

Moringa oleifera Lam.-Based Effervescent Tablets: Design, Formulation and Physicochemical Evaluation

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ABSTRACT

Moringa oleifera Lam., locally known as *Kelor*, is widely acknowledged as phytopharmaceutical herbal due to the ability of increasing the 58% hemoglobin level in pregnant women as well as preventing the decrease of serum ferritin by 50% leading to anemia. Recently, the need of easy-to-dissolve tablet has been increased upon the natural extract and therefore, the choose of effervescent dosage form is highly preferable. This study was aimed at designing the optimal composition of antianemia effervescent drug based on *Moringa oleifera* Lam. leaves extract. The *Moringa* leaves extract was produced by maceration method using 70% ethanol. Effervescent tablets were prepared in four formulas based on acid-base (1: 2 and 1: 3) and taste variations (i.e. lemon and strawberry). The tablet was formulated using wet granulation method. Prior to tablet compressing, the granules were tested for the physical properties including water content, contact angle, flowability, tapped index, compactibility, and granule density. In the form of effervescent tablets, the further tests were applied i.e. weight and size uniformity, hardness, and effervescent time. The four designed formulas show excellent properties either for granules or tablet forms. All formulas showed acceptable physical properties of granules and tablets. In regards of acceptability, all formulas yield a fairly bitter taste which is possibly due to the tannins and phenolic compounds of the extract. Addition of flavoring agents, such as lemon and strawberry, is unable to mask the bitter taste of the final tablet. Herein, the first *Moringa* leaves effervescent tablet prepared using wet granulation was successfully formulated. This study is possibly advantageous as the bottom line for the further formulation of *Moringa oleifera* Lam.-based effervescent products.

Keywords: *Moringa oleifera* Lam.; formulation; effervescent; wet granulation.

INTRODUCTION

Anemia defines the deficit status of hemoglobin in the red-blood cells (erythrocyte) giving impact to the loss of oxygen levels concentrated in blood stream. As its main function, hemoglobin plays an important role in transferring the oxygen throughout the cells, which are essentially needed to building-up the erythrocyte. However, the decay iron levels could fail the hemoglobin production thus, triggering the anemic condition for some ranges of populations, most widely occurred to the women with pregnancy^{1,2}. About 37.1 % of even distribution of its prevalence in Indonesia, anemia spreads thoroughly among the pregnant women in urban area (36.4%), and similar evidence was suggested with those living in rural area (37.8%)³. Nevertheless, lack of significant evidence has been noted magnificently reducing this prevalence even though efforts have been made by increasing the dose administration of the iron supplement. Further, this may indicate the presence of other factors (rather to side effects) that eventually interrupt the drug-uptake itself, such as morning sickness during the first trimester^{4,5}.

Moringa oleifera Lam. (MOL) extract is well-known to significantly improve hemoglobin levels by 58% in pregnant women and indicated to prevent decreasing of ferritin serum levels by 50%^{6,7}. Sindhu and co-workers demonstrated that administration of 100 g of dry MOL *simplicia* and jaggery (dry weight) with a ratio of 80:20 for 30 days is conceivably to raise hemoglobin levels of women with anemia⁸. It is well-known that oral administration is the most convenience route for delivering the drug along with the fact that it has been successfully raising the patient's compliance for many years. However, as such of drawback of its formulation, oral route also gives severe effect to those who have difficulties in taking these dosage form, for instance who are nauseated and have swallowing problem in taking drug orally as well as slow absorption and long onset⁹.

Among the other oral dosage forms, effervescent is one of the best alternative dosage forms selected to overcome those weaknesses, which is characterized by promptly dissolved and or/ dispersed in water before being administered thus, lowering the irritation risk due to direct contact with gastrointestinal tract (GIT)¹⁰. The use of CO₂

