Optimization Combination of Suweg Starch (*Amorphophallus campanulatus Decne*) and Gembili Starch (*Dioscorea esculenta* (Lour.) Burk.) as Filler of Ibuprofen Tablet by Simplex Lattice Design Method

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Abstract: Tablet is pharmaceutical dosage form that simple and efficient in drug delivery system. Ibuprofen tablet is usually taken along with food or milk to reduce side effects on the gastrointestinal tract. Starch of Suweg and Gembili are not yet widely developed as excipients in tablet formulation. Based on Biopharmaceutics Classification Systems, ibuprofen includes in BCS class II with high permeability and low solubility. This study want to formulate ibuprofen tablets using combination of suweg and gembili starch with wet granulation method. However, the optimum proportion of starch composition is not yet known, so optimization is needed with the *simplex lattice design method* using *Design Expert* software. Obtained 8 formulas with physical response: granule flow time, tablet weight uniformity and disintegration time of tablets. The optimization shows that the optimum composition of suweg and gembili starch are 51.809%: 48.191%. The result of statistical analysis [*t*-test] physical parameters of granule and tablet of ibuprofen optimum formula were not significantly different (*p*-value > 0.05) with *Design Expert* prediction. Based on the requirements of Pharmacopeia Indonesia 4th Edition the results of optimum formula test provide good physical test with granule flow time 3.583±0.130 seconds; tablet weight uniformity 498.333±5.080 mg, hardness tablet 4.780±0.130 Kg, friability vvo of tablets 0.904% and the disintegration time of tablets 6.833±0.750 minutes. The dissolution profile of the optimum formula showed %DE at 60 minutes is 76.975±0.037%. Concentration of ibuprofen in tablet is 191.755±5.847 mg and percentage of ibuprofen in tablet is 95.877±2.293%.

1. Introduction
Tablet is one of the most commonly used drug dosage forms because efficient, practical, and ideal for administering orally active substances [1]. Tablet is solid preparation, made in flat or double convex press, generally round, containing one type of drug with or more with or without additives. Additional substances used can function as filler substances, developer substances, and wetting agents [2]. The filler (diluent) functions to increase the volume of the mass to be easily made. The filler material is added if the active ingredient was small or difficult to press. For example lactose, starch, dibase calcium phosphate, and microcrystalline cellulose [3].

Various types of tubers are spread in all regions in Indonesia which have the potential to produce starch, including those that have not been widely developed and the utilization is not optimal is suweg.
tubers (*A. campanulatus Decne*) and gembili (*D. esculenta* (Lour.) Burk.). The results of previous studies by Richana and Sunarti [4] showed that *A. campanulatus Decne* tuber starch had low amylose (19%) and high peak viscosity (700 BU) so that it was well developed for thickening and filling materials. Gembili tubers with high starch yield (21.44%) are also very potential to be developed into starch products. The use of a combination of fillers in the tablet preparation formulation will affect the physical properties of tablets produced because the filler material has a large portion of the overall weight of the tablet.

Ibuprofen tablets are usually taken along with food or milk to reduce the side effects of the drug. Therefore, a new idea was developed to replace the components of tablet fillers with natural ingredients as well as food ingredients, namely suweg tubers (*A. campanulatus Decne*) and gembili (*D. esculenta* (Lour.) Burk.), the aim that Ibuprofen tablets are produced better and could help to minimize the side effects of the drug. Comparison of the filler composition in the formulation of a tablet Ibuprofen preparation can determine the physical properties of the tablets produced. Therefore, the research was optimized to obtain the optimum composition of tuber starch filler mixture with the *simplex lattice design* method using *Design Expert* software.

