Synthesis of Ferrous Fumarate from Indonesian Iron Sand and In Vivo Body Weight Gain Test in Rats

Taufiq Indra Rukmana*, Felicia Natalia Kurniadi, Harmita
Faculty of Pharmacy, Universitas Indonesia, Depok, West Java, Indonesia

ABSTRACT
Iron deficiency anemia (IDA) is a health problem in Indonesia. Prevention and treatment of IDA is carried out by giving fortified foods and oral iron therapy. Both can use ferrous fumarate which is made with reacting bivalent iron and disodium fumarate. Bivalent iron can be obtained from iron sand in Indonesia. This study aims to synthesize ferrous fumarate from Indonesian iron sand, which is from Malang, Sukabumi, and Cianjur area, and to determine its absorption through in vivo body weight gain test in male Wistar white rats (Rattus norvegicus). First, ferrous fumarate was synthesized through reaction of ferrous sulfate, which was made from Indonesian iron sand with the highest iron content, which was from Sukabumi area, and disodium fumarate. Second, in vivo body weight gain test was conducted to 3 rat groups (negative control, ferrous sulfate group, and ferrous fumarate group, respectively) and monitored for two weeks. The results showed that ferrous fumarate was successfully obtained as brownish red-orange fine powder with yield of 62.17 ± 1.66 %. In addition, the in vivo body weight test suggested that the rats from ferrous fumarate group showed similar weight gain (35.1%) compared to those from the ferrous sulfate group (30.6%), indicating a possibility of iron absorption from ferrous fumarate.

Keywords: anemia; iron sand; ferrous fumarate; atomic absorption spectrophotometry; iron absorption

INTRODUCTION
Anemia is a global health problem, including in Indonesia (Suryani et al., 2015 and Rah et al., 2021). Anemia is mostly caused by iron deficiency (Suchdev et al., 2016; World Health Organization, 2015). According to an Indonesian report, Riset Kesehatan Dasar (Basic Health Research), conducted by Badan Penelitian dan Pengembangan Kesehatan (Health Research and Development Agency) (2018), there had been an increase in the proportion of anemia in pregnant women from 37.1% (2013) to 48.9% (2018). Adolescent girls who used iron tablet supplements were 76.2%, while those who did not use the supplements were only 23.8%. This is contradictory, considering that Indonesia has abundant natural resources, so it is expected that Indonesia can meet the needs of iron micronutrients.

The management of iron deficiency anemia is the administration of reduced iron ion or Fe²⁺ (ferrous) because Fe²⁺ is absorbed better than Fe³⁺ (ferric) (Dipiro et al., 2017). Iron is an essential mineral which is important in the formation of haemoglobin and myoglobin, which are protein component of red blood cells and muscles (Seriki et al., 2017 and Taşğın, 2017). Therapy is generally given orally because it is cheaper, safer, and has the same effectiveness as parenteral administration, except in a certain condition that parenteral administration is recommended (Fitriany and Saputra, 2018 and Özdemir, 2015). The adherence to consumption of Fe tablets have an effect on the incidence of anemia in pregnant women (Ernawati and Sety 2023; Salma, 2021; and Nurmasari and Sumarmi, 2019). Oral iron preparations are generally in the form of ferrous iron salts, such as ferrous sulfate, fumarate, and gluconate, all of which are absorbed equally well (Dipiro et al., 2017). Each ferrous iron salt contains a different percentage of the element iron, namely 20% for ferrous sulfate heptahydrate, 12% for ferrous gluconate, and the highest content is in ferrous fumarate which is as much as 33% (Dipiro et al., 2017). Ferrous fumarate has less toxic potential because ferrous fumarate causes fewer side effects due to its low solubility and slower dissolution after oral administration than ferrous sulphate (Crichton et al., 2008). In addition, ferrous fumarate is considered as the cost-effective preference to treat iron deficiency anemia (Panicker et al., 2016).

In addition to medication, the use of iron fortification in food is another method that can be utilized throughout the world in dealing with anemia due to iron deficiency (Uauy et al., 2002 and Wan et al., 2019). Priambudi et al (2017) suggested that the seasoning of instant noodles is
a good candidate for iron fortification. Food fortification is the intentional addition of one or more micronutrients to certain foods with the intention of increasing the intake of micronutrients (Shamah et al., 2008). Ferrous fumarate is one of the most bioavailable iron components in the fortified form (Shamah et al., 2008).

