Pre – Formulation and Evaluation of Jamu Uyup – Uyup (an Indonesian Herbal Galactogogue)

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Abstract. Jamu Uyup – Uyup has established as the most used natural galactagogue in Indonesia, especially among Javanese people. Jamu Uyup – Uyup is available on the market in the fresh liquid form of a herbal mixture. Liquid forms of herbal preparations have certain limitation related to large dose volumes, difficult packaging, and poor stability. Developing and formulation Jamu Uyup – Uyup into solid dosage form would ensure reproducibility of product quality, accurate doses, improve acceptability and easy compliance with usage directives. The preparation of solid dosage form was carried out using spray drying technique. Microparticle comprising Jamu Uyup – Uyup encapsulated in a lactose matrix have medium yellow color, have distinct typical odor of Zingiberaceae, taste mildly bitter, pungent, slightly sweet, and have an acidic pH (4.7) to keep curcuminoids content stable. The solid dosage form had moisture content of 3.21 ± 1.71% dw and curcuminoids content of 35.86 ± 2.13 mg/g dw. Surface morphology showed that microparticles containing Jamu Uyup – Uyup encapsulated in a lactose matrix have spherical shape with a smooth surface and various sizes (20 – 100 µm) with no apparent cracks or fissures.

Keywords: pre-formulation, Jamu Uyup – Uyup, galactogogue, spray drying, encapsulation

1. Introduction

Galactogogues are pharmaceutical agents, foods, or herbal supplements that are used to support the initiation, continuation, or augmentation of breast milk production [1-7]; hence they are often given when a mother has an inadequate milk supply. There are several botanical species ethno – medically used for the galactagogue by Indonesian people, such as katuk (Sauropus androgynus (L.) Merr., family Phyllanthaceae), torbangun (Coles amboinicus Lour, family Lamiaceae), papaya leaf (Carica papaya, family Caricaceae), temulawak (Curcuma xanthorizza, family Zingiberaceae), fenugreek (Trigonella foenicum-graecum L., family Fabaceae), black cumin/habbatussauda (Nigella sativa Linn., family Apiaceae), cumin (Cuminum cuminum, family Apiaceae), fennel (Foeniculum vulgare Miller, family Apiaceae), anise (Pimpinella anism, family Apiaceae), etc. Some of them are ingredient in the traditional galactagogue formulation known as Jamu Uyup – Uyup which has established as the most used natural galactagogue in Indonesia, especially among Javanese people.

Jamu Uyup – Uyup is available on the market in the fresh liquid form of a herbal mixture which may lead to variations in dose each time a treatment is prepared. Furthermore, liquid forms of herbal
preparations have certain limitation related to large dose volumes, difficult packaging, and poor stability. Developing and formulation Jamu Uyup – Uyup into other dosage forms than fresh liquid form would ensure reproducibility of product quality, accurate doses, improve acceptability and easy compliance with usage directives. Solid oral dosage forms represent the preferred class of product for orally administered drugs. Solid preparations often have higher stability and are easier to standardize which adds to an increase in their therapeutic acceptance, efficacy and product value [8]. Pre-formulation testing is the first step in the rational development of dosage forms of herbal preparation. The objective of pre-formulation tests is to develop information useful to the formulator in developing a stable bioavailable dosage form [9]. Pre-formulation involves the characterization of physical, chemical and mechanical properties of an herbal preparation alone and when combined with excipients. The present investigation was carried out to perform pre-formulation testing of Jamu Uyup – Uyup in solid dosage form.