2. **Experimental**

2.1. **Materials**

GenesysTM 10s UV/VIS spectrophotometer, moisture analyzer, Guoming RC-1 paddle type dissolution tester, knife, grater, flannel, oven, mortar, 18 mesh sieve, 16 mesh sieve, 90 mesh sieve, 70 mesh sieve, drop pipette, beaker glass, funnel, ruler, stopwatch, water bath, Prescia BJ 4501C and Sartorius BP 221S analytical balance sheet, Shanghai Tianhe Pharmaceutical Machinery TD punch single tablet printing machine, tablet friability tester C2, YD-1 hardness tester tablet, desintegration tester.

Suweg tubers (*A. campanulatus Decne*) and gembili tubers (*D. esculenta* (Lour.) Burk,) were obtained from Kaliwungu, Kendal, Central Java, Indonesia; Ibuprofen PT Konimex, Indonesia; monobasic potassium phosphate 0.2 M and 0.2 M sodium hydroxide obtained from Universitas Sebelas Maret Chemical Laboratory; and magnesium stearate 1%, talc 2%, amprotab 5%, gelatin 10%, and hydrochloric acid 0.1 N pharmaceutical grade from Bratachem.

2.2. **Methods**

2.2.1. Isolation of Tuber Suweg and Gembili

Determination of suweg and gembili tubers was carried out at the Biology Laboratory of the Mathematics and Natural Sciences Faculty, Universitas Sebelas Maret, Surakarta, Indonesia. The process of making starch from tubers is done by extracted with water solvent twice (1:3 and 5:3) for 15 minutes. After 15 minutes, the extract is filtered so that liquid starch is obtained, then dried using an oven with a temperature of 50±2 °C for 6 hours. Dry starch is ground and sieved then organoletics test.

The sample of 1.0 g of tuber starch was flattened above the pan of the Moisture Analyzer. The tool will heat the sample at 105 °C until it shows a constant readable water content value (± 3-5 minutes).

2.2.2. Wet Granulation and Evaluation

Ibuprofen tablets are made using wet granulation method. The ingredients are weighed according to the desired weight in each formula (Table 1). First, the binder (10% gelatine) is made by 10 g gelatine powder diluted with hot water ad 100 mL. Active substances (ibuprofen), crushers (amprotab) and fillers (suweg and gembili starch) are mixed and ground until homogeneous. Then the binder (10% gelatin) is added until a moist mass can be obtained. When the granule is passed on a 16 mesh sieve, the granule is dried in oven at 60 °C for 2 hours. Dry granules are sieved again with 18 mesh sieve, then mixed with lubricant (Mg stearate and talc) and stirred until homogeneous.

Granule evaluation includes: Flow time test of granule, weighed 50 g of granule and poured into a funnel with stem closed. The stem is opened and the granule is allowed to flow until it runs out. The
time needed for the granule to flow until it is used up is recorded using a stopwatch. The test was repeated 3 times.

Table 1. Ibuprofen tablets formula based on Simplex Lattice Design Methods with variation proportion of suweg and gembili starch

| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|------------------|----|----|----|----|----|----|----|----|
| Ibuprofen        | 200| 200| 200| 200| 200| 200| 200| 200|
| Suweg starch     | 125| 125| 250| 187.5| - | 62.5| - | 250|
| Gembili starch   | 125| 125| - | 62.5| 250| 187.5| 250| - |
| Gelatine         | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Mg stratate      | 5  | 5  | 5  | 5  | 5  | 5  | 5  | 5  |
| Talcum           | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Amprotab         | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |

2.2.3. Tablets and Evaluation
Tablet pressed with each tablet weigh 500 mg with a dose of 200 mg ibuprofen was performed using a single punch tablet pressed. Tablets that have been press then evaluation including:

2.2.3.1. Weight uniformity test
Weighed 20 tablets one at a time with an analytical scale, then the average weight and deviation of each tablet were weighed. The deviation of the weight of two tablets should not be more than 5% of the average weight and none of the tablets deviate more than 10% of the average.

2.2.3.2. Hardness test
The tablet is placed on the hardness tester with the tablet standing, then the tool lever is fully pressed. The test was repeated 3 times.