Ferrous fumarate can be used as an oral iron deficiency anemia medication and iron fortification in Indonesia. This research will utilize Indonesia’s natural resources to produce ferrous fumarate raw materials as an effort to increase domestic production of medicinal raw materials. The sources that will be used to make ferrous fumarate raw materials in this study are fumaric acid and bivalent iron (ferrous) derived from iron sand in Indonesia.

Iron sand is a deposit of sand containing iron particles (magnetite) and mostly can be found along the coast (Hilman et al., 2014). In general, the composition of iron sand is iron oxide (Fe₂O₃ and Fe₃O₄), silicon oxide (SiO₂), and other compounds with lower levels (Suroso, 2017). In Indonesia, iron sand is generally mined and used as a raw material, sold directly without processing, or only used for the cement and steel industries (Hilman et al., 2014). Therefore, iron sand has the potential to be processed into useful products in the health sector for the treatment of iron deficiency anemia.

This study aims to synthesize ferrous fumarate using Indonesian iron sand sources and to conduct in vivo body weight gain test in male Wistar white rats (Rattus norvegicus) to assess the absorption ability of ferrous fumarate which has been synthesized.

**METHODS**

**Instruments and Materials**

Various instruments and tools used in this study were the Shimadzu AA-6300 atomic absorption spectrophotometer equipped with a Hollow Cathode Lamp Fe (Japan); Shimadzu FTIR Infrared Spectrophotometer – 8400S (Japan); Memmert ovens (Germany); Shimadzu AP225WD analytical balance (Japan); OHAUS balance (United States); Branson ultrasonic homogenizer (United States); Hettich centrifuge (Germany); Socorex Acura 825 micropipette (100 – 1000 µL) (Switzerland); beaker glasses; Erlenmeyer; stir sticks; vaporizer cup; measuring cup; volumetric flask; crustang; filter paper; air gas, acetylene and nitrogen gas; tara bottle; centrifuge tubes; and rat pen.

Various materials used in this study were iron sand from 3 different regions, namely Malang, Sukabumi, and Cianjur, Indonesia; fumaric acid (PT Justus Sakti Raya, Indonesia and Merck, Germany); ferrous fumarate; 1 N Sodium hydroxide (Merck, Germany); aquadestilata; hydrochloric acid 37% (Merck, Germany); nitric acid 68% (Merck, Germany); potassium bromide P (Merck, Germany); iron standard (Merck, Germany); phosphate buffer; hydrochloric acid 0.1 N; male Wistar white rats (Rattus norvegicus); sawdust; rat feed Rat Bio (PT Citra Ina Feedmil, Indonesia); drinking water; ferrous fumarate samples; and FeSO₄ standard.

**Synthesis of FeCl₂–FeCl₃ from Iron Sand to Determine the Highest Iron Content**

Iron sand from 3 regions, namely Malang, Sukabumi, and Cianjur, each was weighed approximately 55 grams. Iron sand was put into a beaker glass and washed with distilled water 3 times. Iron sand that had been washed was put into an evaporating cup that had a fixed weight. Iron sand was heated in an oven at 120°C for 30 minutes. The iron sand was left to room temperature and then weighed with an analytical balance. The process was repeated until a stable weight achieved.

After a stable weight achieved, the iron sand was weighed as much as 10 grams, put into a beaker glass, then dissolved in 5 mL of 37% HCl and 15 mL of distilled water. The mixture was stirred with heating for 15 minutes. The formed FeCl₂–FeCl₃ solution was separated into the Erlenmeyer flask. The iron sand residue was dissolved with 2 mL of 37% HCl and 15 mL of distilled water, then stirred with heating again for 15 minutes. The formed FeCl₂–FeCl₃ solution was separated back into the same Erlenmeyer flask. The iron sand residue was rinsed with 5 mL of distilled water twice. The solution of FeCl₂–FeCl₃ was put to 50 mL volumetric flask, added with distilled water up to 50 mL, then homogenized. Determination of iron content from three FeCl₂–FeCl₃ solutions from three different regions was carried out using an atomic absorption spectrophotometer. The solution containing the highest amount of iron was chosen to make FeSO₄ and, in turn, ferrous fumarate.

