,52	5,03 ± 0,12	5,57 ± 0,04	5,77 ± 0,08	0,013
Sudut Diam (°)	28,36 ±	27,28 ± 1,19	28,5 ± 0,91	26,41 ±	0,053
Kadar Lembab (%)	0,45	3,72%	3,23%	0,70	
Kompresibilitas (%)	3,88%	14,66±1,52	13,00±2,00	3,58%	0,802
	14,00±2,64			13,33±2,51	

The weight of the powder is put into a 100 ml measuring cup. Volume changes after determination are expressed in percentage units (Hadisoewignyo and Fudholi, 2013). The compressibility test results show that F1, F2, F3, and F4 are 14.00 ± 2.64, 14.66 ± 1.52, 13.00 ± 2.00, and 13.33 ± 2.51, respectively. Based on the one way ANOVA test, the p-value and significance were obtained (0.802); 0.05, indicating that changes in the concentration of sodium starch glycolate in the ODT aspirin tablet formulation did not have a significant difference in compressibility.

2.2 Evaluation of Physical Properties.

Dosage consistency can be checked with a weight consistency test (Auton and Taylor, 2018). The mass uniformity results for F1, F2, F3, and F4 were 202.93 ± 2.25 mg, 205.18 ± 2.82 mg, 205.98 ± 2.38 mg, and 205.55 ± 2.00 mg. All formulas are free of deviations and meet the requirements of the 151-300 mg tablet weight uniformity test, namely 7.5% (Column A) and 15% (Column B).

Table 3 Results of weight uniformity test

Formula	Bobot (mg)	p-value
1	202,93±2,25	0,000
2	205,18±2,82	
3	205,98±2,38	
4	205,55±2,00	

A tablet uniformity test is carried out to ensure tablet uniformity. The size uniformity test results obtained for formulas 1, 2 and 3 meet the size uniformity requirements. Tablets are considered to meet size uniformity if the diameter of the tablet is at most three times the diameter of the tablet and at least 4/3 of the thickness of the tablet (Ministry of Health of the Republic of Indonesia, 1979). Tablet thickness is influenced by the diameter of the mold, the amount of filler that enters the mold, the compressible nature of the filler and also the pressure exerted during compression (Allen, 2015).

Table 4 Tablet size uniformity test results

Formula	Diameter	Tebal	p-value
1	0,819±0,0030	0,433±0,0326	d: 0,056
2	0,816±0,0048	0,414±0,009	t: 0,086
3	0,823±0,0080	0,413±0,004	
4	0,819±0,0022	0,477±0,029	

The test results show that the hardness increases with increasing content of SSG F1, F2, F3 and F4 viz. 4.56 ± 0.5 kg, 4.63 ± 0.47 kg, 5.56 ± 0.51 kg and 5.56 ±

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0.5 kg. All formulas have good hardness values because the strength required is at least 4 kg (Allen, 2015). The purpose of the hardness test is to determine the tablet's strength against damage and erosion (Auton and Taylor, 2018). The sensitivity test results for F1, F2, F3 and F4 were 4.56 ± 0.5 kg, 4.63 ± 0.47 kg, 5.56 ± 0.51 kg and 5.56 ± 0.5 kg.

Table 5. Tablet Hardness

Formula	Kekerasan (kg)	p-value
1	4,56±0,5	0,000
2	4,63±0,47	
3	5,56±0,51	
4	5,56±0,5	

The test results show that there are real differences in the hardness parameters and dissolution time. This is because SSG has high porosity, resulting in high hardness and longer dissolution time (Putri et al., 2019). In order for the drug to be absorbed, the tablet must disintegrate and release the drug until it dissolves (Allen, 2015).

The results of the artificial saliva tests F1, F2, F3 and F4 were 39.66 seconds, 44.66 seconds, 64.66 seconds and 71.66 seconds respectively. All formulations have good dissolution time values so that they do not require an ODT dissolution time of more than 3 minutes. artificial saliva in a watch glass (European Council, 2020). The dissolution time parameters have significant differences compared to the experimental results. This is because the higher the SSG content, the slower the tablet disintegration time (Putri et al., 2019). The dissolution test begins with determining the maximum wavelength which is carried out with a solution with a concentration of 50 ppm. Aspirin has a maximum wavelength of 268 nm. Serial solutions of 50, 60, 70, 80, and 90 ppm were then read at a maximum wavelength of 268 nm, resulting in absorbances of 0.274, 0.315, 0.341, 0.405, and 0.427, respectively. The resulting equation is y = 0.0396 (x) + 0.0752 and the value of r = 0.9897.

