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# Preformulation Study of Pugun Tano (*Curanga fel-terrae* [Lour.] Merr) Ethanolic Extract Granule Mass in Capsule as Hepatoprotective Drug

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**Keywords:** Curanga fel-terrae; Capsule; Ethanolic extract of pugun tano; Preformulation

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**Abstract**

**BACKGROUND:** Pugun tano extract had been studied for its effect as hepatoprotector. However, the usage of the plant in the form of extract has a limitation, especially if the extract is consumed by the people due to the unpleasant taste and odour. Then, the extract needs to be transformed into a particular dosage form, such as a capsule. But before the capsule can be produced, a preformulation study of pugun tano extract into a granule mass in capsule need to be evaluated.

**AIM:** The study aimed to formulate the ethanolic extract of pugun tano (*Curanga fel-terrae* (Lour.) Merr) as granule mass in the capsule dosage form.

**METHODS:** The pugun tano ethanolic extract was formulated in several steps included preparation of dry extract using coating method with polyvinylpyrrolidone (PVP) and granule mass production. The excipients used for the granule mass were lactose granules (made with tapioca starch using wet granulation), corn starch (made with 3 concentrations of 5% (F1), 7.5% (F2) and 10% (F3)), talcum, magnesium stearate, methylparaben, and propylparaben. The granule mass was evaluated for the bulk density, tapped density, inter-particle porosity, Carr's index, Hausner ratio, angle of repose, and flowability.

**RESULTS:** The results showed that all of the formulae passed the requirement of the preformulation test. The bulk density of the granule mass was 0.79 – 0.86 g/ml; the tapped density was 0.88 – 0.90 g/ml; the inter-particle porosity was 0.03 – 0.14; the Carr's index was 2.71 – 11.94%; the Hausner ratio was 1.09-1.12; the angle of repose was 26.10 – 28.90°; and the flowing time was 5.97 – 6.63 seconds. All of the formulae showed good flowability and free-flowing properties.

**CONCLUSION:** It is concluded that the obtained formula containing pugun tano ethanolic extract can be formulated into granule mass for the capsule dosage form.

## Introduction

The liver is a very important organ in the human body. The liver has to be protected due to its main role that metabolises all of the substance's presence in the blood, including drugs. The drugs have the possibility to damage the liver if they have hepatotoxic properties, such as the usage of overdose paracetamol [1], [2]. Paracetamol or acetaminophen is the most widely used antipyretic and analgesic drug in the world, particularly in the United State [2]. The prevalence of the drug-induced liver failure was also detected approximately 20% in children and above 20% in adults [3]. Therefore, we need to protect the liver from those kinds of substances. Since the drugs or supplements with hepatoprotective function are very limited, it is necessary to explore other alternatives to be used for that purpose.

Curanga fel-terrae (Lour.) Merr is one of the plants which are abundant in East Asia-southern China, India through Myanmar, Malaysia to Indonesia and the Philippines. It has synonym of Picria fel-terrae (Lour) which belongs to Sapindaceae family [4]. The North Sumatera people usually called it as "pugun tano". It contained some of the flavonoid compounds [5], which may act as the source of antioxidant that will maintain homeostasis and protect the liver [6]. The activity of this plant in the ethanol extract form as a hepatoprotective agent had been investigated by Harahap et al., in 2017 [7]. The subchronic toxicity of the ethanolic extract had also been studied [8]. The

usage of the plant in the form of extract has a limitation, especially if the extract is consumed by the people due to the unpleasant taste and odour. The right and practical dose are also other reasons whereby the extract needs to be formulated into a dosage form.

The capsule is one of the solid dosage forms that is mostly used due to its simple preparation. The formulation and evaluation of the granule mass are the important aspects that need to be carried out to assure that the capsule exhibit a stable and effective dosage form. The characteristics of the granule mass are mostly affected by the particle properties. The flowability of the granule is the most important issue and it can affect the efficiency of the pharmacy production, particularly in hard gelatine capsule filling [9], [10]. Therefore, a preformulation study of granule mass for ethanolic extract of Curanga fel-terrae was conducted in a view to developing a pharmaceutical dosage form.

## Material and Methods

### *Plant extraction*

The extraction of pugun tano was carried out, followed the method described in Harahap et al., [7]. The extraction was done using 96% of ethanol as the solvent. The result was stated as pugun tano ethanolic extract (PEE).