**Synthesis of FeSO₄ from Iron Sand with the Highest Iron Content**

Iron sand from the region with the highest iron content was selected based on the results of the assay of FeCl₂–FeCl₃ above. FeSO₄ was prepared with dissolving 5 grams of iron sand, that had been washed and dried, in 50 mL of 6 M H₂SO₄. The dissolving process was carried out for 5 – 6 hours at a temperature of 112 – 115°C. After heating, the solution was cooled down to about 15°C. The solution was put in the refrigerator to produce a greenish-white FeSO₄ precipitate. The precipitate was separated with filtration and decantation, then dried at room temperature on filter paper. The process was adapted from Kapor et al., 2012. Determination of FeSO₄ levels was carried out using an atomic absorption spectrophotometer (AAS).
Synthesis of Ferrous Fumarate Complex from FeSO$_4$

Fumaric acid was dissolved in 1 N NaOH in an amount according to stoichiometric calculations at a molar ratio of 1:2. Fumaric acid was stirred until completely dissolved in the NaOH solution to produce disodium fumarate. The ferrous fumarate complex was prepared with mixing FeSO$_4$ into a solution of disodium fumarate in an amount according to stoichiometric calculations at a molar ratio of 1:1. The mixing process was put under N$_2$ gas so that the reaction was free of O$_2$ gas. The mixture was then heated while stirring at 90°C for 30 minutes. The mixture was allowed to stand until a brownish red precipitate was obtained.

The filtrate was separated from the precipitate with decantation. The precipitate was then rinsed with water and separated with centrifugation. Impurities from other salts that might be formed were removed with washing the residue of the precipitate with distilled water, centrifuging the precipitate again, and then taking the precipitate. The washing and centrifugation stages were carried out three times. The precipitate, that had been washed, was then dried at 105°C for 12 hours until a stable weight achieved. The process was adapted from Kapor et al., 2012. Determination of ferrous fumarate levels was carried out using an atomic absorption spectrophotometer.

Identification of Ferrous Fumarate and Loss on Drying

Identification test was carried out based on the Indonesian Pharmacopoeia VI (Farmakope Indonesia Edisi VI, published by Direktorat Jenderal Kefarmasian dan Alat Kesehatan, Kementerian Kesehatan Republik Indonesia, 2020). After going through the test reaction procedure on ferrous fumarate from the monography, there were dry precipitate and filtrate. The dry precipitate was used for the fumaric acid identification test with an infrared spectrophotometer. The sample spectra was compared to the reference fumaric acid spectra. The filtrate was used to identify iron based on general identification in the Indonesian Pharmacopoeia VI. The identification of iron used was identification using 1 N NaOH. The addition of 1 N NaOH to the filtrate caused the formation of a green precipitate which became brown or red-brown when shaken. In addition, for the loss on drying test, 1000 – 2000 mg of ferrous fumarate was dried at 105°C for 16 hours. The loss on drying requirement for ferrous fumarate was not more than 1.5%.

Assay of Ferrous Fumarate with Atomic Absorption Spectrophotometer

Iron standard solutions were prepared with concentrations of 5; 10; 15; 20; 30, and 50 ppm, respectively. The assay was carried out using an atomic absorption spectrophotometer. The relationship between the concentration of the solution as the x-axis and the absorption (A) obtained as the y-axis was plotted so that a linear regression equation y = a + bx and a coefficient correlation r were obtained. Ferrous fumarate sample of 50 mg was dissolved with 10 mL HNO$_3$ at 100°C, then put into a 50 mL volumetric flask. Aquadest was added up to the 50 mL limit. The ferrous fumarate sample solution was then diluted to a concentration of 80 ppm, containing about 26.3 ppm iron, which was proportional to the atomic weight of iron (55.8 g/mol) compared to the molecular weight of ferrous fumarate (169.9 g/mol). Then, the determination of the iron content of sample was carried out using the same atomic absorption spectrophotometer instrument.