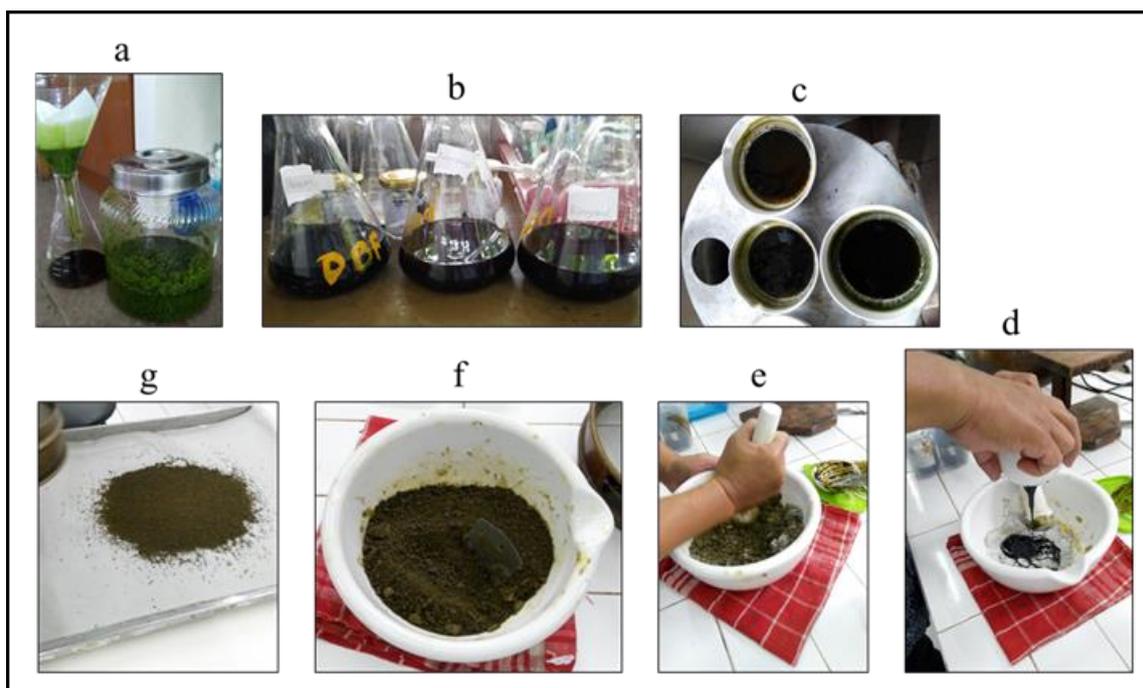


Figure 1: Step-by-step preparation of MOL leaves extract: the soaked (a), re-concentrated (b), and thickened (c) extracts, the mixing process between re-concentrated extract and other excipients (d) till homogenized (e) and being final granule (f), the granules were then sieved (g).

Table 1: Formulations (*F*) of the Moringa's effervescent tablet with various amount of acids-base and flavoring agent.

Composition	F ₁ (mg)	F ₂ (mg)	F ₃ (mg)	F ₄ (mg)
Granule of Moringa leaves extract	1500	1500	1500	1500
Citric acid	500	500	375	375
Tartaric acid	50	50	37.5	37.5
Sodium bicarbonate	1100	1100	1237.5	1237.5
Aspartame	50	50	50	50
PEG 600	50	50	50	50
Lemon flavor	100	-	100	-
Strawberry flavor	-	100	-	100

in its composition enhances the active ingredients penetrated into the paracellular pathway as well as involved in absorption process, also giving the pleasant taste to the patients which prompts better among the other oral dosage forms. This product contains sweetener and available in several flavors which is prospective to elevate the rates of patient's compliance in taking the medication, especially for the pregnant women¹⁰.

Herein, we designed and evaluated physiochemically the anti-anemic dosage composition of effervescent tablet of MOL leaves extract which can be consumed by pregnant mother as substitute of iron tablet. Due to the presence of carbonate and considering that this typical dosage form, it is believed that this product is easy to take, acceptable, produce better tasting, and tolerable with GIT problems thereby, possible to improve the patient's compliance¹¹. The use of citric acid in wet granulation conferring several benefits for effervescent tablets, especially in reducing the flow-time and propose angle, whereas the use of tartaric acid may also speed up the crushing time of tablets. At the end, designing the plant-based formula for the drug-consumable dosage form for the pregnant women is

conceivably to achieve by emerging effervescent in the design of herbal formulation.