### *Preparation of the granule mass*

The PEE was first coated with PVP as the coating agent; then this coated PEE was called dry pugun tano extract (DPE). The DPE was mixed with the other excipients to form the granules mass. The final mass of a capsule was determined by subtracting the total weight of a capsule with the capsule shell. The capacity for each capsule was 571 mg. The dose of DPE was chosen from the previous study by Harahap et al. as a hepatoprotective agent in rats [7] then the dose was converted to the dose of rabbit since the capsule will be evaluated for the hepatoprotective effect in the rabbit. The formula of the granule mass is shown in Table 1.

**Table 1. The formula of granule mass of pugun tano ethanolic extract**

| Composition | Weight (mg) | | |
|---|---|---|---|
| | F1 | F2 | F3 |
| DPE | 406.25 | 406.25 | 406.25 |
| Corn starch | 28.55 | 42.83 | 57.1 |
| Talc | 5.71 | 5.71 | 5.71 |
| Mg stearate | 5.71 | 5.71 | 5.71 |
| Methyl paraben | 1.03 | 1.03 | 1.03 |
| Propyl paraben | 0.11 | 0.11 | 0.11 |
| Lactose to | 571 | 571 | 571 |

### *Preformulation test of the granule mass*

The granules mixture was evaluated for its bulk density, tapped density, inter-particle porosity, Carr's Index, Hausner ratio, angle of repose and flowability as described in previous studies [10], [11].

### *Bulk and tapped density*

The bulk density was measured by recorded the volume (Vo) of known weight (M) of the granules mixture as well as after taping till constant volume (Vt) in a measuring cylinder. The bulk density (Pb) and tapped density (Pt) were calculated as M/Vo and M / Vt, respectively.

### *Inter-particle porosity*

The inter-particle porosity of the granules mixture was calculated using the equation as described in Carbinato et al., [10].: Ie = {(Pb – Pt) / (Pb x Pt)}.

### *Carr Index (CI%)*

This value was calculated from the bulk density and tapped density value as CI = ((Pt – Pb) / Pt).

### *Hausner ratio (HR)*

This ratio was calculated by dividing the tapped density to the bulk density as HR = Pt / Pb.

### *The angle of repose (α)*

The angle of repose (α) was measured by determining the height (h) and the diameter (d) when a conical pie formed from flowing over a funnel and then calculated the tangent as follow: tan α = h / r. α was then deduced from its tangent.

### *Flowability*

The flowability was determined by calculating the time consumed for the bulk to flow from a funnel.

## Results

### *The result of coated PEE (DPE) and granule mass*

The DPE acted as a base active ingredient in the capsule. The DPE was made in the form of a granule, therefore the additional excipients added

were in the form of fines and granules particle. The coated PEE (DPE) is shown in the Figure 1.

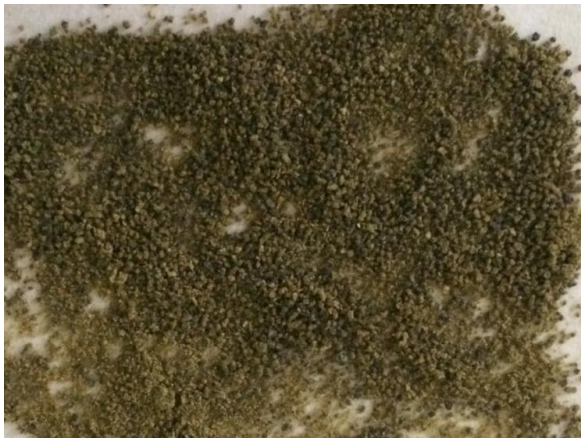

*Figure 1: The dry pugun tano extract (DPE) coated in polivynilpyrollidone as the base active ingredient*

The DPE was mixed with the other ingredients to form granule mass as the content of the capsules. Lactose was chosen as the filler and to increase the flow property of lactose; it was made in granules form. The modification of shape and size of powder will affect the flow properties more efficiently [12]. The granulation of lactose was also done to reduce the interparticle cohesive forces [13]. The difference made in the formula was the concentration of corn starch as the disintegrant. Assuming that the granule form from the DPE and lactose as the filler will make the pore and space increase, then the rest ingredients were in the fine powder form. The mixture of all of the ingredients can be seen in Figure 2.