DISCUSSION

1. Evaluation of Aspirin Imprint Mass

The goal of flow time testing is to achieve flow consistency and thereby ensure that each tablet has the same or nearly the same powder mass. (Auton and Taylor, 2018). From the flow time test, it was obtained 4.95 ± 0.51 gram/s, 5.03 ± 0.12 gram/s, 5.57 ± 0.04 gram/s, and 5.77 ± 0 for F1, F2, F3, and F4, 08. Based on the literature, the test results are in the good category, namely, the flow rate is in the good range of 4–10 grams per second (Lachman et al., 2008).

Based on Table 2. Show that The weight of the powder is put into a 100-ml measuring cup. Volume changes after determination are expressed in percentage units

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A tablet uniformity test is carried out to ensure tablet uniformity. The size uniformity test results obtained for formulas 1, 2, and 3 meet the size uniformity requirements. Tablets are considered to meet size uniformity if the diameter of the tablet is at most three times the diameter of the tablet and at least 4/3 of the thickness of the tablet (Ministry of Health of the Republic of Indonesia, 1979). Tablet thickness is influenced by the diameter of the mold, the amount of filler that enters the mold, the compressible nature of the filler, and also the pressure exerted during compression (Allen, 2015).

The test results show that the hardness increases with increasing content of SSG F1, F2, F3, and F4, viz., 4.56 ± 0.5 kg, 4.63 ± 0.47 kg, 5.56 ± 0.51 kg, and 5.56 ± 0.5 kg. All formulas have good hardness values because the strength required is at least 4 kg (Allen, 2015). The purpose of the hardness test is to determine the tablet's strength against damage and erosion (Auton and Taylor, 2018). The sensitivity test results for F1, F2, F3, and F4 were 4.56 ± 0.5 kg, 4.63 ± 0.47 kg, 5.56 ± 0.51 kg, and 5.56 ± 0.5 kg. The test results in Table 5 show that there are real differences in the hardness parameters and dissolution time. This is because SSG has high porosity, resulting in high hardness and a longer dissolution time (Putri et al., 2019). In order for the drug to be absorbed, the tablet must disintegrate and release the drug until it dissolves (Allen, 2015).

The results of the artificial saliva tests F1, F2, F3, and F4 were 39.66 seconds, 44.66 seconds, 64.66 seconds, and 71.66 seconds, respectively. All formulations have good dissolution time values, so they do not require an ODT dissolution time of more than 3 minutes. artificial saliva in a watch glass (European Council, 2020). The dissolution time parameters have significant differences compared to the experimental results. This is because the higher the SSG content, the slower the tablet disintegration time (Putri et al., 2019). The dissolution test begins with determining the maximum wavelength, which is carried out with a solution with a concentration of 50 ppm. Aspirin has a maximum wavelength of 268 nm. Serial solutions of 50, 60, 70, 80, and 90 ppm were then read at a maximum wavelength of 268 nm, resulting in absorbances of 0.274, 0.315, 0.341, 0.405, and 0.427, respectively. The resulting equation is $y = 0.0396 (x) + 0.0752$, with the value $r = 0.9897$.

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CONCLUSION

From the research results and data analysis, it can be concluded that:

1. In the test of the physical properties of F1, F2, F3 and F4 tablets including the tablet weight uniformity test, the ANOVA results obtained were 0.000, less than 0.05, namely there was a difference, the diameter result of the size uniformity test was 0.056, more than 0.05, namely there was no difference and the thickness results There is a difference of 0.086 more than 0.05, a hardness test result of 0.000 is less than 0.05, that is, there is a difference, a fragility test result of 0.125 is more than 0.05, there is a difference and a time-soluble test result of 0.03 is less than 0.05, that is, there is a difference.
2. In the dissolution test, the results obtained were F1 10.1%, F2 10.06%, F3 9.12% and F4 9.3%. The higher the concentration of sodium starch glycolate, the lower the dissolution rate.
3. Chemical stability testing, dissolution test, there was a change in dissolution percentage on the 14th day of stability, F1 9.3%, F2 5.8%, F3 12.6% and F4 12.6%, on the 28th day of stability, F1 10, 6%, F2 8.88%, F3 8.9% and 8.9%. The dissolution rate is influenced by the nature and characteristics of the dissolution medium, temperature, PH and stirring speed. In physical stability, the results obtained were uniformity of tablet weight, uniformity of size, tablet hardness, tablet friability and tablet dissolution time tests were stable, because in the 0th, 14th and 28th stability tests the same results were obtained.

RECOMMENDATION

Further research needs to be carried out on antiplatelet tests to determine the effect of the drug in preventing blood clots.

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