MATERIAL AND METHODS

All standardized laboratory-glass wares were utilized during the experiment. For 70% ethanol, lactose, citric acid, tartaric acid, and sodium bicarbonate were purchased from Sigma Aldrich, Indonesia. Aspartame and PEG600 were purchased from Bratachem, Indonesia, whereas the flavors were purchased from Stockmeier, Germany. All other chemicals involved were purchased and used as received.

Determination of MOL leaf

The leaf of *Moringa oleifera* Lam. was determined by biologist in Biology Division of Pharmaceutical Department, University of Gadjah Mada, Yogyakarta.

Preparation of MOL powder

The raw material of green MOL leaves were procured freshly from Sleman District of Yogyakarta, Indonesia, where these plants are available. Roughly 388.59 g of the MOL leaves powder was obtained by air-drying the fresh leaves at 50°C for 24 hours, then grinded, until the homogenized fine powder attained.



Figure 2: MOL effervescent tablet. The aluminium foil was used as tablet's wrapper due to the hygroscopic nature of the tablet containing plant extract (a). The effervescent tablet upon the solvation into water producing CO_2 gas as the result of the chemical reaction with citric and tartaric acids (b).

Preparation of MOL extract

The extraction method was adopted from Mun'im and coworkers¹² with slight modification. Firstly, the leaves powder was soaked into 2.5 L of 70% ethanol in sealed jar for 24 hours at room temperature (Fig. 1a). The extract obtained was filtered through Whatman filter paper No.1 and re-concentrated by repeating the method twice in every 24 hours using 1.5 L and 1 L of ethanol 70%, respectively (Fig. 1b). The filtrate was evaporated on water bath until the thickened extract obtained (Fig. 1c). The final filtrate of ethanolic extract of fine-dried leaves were then weighed and used in further study.

Organoleptic test of the MOL extract

The organoleptic test of the extract was carried out by examining the color, odor, as well as the taste.

Formulation of the MOL effervescent tablet and physical test of MOL powder

In order to determine the best effervescent formulation, four different formulations were prepared by varying the ratio of the acid-base compositions as well as the flavors (Table 1). Following the wet granulation method, the preparation of effervescent tablet was firstly started by mixing of an amount of the MOL powder with lactose, proper sweeteners as well as effervescent base till attaining appropriate physical appearance (Fig. 1d-f). The granule was then loaded into the sieve with a rod number of 12, and dried for 24 hours at 50°C (Fig. 1g). In order to maintain the humidity, the granule was further mixed with citric acid and tartaric acid and dried for an hour at temperature not more than 50°C . The resulting granule was sieved and finally tested for physical characteristic.

Evaluation of water content

The water content of the final granule was calculated by means of *moisture balance* (Ohaus, ltd).

Angle of repose

The angle of repose calculation was determined by measuring the critical probable angle of the granule surface toward the plane surface. First, the granules of 100.00 g were weighted and flown slowly into a funnel fixed-to-stand with the bottom layer covered. The cover was then removed and the granules were allowed to drop on the graphical paper surface of the bottom most. The repose angle (α) was subsequently defined by measuring the height (h) and distance (d) of the formed granules then, involving the values into the equation:

$$\tan \alpha = \frac{2h}{d}$$

Flowability time test

The flow time test was done by counting the time length once the granules was set up till dropped as prepared in the angle of repose test section.

Tapped index

The granules were evaluated by comparing the bulk and tapped volumes of the flown granules as well as the rates when they were packed down. The values obtained was defined as the percentage of constant volume, as calculated as follows:

$$\%V_{\text{constant}} = \frac{V_{\text{tapped}} - V_{\text{bulk}}}{V_{\text{tapped}}} \times 100$$

Compactibility Test

The granules were subsequently tested for the compactness by applying certain force to their mass until the tablet disintegrated. Herein, a hardness tester (Stokes Monsanto) was set up for the upper punch and bottom punch in scales of 7 and 10, respectively (Korsch, Germany). Some randomly selected tablets were then loaded one by one in a hardness tester, with the final values reported in kg.