2.2.3.3. Fragility test
Weighed a total of 20 tablets, then put into the cylinder friabilator. The friabilator test equipment is run for 4 minutes or 100 rounds. Then the tablet is taken and released again, the tablet is weighed again and the difference in weight is calculated before and after testing.

\[
\text{% Fragility} = \frac{\text{initial weight-end weight}}{\text{initial weight}} \times 100\% \quad (1)
\]

2.2.3.4. Disintegration time
Inserted 6 tablets one at a time into the tube of disintegration test equipment, then the device moved up and down regularly 30 times per minute in medium water temperature of 36-38°C. Tablets are disintegrated if there are no tablet parts left behind.

2.3. Concentration of Ibuprofen in Tablet
2.3.1. Medium of Ibuprofen tablets
Medium of 0.1 N NaOH was made by dissolving 4.0 g of NaOH with distilled water in a 1.0 L. Maximum wavelength of ibuprofen into 0.1 N NaOH medium.

Liquid stock of Ibuprofen was prepared by dissolving 50.0 mg of ibuprofen ad 10.0 mL ethanol 96%, then put 1.0 mL solution was dissolved with 0.1 N NaOH solution ad 100.0 mL volumetric flask and obtained a solution with a concentration of 50.0 μg/mL. The solution was pipetted 12.0 mL put into a 25.0 mL volumetric flask dissolved with 0.1 N NaOH solution sufficiently, so that a solution with a concentration of 24.0 μg/mL was obtained. The maximum absorption of ibuprofen was measured at a wavelength of 200-400 nm.

2.3.2. Calibration curves of ibuprofen in the medium of 0.1 N NaOH
From stock liquids, dilution of 0.1 N ibuprofen in NaOH was performed with a concentration of 12.0; 16.0; 20.0; 24.0; 28.0; and 32.0 μg/mL ibuprofen.

2.3.3. Ibuprofen concentration in tablets
Taken 10.0 tablets randomly, weighed and determined the average weight. Ten tablets were ground to powder, then weighed as much as 100.0 mg of tablet weight. Then dissolved in 0.1 N NaOH into
100.0 mL flask, shaken until homogeneous, then filtered. The filtrate obtained was pipetted as much as 2.0 mL and put in a measuring flask ad 10.0 mL, then added 0.1 N NaOH. The absorbance was observed at the maximum wavelength using a UV-VIS spectrophotometer.

2.4. Dissolution Test
2.4.1. Dissolution media
Dissolution media used phosphate buffer pH 7.2. This buffer was prepared by mixing 50.0 mL of monobasic potassium phosphate 0.2 M and 22.4 mL of sodium hydroxide 0.2 M then diluted with distilled water ad 200.0 mL. Put of 100.0 mL solution and diluted with distilled water ad 1.0 L, then for pH adjustment 0.1 N HCl or 0.1 N NaOH was added.

2.4.2. Determination of the maximum wavelength of ibuprofen
Ibuprofen stock liquid was prepared by dissolving 50.0 mg of ibuprofen ad 10 mL ethanol 96%. Put of 1.0 mL ibuprofen solution then dissolved ad 100 mL of phosphate buffer pH 7.2 in a 100 mL volumetric flask and obtained with a concentration of 50 μg/mL. The solution was pipetted 12.0 mL into a 25.0 mL volumetric flask dissolved with phosphate buffer pH 7.2 sufficient until the flask boundary mark was obtained solution with a concentration of 24.0 μg/mL. The maximum absorption of ibuprofen in buffer solution was measured at a wavelength of 200-400 nm.

2.4.3. Calibration curves of ibuprofen in phosphate buffer pH pH 7.2
Ibuprofen liquid stock was then diluted in phosphate buffer pH 7.2 with a concentration of 8.0; 12.0; 16.0; 24.0; 28.0; and 32.0 μg/mL.