2. Materials and Methods

2.1. Preparation of Jamu Uyup – Uyup dried extract
Formula of an herbal mixture was based on formula given by one of producers of Jamu Uyup – Uyup in Yogyakarta, shown at table 1. Fresh rhizomes of some Zingiberaceae family (C. aeruginosa, C. xanthorrhiza, C. domestica, and Kaempferia galanga) and pulp of tamarind (Tamarindus indica) fruit were pureed and squeezed to collect the juice. The resultant juice was mixed with lemon (Citrus aurantifolia) juice and honey (Mel depuratum). Beside of its functional constituent, tamarin and lemon were used as natural acidity regulator, while honey was used as a sweetener. The fresh liquid form of a herbal mixture was evaporated to dryness under reduced pressure at 45 °C.

| Formula | Dose |
|---------|------|
| Curcumae aeruginosae rhizoma succus | 60 mL |
| Curcumae xanthorrizae rhizoma succus | 60 mL |
| Curcumae domesticae rhizoma succus | 60 mL |
| Kaempferiae galangae rhizoma succus | 60 mL |
| Mel depuratum | 60 mL |
| Citri auranti fructus succus | 20 mL |
| Tamarindi pulpa succus | 10 mL |

2.2. Preparation of Jamu Uyup – Uyup powder
The aqueous phase was prepared by dissolving the lactose at a suitably selected concentration (10% w/v) in deionized water. 160 grams of aqueous dried extract was added into solution and stirred vigorously. The suspension was dehydrated using spray drying. The spray dryer (Buchi Mini Spray Dryer B – 290) was operated at an inlet temperature of 110 °C, aspirator of 90%, pump of 5%, and nozzle cleaner of 5. The spray – dried samples were kept at −18 °C for further analysis.

2.3. Physicochemical evaluation
Determination of physical characteristics of extract and powder include organoleptic properties, pH, moisture content, and Scanning Electron Microscopy (SEM). pH of 1 % solution of the formulation was determined by means of a digital pH – meter (Eutech PC 700). Moisture content was measured by moisture analyzer digital (AND MX – 50). The surface morphology of the spray-dried lactose microcapsule loaded with an active compound was examined by means of a Hitachi SU – 3500 microscopes. Photographs were taken at an excitation voltage of 5 kV.

2.4. Determination of the total curcuminoid content
The quantification of curcuminoid was performed using UV – Vis spectrometry method from Pothitirat and Gritsanapan (2006) [10] with slight modification. Calibration curve was made by
curcumin added with methanol and adjusted to a final concentration of 2, 3, 4, 5, and 6 ppm. The absorbance was measured at 422 nm. The estimation of total curcuminoid content was carried out in triplicate and the results were averaged.

2.5. Determination of the total terpenoid content

The determination of total triterpenoids was performed according to the colorimetric method of Lin et al. (2015) with slight modification [11] and then expressed as milligram ursolic acid equivalent/gram dry weight (dw). The test samples or ursolic acid standards in tubes were added with 0.4 mL of 5% vanillin/glacial acetic acid (w/v) and 1.0 mL of perchloric acid solution. For the reaction, the tubes were placed in a water bath at 60°C for 45 min. Then the mixed solution was cooled and diluted with 5 mL of acetic acid solution. The absorbance was measured at 548 nm against blank using a spectrophotometer.

3. Results and Discussion

The present study demonstrates pre-formulation testing of Jamu Uyup – Uyup in solid dosage form. The preparation of solid dosage form was carried out using a spray drying technique. A microparticle comprising Jamu Uyup – Uyup encapsulated in a lactose matrix. Lactose is odorless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet. Lactose is widely used in pharmaceutical formulations as a filler [12]. The carbohydrate (such as lactose) has properties such as low viscosities at high solids contents and good solubility that are desirable in an encapsulating agent [13]. In addition, their diversity, low cost and widespread use in foods and drinks make them the preferred choice for encapsulation. Spray drying technique has been widely used for drying heat-sensitive foods, pharmaceuticals, and other substances, because of the solvent rapid evaporation from the droplets. Although most often considered a dehydration process, spray drying can also be used as an encapsulation method when it entraps active material within a protective matrix, which is essentially inert to the material being encapsulated. Compared to the other conventional microencapsulation techniques, it offers the attractive advantage of producing microcapsules in a relatively simple continuous processing operation. The encapsulation process comprises the steps of forming an aqueous solution, with stirring for an appropriate amount of time and at certain temperature to form a homogeneous solution; incorporating at least one active compound defined above into the previous solution; spray-drying the aqueous solution at certain temperatures to obtain a stable product encapsulated within the active compound. The encapsulation of Jamu Uyup – Uyup may improve their cohesion and bioavailability. The encapsulated Jamu Uyup – Uyup can be used in various applications of oral solid dosage form, such as instant drink powder, capsule, tablet, etc.