In Vivo Body Weight Gain Test in Rats

Acclimatization of rats was carried out for 1 week. Rats were divided into 3 groups. The first group was given rat food only as the negative control group. The second group was given rat food containing 300 mg FeSO$_4$/kg of food as the comparator group. The third group was given rat food containing 300 mg ferrous fumarate/kg of food as the test group. The number of rats for each treatment group was 7. Rat food was given every day as much as 15 grams/rat in the first week. The amount of food per day was then increased to 20 grams/rat in the second week. The weighing data of rats measured was the initial weighing data (after acclimatization) and subsequent weighing every week for 2 weeks. The increase in weight was compared between the negative control group, the comparator group (FeSO$_4$), and the test group (ferrous fumarate). Quantitative data on the body weight increase of the rats were analyzed statistically using the one-way ANOVA test method with the post-hoc test with the smallest significant difference or the Kruskal-Wallis test which was determined by the normality test. Data were analyzed with SPSS statistical software. All data is shown as the mean ± standard deviation (SD). This test was carried out based on the research by Lawless et al (1994) and Kilic et al (2014).

RESULTS AND DISCUSSION

Synthesis of FeCl$_3$–FeCl$_2$ from Iron Sand to Determine the Highest Iron Content

Bivalent iron FeCl$_2$ was selected because HCl, as a material for the synthesis of FeCl$_3$, is more reactive than H$_2$SO$_4$ as a material for the synthesis of FeSO$_4$, so that in theory it can extract more iron than H$_2$SO$_4$ (Aliwarga et al., 2019). In determining the iron content in the FeCl$_3$–FeCl$_2$ solution, 1 mL of the solution was taken and dissolved in distilled water in a 100 mL volumetric flask. The solution was then used for the determination of iron content. Table 1 below shows the results of the determination of the FeCl$_3$ – FeCl$_2$ content of iron sand from 3 regions, namely Malang, Sukabumi and Cianjur.
Fe²⁺ still left in the solution, together with Fe³⁺, which does not form precipitates. The small amount of FeSO₄ precipitate formed could be due to a lack of water added in the process of FeSO₄ precipitate formation. It needs 7 water molecules to form a precipitate of FeSO₄ at a cooling temperature of around 15°C (Vidianti, 2014). The small amount of extracted iron could also be due to impurities that interfere with the formation of FeSO₄ precipitate, such as TiSO₄. In addition, different results may also occur due to differences in the conditions of the synthesis process, especially during the heating process of iron extraction. The characteristics of iron sand, composition, and impurities in iron sand could be factors that cause the differences in the results of iron extraction from iron sand with H₂SO₄ (Aliwarga et al., 2019).

### Synthesis of Ferrous Fumarate from FeSO₄

Ferrous fumarate was synthesized through reacting bivalent iron FeSO₄ with disodium fumarate solution. The chemical reaction between disodium fumarate and FeSO₄ to produce ferrous fumarate is shown below (Kapor et al., 2012).

\[
\text{Na}_2\text{CCH} = \text{CHCO}_2\text{Na} + \text{FeSO}_4 + \text{H}_2\text{O} \rightarrow \\
\text{Fe}^{2+}(\text{O}_2\text{CCH} = \text{CHCO}_2^-) + \text{Na}_2\text{SO}_4 + \text{H}_2\text{O}
\]

The bivalent iron FeSO₄ was selected because the substance was usually used in the manufacture of ferrous fumarate, as in the study by Kapor et al (2012). The ferrous fumarate precipitate, from the reaction of FeSO₄ with disodium fumarate, was then dried and weighed to calculate the yield. Table 3 shows the yield of ferrous fumarate. The synthesized ferrous fumarate is shown in Figure 1.
process, such as unstable heating temperature, less airtight atmosphere, even though it has been supplied with nitrogen, and less homogenized mixing. This might make the reaction process incomplete so the obtained results were less than expected. In addition, there could be unknown impurities from the extraction of FeSO$_4$ which could affect the reaction. One of the predicted impurities was excess acid content (H$_2$SO$_4$). Excess acid can be known by measuring the pH of dissolved FeSO$_4$ based on the Indonesian Pharmacopoeia VI (2020). H$_2$SO$_4$ which is acidic could dissolve some of the ferrous fumarate that had been formed or hinder the process of forming the ferrous fumarate by binding to NaOH which played a role in the reaction between fumaric acid and FeSO$_4$. Even in small amounts, the presence of H$_2$SO$_4$ may produce other contaminants, namely Fe$_2$(SO$_4$)$_3$ due to oxidation of FeSO$_4$ during storage (Herrly et al., 1922). However, FeSO$_4$ precipitate undergoes slow oxidation, even though it has been exposed to air, so that the amount of Fe$_2$(SO$_4$)$_3$ could be very small.