2.4.4. Tablet dissolution
Pour of 900 mL dissolution medium into a vessel, then heated at temperature of 37±0.5°C. The ibuprofen tablet was put into the dissolution vessel then rotated at a speed of 50.0 rpm. Samples were taken as much as 10.0 mL at intervals of 0, 2, 5, 10, 15, 20, 30, 45, and 60 minutes. Each sample taken is then replaced with 10.0 mL dissolution medium. The absorbed sample is measured at it’s maximum wavelength. According to the Indonesian Pharmacopeia 5th Edition [5], within 60 minutes it must dissolve not less than 80% C13H18O2 of the amount indicated on the label.

2.5. Data Analysis
Optimum formula was obtained by Simplex Lattice Design methods using Design Expert software. Data on the physical properties of tablets obtained by measurement of time until the granules flow out for flow time, calculation of the Coefficients of Variation (CV), balancing tablet weight of 5% and 10% for tablet weight uniformity, average scale value on hardnness tester tools for tablet hardness, calculation of tablet fragility%, tablet disintegration time with disintegration test equipment.

Profiles of dissolution of ibuprofen tablet optimum formula for the combination composition of tuber starch fillers was obtained by comparing the dissolution test results with the requirements listed in Indonesian Pharmacopeia 5th Edition (2014).

The data obtained were analyzed statistically using a T-Test for one sample (one sample T-Test) with a 95% confidence level. Test results are compared with predictive results.

3. Results and Discussion
The results of the determination in the Biology Laboratory of the Mathematics and Natural Sciences Faculty, Sebelas Maret University Surakarta, Indonesia based on Flora of Java book stated that the plants used in this study were Suweg (A. campanulatus Decne) and Gembili (D. esculenta (Lour.) Burk.).

High moisture content can increase the growth of microbes and enzymes that cause damage to starch. The limit of microbial water content can still grow is 14-15%. Water content of tuber starch with replications resulted in an average water content in suweg tuber starch (A. campanulatus Decne) which was 16.6% and gembili tuber starch (D. esculenta (Lour.) Burk.) was 18.7%. The test results of water content in tuber starch showed high values can be made possible due to environmental conditions when the research is still entering the rainy season so the air is more humid.
3.1. Flowing Time of Granules
The mathematical equation for the granule flow time is \( Y_1 = 0.03 (A) + 0.04 (B) + 2.79 (A) (B) - 1.23 (A) (B) (A-B) \) where A is suweg tuber starch and B is gembili tuber starch. The graph of mixing 2 components of suweg and gembili starch shows that the greatest response value is the combination of +2.79 (A) (B) which means that the mixture of suweg starch and gembili can increase the flow time of ibuprofen tablet granules (Figure 1).

3.2. Uniformity of Tablet Weight
Mathematical equation for granule flow time is \( Y_2 = 5.03 (A) + 5.03 (B) - 7.77 (A) (B) \) where A is suweg tuber starch and B is gembili tuber starch. The graph of mixing 2 components of suweg and gembili starch shows that the greatest response value is –7.77 (A) (B), which means that the mixture of suweg and gembili starch can reduce the uniformity of ibuprofen tablet weight (Figure 1).

3.3. Disintegration Time
The mathematical equation for granular flow time is \( Y_1 = 7.39 (A) + 9.61 (B) \) where A is suweg starch and B is gembili starch. The graph of mixing 2 components of suweg and gembili starch shows that the greatest response value is +9.61 (B) which means that the gembili starch may reduce the disintegration time of ibuprofen tablets (Figure 1).

The formula of the highest response is chosen as the optimum formula. From these optimization obtained the optimum formula proportion combination of suweg and gembili starch. The results of the prediction of Simplex Lattice Design with a optimum ratio of 51.809 % : 48.191 % has the highest total response value.

From the optimization results, it was made ibuprofen tablets with the same method with ibuprofen tablets made for optimization. Furthermore, ibuprofen tablets with the optimum formula composition combination of suweg starch and gembili starch were obtained from the optimization using Simplex Lattice Design method from the physical properties of granules and tablet.