Granule density test

The granules density was defined by calculating the granules weights according to the below equation. The

Table 2: Physical characteristic of effervescent granule with the variation of acids-base and flavoring agent.

Physicochemical evaluation	F ₁ (mg)	F ₂ (mg)	F ₃ (mg)	F ₄ (mg)	Ref. ^{a,b,c}
Water content (%)	5.06 ± 0.04	5.09 ± 0.03	4.67 ± 0.03	4.80 ± 0.08	<2.00%
Angle of repose (Θ; °)	34.2 ± 1.4*	34.5 ± 1.2*	34.5 ± 0.9*	33.9 ± 1.2*	25 ⁰ -45 ⁰
Flowability (s)	6.6 ± 1.9*	6.4 ± 1.4*	5.3 ± 0.4*	5.7 ± 0.8*	<10 s
Tapped density (%)	17.3 ± 2.1*	18.0 ± 2.0*	16.7 ± 0.6*	18.7 ± 1.5*	<20%
Compactibility (kg)	4.60 ± 0.21*	4.73 ± 0.17*	4.70 ± 0.10*	4.75 ± 0.10*	4-8 kgs
Granule density (g/mL)	0.4977 ± 0.0137	0.4949 ± 0.0067	0.5088 ± 0.0051	0.4958 ± 0.0075	-

*meet the requirements

^aUnited States Pharmacopeia and National Formulary²¹, ^bParrott¹⁴, ^cMohrle²²

weight difference was obtained after the granules were filled up into a measurable flask till the volume reached 100 mL.

Granule density (g/mL)

$$= \frac{(\text{weight of granules \& flask} - \text{weight of empty flask})}{\text{volume of measurable flask}}$$

Preparation and physicochemical test of effervescent tablet

The obtained granules were mixed with bicarbonate sodium, aspartame, flavor, and PEG600 at 25 °C until the mixture was homogenized. The mixture was subsequently pressed in a single punch machine at 40-50% RH (relative humidity).

Weight variation

Twenty tablets were weighed discretely, and the weight mean was compared with each other to check the variation of the tablets. Herein, the deviation of the two tablets should have not more than the limit of the pharmacopeia weight¹³.

Thickness and diameter variation

Twenty tablets were selected randomly and each was examined for the thickness and diameter.

Hardness

A tablet was selected and placed in the middle perpendicularly toward the hardness tester. The hardness level was scaled during the tablet breaking process mechanically¹⁴.

Effervescent time

A tablet was randomly selected and put into a glass of 100 mL water. The dissolved tablet was subsequently evaluated using stopwatch until a clear solution was obtained.

RESULTS AND DISCUSSION

Oral pharmaceutical dosage form remains popular route of the drug administration regardless of the several drawbacks which need to be unraveled i.e. causing slow absorption, low acceptance due to the bitter taste and even peculiar odor (i.e. antibiotics and natural extract based-tablet), frequent compliance problem on pediatric and geriatric patients, and the delayed action of onset¹⁰. On the other hand, natural extract draws massive attraction as an alternative towards conventional drugs owing to their safety and efficacy, despite of the unpleasant appearance, odor, and taste. To solve so, the advanced pharmaceutical dosage form i.e. effervescent tablet (Fig. 2a) was successfully formulated for the selected herbal (i.e. MOL) corresponding to a breakthrough in oral based-herbal drug formulation giving benefits in rapid adsorption, friendly use for majority

patients due to instantly dissolved in water, widely accepted by maternal who have symptom nausea vomiting in their first trimester of their pregnancy attributable to its *yummy* taste.