### Identification of Ferrous Fumarate and Loss on Drying

Identification test of ferrous fumarate, synthesized from FeSO$_4$ and disodium fumarate, was carried out based on the Indonesian Pharmacopoeia VI. The precipitate, obtained from the monograph procedure, was used for the fumaric acid identification test, while the filtrate was used for the iron identification test.

The precipitate, which should be fumaric acid, was then identified using an infrared spectrophotometer. Figure 2 below is a comparison of the infrared spectra of the sample fumaric acid with that of the reference fumaric acid.

#### Table 3. Yield of ferrous fumarate synthesized from FeSO$_4$ and disodium fumarate

<table>
<thead>
<tr>
<th>Results</th>
<th>Batch 1</th>
<th>Batch 2</th>
<th>Batch 3</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theoretical yield</td>
<td>98.83</td>
<td>98.83</td>
<td>98.83</td>
<td>98.83 ± 0.00</td>
</tr>
<tr>
<td>Obtained yield</td>
<td>61.09</td>
<td>64.08</td>
<td>61.34</td>
<td>62.17 ± 1.66</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Brownish red-orange fine powder</td>
<td>Brownish red-orange fine powder</td>
<td>Brownish red-orange fine powder</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 2. Comparison of the infrared spectra of the sample fumaric acid (blue), from ferrous fumarate sample, with that of the reference fumaric acid (black)
In the iron identification test, identification was carried out to determine the presence of iron. The result obtained was a red-brown precipitate, indicating the presence of iron in the solution, as shown in Figure 3. Based on the results, the identification of iron meets the requirements of the Indonesian Pharmacopoeia VI.

The loss on drying test was carried out on ferrofumarate, which had been identified according to the Indonesian Pharmacopoeia VI (2020). Loss on drying is the difference in the weight of the substance before and after drying, divided by the weight of the substance before drying, multiplied by one hundred percent. The requirement of the loss on drying shrinkage for ferrous fumarate based on the Indonesian Pharmacopoeia VI (2020) is no more than 1.5%. The ferrous fumarate sample meets the loss on drying requirement, as can be seen in Table 4.

**Assay of Ferrous Fumarate with Atomic Absorption Spectrophotometer**

The calibration curve equation obtained from iron standard solution is $y = 0.0159x + 0.1480$ with $r = 0.9956$. The sample solution had a concentration of 80 ppm ferrous fumarate, containing about 26.3 ppm iron. The iron content obtained from the samples is shown in Table 5. The average iron content obtained was 13.01 ppm from 80 ppm ferrous fumarate, or 16.26%. According to Dipiro et al (2017), the percentage of iron content in pure ferrous fumarate is 32.87%, which roughly corresponds to the ratio of the atomic weight of iron (55.8 g/mol) to the molecular weight of ferrous fumarate (169.9 g/mol). Therefore, the purity of the synthesized iron fumarate samples is about 49.47%.

One of the factors causing the low purity of ferrous fumarate samples could be the presence of foreign substances that interfere with the reaction process between FeSO$_4$ and disodium fumarate, such as sulfuric acid (H$_2$SO$_4$). Sulfuric acid could dissolve the ferrous fumarate precipitate back to the solution. Sulfuric acid might also inhibit the process of ferrous fumarate

### Table 4. The results of loss on drying test of ferrous fumarate sample

<table>
<thead>
<tr>
<th>No</th>
<th>Sample</th>
<th>Ferrous fumarate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Before drying</td>
<td>1.0935 g</td>
</tr>
<tr>
<td>2</td>
<td>After drying</td>
<td>1.0883 g</td>
</tr>
<tr>
<td>Difference</td>
<td></td>
<td>0.0052 g</td>
</tr>
<tr>
<td>Loss on drying</td>
<td></td>
<td>0.48%</td>
</tr>
</tbody>
</table>

### Table 5. Iron content of ferrous fumarate sample

<table>
<thead>
<tr>
<th>No</th>
<th>Iron Concentration (ppm)</th>
<th>Average (ppm)</th>
<th>Ferrous Fumarate Concentration (ppm)</th>
<th>Iron Content (%)</th>
<th>Average (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.07</td>
<td>13.01 ± 0.05</td>
<td>80.00</td>
<td>16.34</td>
<td>16.26 ± 0.07</td>
</tr>
<tr>
<td>2</td>
<td>13.00</td>
<td></td>
<td></td>
<td>16.25</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>12.97</td>
<td></td>
<td></td>
<td>16.21</td>
<td></td>
</tr>
</tbody>
</table>