3.1. Physicochemical evaluation

Measurable properties that describe a state of a physical system were reported. The changes in the physical properties of a system can be used to describe its alteration between its transient states. Physical properties are often exhibited as observables. Organoleptic are physical characteristics which are easily identified by simple methods as visualization, touch, smell or taste. All these are used for the preliminary identification of the herbal extract [14]. The fresh liquid of Jamu Uyup – Uyup was a suspension since the liquid form was heterogeneous system consisting of two phases. Finely divided solid particles were dispersed in a liquid phase and prone to settle out become sediment. Sediment produced easily re-suspended using a moderate amount of shaking. Curcumin content tended to crystallize out of aqueous acidic solutions (pH < 7). The curcumin crystals formed were relatively large (10–50 μm), which made them prone to rapid sedimentation [15]. The aqueous dried extract was viscous and sticky, whereas the spray – dried samples were in the form of fine powder. The color of fresh liquid was dark yellow, the aqueous dried extract is brownish yellow, and the spray – dried powder was medium yellow. Yellow color is related to curcuminoid compounds. The fresh liquid and dried extract had strong typical odor of Zingiberaceae whiles powder had distinct typical odor of Zingiberaceae. The taste of fresh liquid, dried extract, and powder successively as follow: moderately bitter, extremely bitter, and mildly bitter. The three of these were slightly sweet and had an unequal
strength of pungent taste. Odor comes from the essential oil or other compounds while taste varies depending on the constituent of material. The bitter taste mainly comes from bitter substances of *Curcuma aeruginosa* and *Curcuma xanthorrhiza*.

### Table 2. Physicochemical properties of Jamu Uyup – Uyup

| Parameters          | Description                                                                 |
|---------------------|----------------------------------------------------------------------------|
| Texture             | Fresh liquid: Suspension, finely divided solid particles are dispersed in a liquid phase and prone to settle out; Dried extract: Viscous, sticky; Spray – dried powder: Fine powder |
| Color               | Fresh liquid: Dark yellow; Dried extract: Brownish yellow; Spray – dried powder: Medium yellow |
| Odor                | Fresh liquid: Typical of Zingiberaceae, strong; Dried extract: Typical of Zingiberaceae, strong; Spray – dried powder: Typical of Zingiberaceae, distinct |
| Taste               | Fresh liquid: Moderately bitter and pungent, slightly sweet; Dried extract: Extremely bitter and pungent, slightly sweet; Spray – dried powder: Mildly bitter and pungent, slightly sweet |
| Moisture content    | 85.71 ± 1.24% DW; 11.73 ± 1.54% DW; 3.21 ± 1.71% DW |
| pH                  | 4.2; 4.3; 4.7 |

The results of moisture content as shown in table 2 indicates that the fresh liquid had a moisture content of 85.71 ± 1.24%, the aqueous dried extract had 11.73 ± 1.54%, and the powder had 3.21 ± 1.71%. Examination of moisture content help reduce mistakes in the valuation of the real weight of drug material. According to the European Pharmacopoeia [16] and Indonesian Herbal Pharmacopeia [17], weight loss on drying should not pass 10%. The lower moisture content of Jamu Uyup – Uyup powder is always requested since it contains sugar from honey and lactose which can absorb moisture easily or deteriorate quickly in the presence of water. Lactose may develop a brown coloration on storage, the reaction is accelerated by warm, damp conditions [12]. So, the powders must be stored in an airtight container and provided with moisture absorbent hence not to absorb excessive moisture. An excess of water will promote microbial growth (especially mold) and deterioration subsequently hydrolysis. Low moisture of solid dosage form is very crucial to provides better stability against degradation of product.