A part of the preparation of herbal extract, the maceration was used as primary extraction procedure owing to its simplicity and ability to yield adequate alcoholic extract of the MOL leaves. Herein, 70% alcohol was selected as the solvent throughout the extraction in order to obtain the desired phytochemical compounds such as the essential oil, steroidal alkaloid, glycoside, tannin, and phenol¹⁵. The obtained MOL extracts were subsequently identified as brownish viscous solutions with peculiar odor and bitter taste (Fig. 1a). In total, about 26.08% of extract was yielded according to the equation below while *a* and *b* correspond to the final mass upon extraction and initial mass prior to extraction, respectively.

$$\text{Extraction yield/rendement} = \frac{a}{b}$$

At first, four formulas were prepared according to the variation of acid-base and flavoring agents (Table 1). The results show that the best acid-base compositions are 1:2 and 1:3 due to better characteristic of granule mass and compatibility. The acid component selected herein are the citric acid and tartaric acid with regards to the suitable granule characteristic as described in previous reference¹⁶. Indeed, orange and strawberry flavors were selected to amend the taste of formulation because of their acceptance and popularity among Indonesians and was commonly used by previous similar research on effervescent^{10,17}.

The used dose of MOL leaves extract was reported on literature¹⁸ in which the given of 100 g Moringa's dry leaves in a week, partly divided into three dosage forms for three months, could potentially increase the hemoglobin concentration for the breastfeeding women suspected to anemia. However, this particular treatment is not able to restore the ferritin levels for those subjects. Therefore, it can be concluded that the daily dose of Moringa's leaves extract is 4.76 g/day. In regard to the total yield of the extract, the daily dose was then definitively determined as 1.2 g/day.

The wet granulation method was judiciously employed in producing the effervescent granules of *Moringa* leaves extract in order to ensure the following properties: homogeneity, ease to compression, and well uniformity of mass and active substances over each tablet¹¹. Controlled

Table 3: Tablets characteristics for F₁₋₄ in regards of acids-base amount variation.

Physical properties	F ₁ (mg)	F ₂ (mg)	F ₃ (mg)	F ₄ (mg)	Ref. ^{a,b,c}
Weight variation (%CV)	0.811*	0.837*	0.892*	0.889*	<5
Thickness variation (%CV)	0.889*	0.914*	1.195*	1.046*	<5
Diameter variation (%CV)	0*	0*	0*	0*	<5
Hardness (kg)	4.73 ± 0.12*	4.77 ± 0.06*	4.60 ± 0.10*	4.60 ± 0.17*	4-8 kgs
Effervescent time (s)	75 ± 5*	76 ± 4*	76 ± 2*	75 ± 3*	60-120 s

*meet the requirements

^aUnited States Pharmacopeia and National Formulary²¹, ^bParrott¹⁴, ^cMohrle²²

circumstance is essential during the tablet production. Since these particular products are very sensitive to temperature and moisture, the relative humidity should be maintained at 20% or less than the temperature of 21°C. However, the 25% RH and 25°C are sufficient to avoid instability of the tableting process¹¹ and to prevent auto-granulation or adhesion of effervescent tablets into the pressing machine by means of absorbed moisture^{17, 19}. In this study, the RH of the laboratory was recorded at 40-50%, therefore the mixing process of acid-base compositions was augmented prior to compression.

The physical properties of the pre-compression stage (i.e. granules) merely determine the successful tableting process of the effervescent. Herein, the granular properties evaluation included moisture test, angle of repose, flowability test, tapped density, compactibility, and granule density test (Table 2).

The water content of all formulas was greater than 2%, therefore it may complicate the tablet compressing. This is possibly due to the citric acid and tartaric acid which are hygroscopic²⁰, causing higher water content of the effervescent granule. In order to diminish the water content, the granule was then further dried using Fluid Bed Dryer, reaching <2% water content. For the drying time, one hour was not adequate to formulate the active substances, citric acid, and dry tartaric acid. Consequently, this procedure was set to be more than an hour till the remained water content was accomplished.

The angle of repose (Θ) evaluation shows that all the formulas are very well concordance with the requirements. Its magnitude shows the cohesiveness and friction within the particles. Additionally, the ratio difference between citric acid and tartaric acid (10:1) of the formulation also indicates no variation in the particle cohesivity.

The flowability test of 100.00 g granules shows that all formulas were capable to meet the general requirement (i.e. <10 s). Citric acid releases the crystalline water which enables to bind the neighboring particles to form a larger granule. Larger granules will flow faster due to the influence of gravity. Herein, F₁ and F₂ require a greater citric acid than F₃ and F₄, yet the flowability of F₁ and F₂ remain slower than the others.