### Table 6. Weight gain of control, FeSO$_4$, and ferrous fumarate group

<table>
<thead>
<tr>
<th>Group</th>
<th>Average Weight (g)</th>
<th>Average Weight Gain (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Week 1</td>
</tr>
<tr>
<td>Control</td>
<td>124.5 ± 11.0</td>
<td>142.3 ± 9.0</td>
</tr>
<tr>
<td>FeSO$_4$</td>
<td>125.2 ± 14.3</td>
<td>139.7 ± 12.4</td>
</tr>
<tr>
<td>Ferrous Fumarate</td>
<td>117.8 ± 8.3</td>
<td>137.7 ± 6.7</td>
</tr>
</tbody>
</table>

E-ISSN 2477-0612
formation by binding to NaOH, which had a role in the reaction between fumaric acid and FeSO₄. In addition, the unreacted fumaric acid, during the synthesis process of ferrous fumarate, may be mixed into the sample precipitate, diluting the ferrous fumarate content in the precipitate.

### In Vivo Body Weight Gain Test in Rats

Table 6 and Figure 4 show the increase of rat body weight, in absolute number (gram) and percentage (%), respectively, in the first week, the second week, and the cumulative weight (total) for two weeks. Although the three groups did not show significant differences (p>0.05) in weight gain statistically, it appears that ferrous fumarate group has the highest effect on weight gain. The increases in total body weight in the ferrous fumarate and ferrous sulfate groups are also higher than the control group. This suggests that the absorption of iron from the two active substances leads to the effect of increasing body weight, albeit insignificant. This might be due to the observation was only for 2 weeks in this study. There is a possibility that with enough iron level in blood, the blood function to distribute oxygen and nutrition to body cells would be optimal, so the body growth, including weight gain, would also be optimal. However, more studies need to be done to elaborate the correlation (or not) between iron absorption (i.e. the increase of iron level in blood) and body weight gain. As an information, the normal iron content in blood serum is 80-180 mcg/dL (14-32 μmol/L) in men and 60-160 mcg/dL (11-29 μmol/L) in women (Devkota, 2019). It is also recommended that the observation of body weight gain is conducted in longer time frame (for more than 1 month) to assure the significance of the result difference between groups. According to the National Health Service (United Kingdom) (2019), generally it takes up to 4 weeks for ferrous sulfate and ferrous fumarate to have full effect as anemia treatment.

The results of this study are in accordance with the results of a study by Harrington et al (2011) about the absorption of iron fortified foods in children. The absorption of ferrous fumarate and ferrous sulfate was equally good because the difference was not significant (p>0.05) between the two substances. In that study, absorption of iron ferrous fumarate and ferrous sulfate respectively in the mother group was 17.5% and 20.5%; babies 7% and 7.2%; and children 6.3% and 5.9%. According to the study of Moreno-Fernandez et al (2019), there was a body weight gain effect due to iron therapy in a group of anemic rats with various action mechanisms of the body’s homeostasis. Research by Lawless et al (1994) and Kilic et al (2014) also showed an increase in body weight due to iron supplements in children and adults with and without anemia. The increase in body weight could be said to be proportional to the absorption of iron fortification.

### CONCLUSION

Ferrous fumarate was successfully synthesized through the reaction of disodium fumarate and bivalent iron FeSO₄, which, in turn, was extracted from Indonesian iron sand with H₂SO₄. The synthesized ferrous fumarate met the identification and loss on drying requirements based on the Indonesian Pharmacopoeia VI. The in vivo weight gain test in rats showed that ferrous fumarate had similar effect on the total weight gain of rats compared to ferrous sulphate.

### ACKNOWLEDGEMENT

The authors thank to PT Akurat Spektra Prima for the permission to use facilities, materials and instruments during this research.
CONFLICT OF INTEREST

The authors do not have any conflict of interest to declare.

REFERENCES


Vidianti, I.A. (2014). Extraction of titanium dioxide from lumajang beach sand by H3PO4 leaching and NaOH as decomposition agent. Surabaya: Chemistry Department Faculty of Mathematics and Natural Sciences Sepuluh...