The uniformity of ibuprofen tablet weight of the optimum formula test results were significantly different from the predictive results (p>0.05), but it was acceptable because it was still included in the requirements of tablet weight uniformity. The deviation of the weight of two tablets no more than 5 % of the average weight of 20 tablets and none of the tablets deviate more than 10 % from an average of 20 tablets.

Table 2. Physical response results of granule and tablets ibuprofen based on Simplex Lattice Design method

| Formula | %w/w Suweg | %w/w Gembili | Flowing time (second) | Weight uniformity (mg) | Disintegration time ( minute) |
|---------|------------|--------------|-----------------------|------------------------|------------------------------|
| 1       | 50         | 50           | 3.3                   | 500.1                  | 6.7                          |
| 2       | 50         | 50           | 2.9                   | 500.2                  | 7.3                          |
| 3       | 100        | 0            | 3.3                   | 502.7                  | 5.8                          |
| 4       | 75         | 25           | 3.0                   | 501.9                  | 7.7                          |
| 5       | 0          | 100          | 4.2                   | 502.8                  | 9.0                          |
| 6       | 25         | 75           | 5.6                   | 501.8                  | 7.2                          |
| 7       | 0          | 100          | 3.2                   | 502.5                  | 8.8                          |
| 8       | 100        | 0            | 3.1                   | 502.0                  | 5.3                          |

Table 3. Point prediction value of physical respon of granule and tablet ibuprofen optimum formula based on Simplex Lattice Design method using Design Expert software

| Suweg starch | Gembili starch | Flowing time of granul | Weight uniformity | Disintegration time | Desirability value |
|--------------|---------------|-------------------------|-------------------|--------------------|-------------------|
| 51.81%       | 48.19%        | 3.50                    | 500.66            | 7.08               | 0.86              |
The test results of determining the optimum formula levels of ibuprofen tablets using UV-VIS spectrophotometer show that on average each tablet contains 191.76 ± 5.85 mg ibuprofen with concentration of 95.88 ± 2.29 % ibuprofen. According to the requirements listed [5], ibuprofen tablets are not less than 90% and not more than 110%, so that the optimum level of the active ingredient of ibuprofen each tablet meets the requirements. From the results of the analysis showed that the optimum formula ibuprofen tablet had dissolution profiles which meet the requirements of Indonesian Pharmacopoeia 5th edition (2014) with %DE (Disolution Efficiency) which was not less than 80 % within 60 minutes which was 94.85 ± 0.037 %.

**Figure 1.** Diagram counter plot of filler combination suwe-gembroli of ibuprofen tablets with phsical responses: flowing time of granule which means that the mixture of suwe starch and gembroli can increase the flow time of granules [a]; uniformity of tablet weight, the mixture of suwe and gembroli starch can reduce the uniformity of ibuprofen tablet weight [b]; and disintegration time the gembroli starch may reduce the disintegration time of ibuprofen tablets [c]
4. Conclusion

The results showed that the optimum formula ibuprofen tablet was obtained from the composition of the ingredient suweg starch (*A. campanulatus Decne*) and gembili starch (*D. esculenta* (Lour.) Burk.) with a ratio of 51.809% : 48.191%. The increase in the proportion of suweg starch as a filler on the ibuprofen tablet optimum formula gave better physical properties of granules and tablets: granule flow time 3.583±0.130 seconds; tablet weight uniformity 498.33±5.080 mg with CV value is 0.021%, tablet hardness is 4.780±0.130 Kg, tablet fragility is 0.904% and disintegration time is 6.833±0.750 minutes. The optimum dissolution profile of ibuprofen tablet showed that %DE at 60 minutes is meet the requirements of not less than 80%, namely 94.85±0.037%. While the results of the determination of the levels showed that on average each tablet contained 191.76±5.85 mg ibuprofen and the concentration of ibuprofen each tablets is 95.88±2.29%.

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