The study of the tapped density demonstrates that all formulas had <20% tap index suggesting that four formulations have a virtuous flowability. The smaller tapped index, the better flowability is. The formula with a larger composition of tartaric acid produces a smaller

granule mass therefore when the small granule particle can fill the granular slit causing a decrease in the granule volume. Here, F₁ and F₂ required a greater tartaric acid. However, the tapped index over four formulas indicates no difference.

Further physical assessment remains to be compactibility test, in which all formulas yielded an acceptable hardness of 4-8 kg, suggesting no differences over all formulations. The granules with a good compactibility produced tablets with satisfactory hardness. Instead, the granule density of all formulations also showed no difference implicating that the particle density within the all formulas (in terms of the ratio of citric acid: tartaric acid) remains reliable.

The compliance granule was then mixed with the rest of materials and compressed using tablet machinery. The effervescent tablet was designed at 3,350 mg weight. The physical properties of the resulting tablets were subsequently evaluated to ensure their acceptance criteria. Physical properties evaluation included weight and size (rather 'thickness and diameter') variation, hardness, and effervescent time. The result was thoroughly resumed in Table 3.

Weight variation directly associates with the uniformity of active substances in tablets affecting the consistency of their therapeutic effects. The result of weight variation assay shows that all formulas comprised less than 5% coefficient of variation (CV), while F₁ remains the smallest. It means none of the tablets weighed more than 5% from the average weight, thus can be concluded to concordance with the range of United States Pharmacopeia²¹. Meanwhile, the variation of the thickness and diameter also indicate dependable results which are still acceptable in regard to pharmacopoeia standard²¹. Further, the hardness of the tablets is in line with the standard, implicating that the resulting tablets enable to resist from either physical or mechanical pressure.

Effervescent time is such an important parameter determining CO₂ release (Fig. 2b) in effervescent tablets. The effervescent times of all formulations were less than two minutes and thus, all were within the range mentioned in pharmacopoeia standard²¹. All formulas demonstrated effervescent time within 70-80s.

Finally, a panel test was conducted involving several participants to evaluate the two-foremost issues in effervescent, i.e. taste and color. As mentioned earlier, the bitter taste and unpleasant color of plant extract are major problems for the herbal-based medicine. Hence, the use of

flavoring agent was necessary to improve the final composition and to enhance the patient's acceptance¹⁰. In this study, the additions of two types of lemons and two types of strawberry flavors were not able to mask the bitter taste of the final product. This may be due to that the extract was taken using alcohol as solvent and consequently, only the polar active substance was sought out. Tannin and phenolic contents are putatively responsible for the bitter taste of the extract. Tannin, a polymer of phenolic or flavonoid, provided in the form of hydrolyzed or its origin in nature. The hydrolyzed tannin called by proanthocyanidin, is a main flavonoid's polymer causing a bitter taste in plants, commonly used to protect them from predators²³. This, however, affects the final taste and appearance of the formulated effervescent tablets. Future works can be directed towards the use of powerful bitter masking in the formulation such as chitosan-cyclodextrin which was previously reported to significantly attenuate the bitterness of natural extract²⁴. Chitosan remains as a biodegradable polymer that has been widely used in biomedical and drug delivery applications²⁵ while cyclodextrin is foremost a bitter masking-agent used in food and pharmaceutical products. Other bitter masking-agents may be considered including wide-ranging polymers and surfactant, thoroughly reviewed by Coupland and Hayes²⁶.

CONCLUSIONS

The first report on MOL-based effervescent product prepared using wet granulation method has been successfully conducted. The formulation was designed with 1:2 and 1:3 acid-base variations, while lemon and strawberry flavors were employed as the masking agent to conceal the bitter taste of the final product. In general, all formulas yielded acceptable physical properties of either granules or tablets. The variation of acid-base ratios showed no remarkable effect toward the physical properties of both. On the other hand, the addition of lemon and strawberry flavors cannot be employed since they are unable to mask the bitter taste of the natural extract in which phenolic content is likely the 'culprit' for the bitter taste. The use of powerful bitter masking-agent may be advantageous as the future directions of the study.

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