The term pH refers to the relative amounts of hydrogen in a given chemical environment. It is a measure of the acidity or alkalinity of a given formulation. The pH is important in aqueous drug product formulation, especially since it involves drug solubility, activity, absorption, stability, sorption and patient comfort [18]. The rate of hydrolysis of product may vary depending on the pH of the solution. Determination of the pH will give information as to which excipients could be added to a drug to ensure that the product is stable and can be tolerated physiologically. Curcumin is a terpenoid – related polyphenol constituent, an oil-soluble pigment, practically insoluble in water at acidic and neutral pH, and soluble in alkali, and highly susceptible for pH change. In aqueous systems like water, at neutral and alkaline pH, curcumin is not stable to chemical degradation and gets easily degraded into compounds like vanillin, ferulic acid, etc. since the acidic phenol group in curcumin donates its hydrogen, forming the phenolate ion. In the pH range 1-7, water solubility is very low, and solutions are yellow. At pH>7.5, the color changes to red [15]. It is very important to keep the dosage form contained curcuminoids in acidic pH.
Figure 1. SEM images of the surface morphological structure of lactose monohydrate (Bratachem), voltage 5.00 kV, magnification: (a) 500x; (b) 1,000x; (c) 2,500x; (d) 5,000x

Figure 2. SEM images of the surface morphological structure of spray – dried Jamu Uyup – Uyup microparticles, voltage 5.00 kV, magnification: (a) 500x; (b) 1,000x; (c) 2,500x; (d) 5,000x
SEM pictures of lactose particles are presented in figure 1 and spray-dried active compound-loaded lactose microparticles are presented in figure 2. Observing the external morphology, spray – dried Jamu Uyup – Uyup particles showed a spherical shape, smooth surface, and various sizes (20 – 100 µm) with no apparent cracks or fissures, which is an advantage, since it implies that capsules have lower permeability to gases, increasing protection and retention of the active material. Moreover, the variety in size is a typical characteristic of particles produced by spray drying. According to Ré (1998) [19], imperfections are formed when there is a slow process of film formation during drying of the atomized droplets, associating the presence of surface depressions to the collapse suffered by the droplets during the initial stages of drying. Similar morphological characteristics were found on encapsulation of flaxseed oil by Tonon et al. (2011) [20] and d-limonene by Soottitantawat et al. (2005) [21].

3.2. Phytochemical evaluation

Analyzing the phytochemicals in medicinal plants provides scientists with insight into how effective plants are medicinally and understanding how and why they are effective can lead to the development of new medicines [22]. The main phytochemical in Jamu Uyup – Uyup is curcuminoid compounds which come from Zingiberaceae ingredients (Curcuma aeruginosa, Curcuma xanthorriza, and Curcuma domestica). The scientific correlation between curcuminoid and galactagogue is still not clearly understood, nevertheless Zingiberaceae family has been used empirically as a galactagogue in Indonesia for a long time ago. Although curcumin is relatively stable to heat and can be used in thermally treated, there is a decrease in curcuminoid level of encapsulated powder. Similarly, it occurred with terpenoid level (table 3). Curcumin has antibacterial activity [23] and a very powerful antioxidant effect [21, 22, 23]. So, it may be a preservative of the dosage form as well.

| Parameters     | Dried extract | Spray – dried powder |
|----------------|---------------|----------------------|
| Curcuminoid    | 48.78 ± 1.62  | 35.86 ± 2.13         |
| Terpenoid      | 131.95 ± 1.32 | 113.95 ± 2.16        |

4. Conclusion

The present investigation demonstrates that the fresh liquid form of Jamu Uyup – Uyup can be formulated into solid dosage form. The preparation of solid dosage form was carried out using spray drying technique. Microparticles containing Jamu Uyup – Uyup encapsulated in a lactose matrix have spherical shape with a smooth surface and contained 35.86 ± 2.13 mg/g dw of curcuminoid. The solid dosage form has an acidic pH (4.7) to keep curcuminoids content stable. The encapsulated Jamu Uyup – Uyup can be used in various applications of oral solid dosage form, such as instant drink powder, capsule, tablet, etc.

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6. References

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