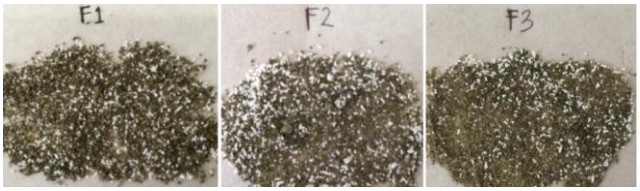


*Figure 2: The mixture of all of the ingredients as the granules mass content of the capsule;, F1 = mixture contained 5% of corn starch; F2 = mixture contained 7.5% of corn starch, and F3 = mixture contained 10% of corn starch*

### *Preformulation Results*

The preformulation tests demonstrated the properties of the granules mass for each formula. The results of the preformulation tests are given in Table 2.

**Table 2: The properties of granules mass for each formula (n = 3), data are presented as mean ± SD**

| Parameters | F1 | F2 | F3 |
|---|---|---|---|
| Pb (g/ml) | 0.86 ± 0.06 | 0.79 ± 0.03 | 0.82 ± 0.02 |
| Pt (g/ml) | 0.90 ± 0.06 | 0.88 ± 0.03 | 0.89 ± 0.03 |
| Ie | 0.03 ± 0.00 | 0.14 ± 0.00 | 0.10 ± 0.00 |
| Carr's Index (%) | 2.71 ± 0.00* | 11.94 ± 0.00* | 8.70 ± 0.00* |
| Hausner ratio | 1.04 ± 0.00 | 1.12 ± 0.00 | 1.09 ± 0.00 |
| Angle of repose α (°) | 26.10 ± 0.02 | 28.90 ± 0.10 | 27.62 ± 0.08 |
| Flowing time (sec) | 6.62 ± 0.07 | 5.97 ± 0.06 | 6.63 ± 0.09 |

## Discussion

The bulk densities of all of the formula gave value above than 0.5 g/ml; it was shown that the granules mass had the denser characteristic. The high value of bulk density normally indicates great limitation to flow since the contact occurs among the particles. The tapped density value for each formula showed above than the bulk density value which indicated that there were empty spaces between the particles. The inter-particle porosity (Ie) result demonstrated the highest value obtained by F2 which was 0.14 ± 0.00 which supported that the biggest difference between bulk and tapped density in F2. It is indicated that there were plenty of pores and space between the particles in the F2 formula. The smallest Ie value was shown by F1 formula which had less space between the particles. The pores and empty spaces between the particles could influence the compressibility of the granules; therefore, it can affect the final volume of the capsule. The less Ie value would give compact granules mixture in a capsule which resulting in the weight of the granules mass had a small difference with the planned weight.

The flowability of a granule mixture is influenced by the indirect flow-related properties such as Carr's Index, Hausner ratio, and angle of repose. The Hausner ratio of all of the formula showed value in the range of 1.04 ± 0.00 to 1.12 ± 0.00 which indicated that the granule mixture had the good flowing characteristic. The Carr's indexes were 2.71 ± 0.00, 11.94 ± 0.00, 8.70 ± 0.00% for the formula F1, F2, F3, respectively. Based on Carr category on Carr's index and Hausner ratio, F1 and F3 showed excellent flow properties and F2 showed good flow property [14]. Carr's index below than 16% showed free-flowing property [15]. However, there was a significant difference between the F1, F2 and F3 based on Carr's index. The highest Carr's index was resulted by F2 which mean that this formula was less free-flowing than other formula but still in the good flowing category [14]. The smallest Carr's index was given by the formula F1 which was 2.71 ± 0.00%. The smallest Carr's index indicating the higher compressibility, therefore, could gain more compact content of granule mass in the capsule [16].

The angle of repose of all of the formula gave value in the range of 26.10 ± 0.02° to 28.90 ± 0.10° which were between 25 – 30° indicating an excellent flow property [14]. These data were also supported by the result given by the flowing test. The flowing time for F1, F2 and F3 were 6.62 ± 0.07, 5.97 ± 0.06, and 6.63 ± 0.09 seconds, respectively. All of the flow time demonstrated below than 10 seconds which mean that all of the formulae had excellent flow properties. However, there were no significant differences in the angle of repose and flowing time between each formula, indicating that all of the formula had the desirable flowing characteristic.

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