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Optimization of Mannitol-Sucrose Mixture in Lozenges Containing Temu Ireng, Curcuma, Sand Ginger, and Ginger Using the SLD Method

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Abstract.*Reduced appetite, diarrhea, cough, and joint pain are common health issues. Traditional medicinal plants such as Temu Ireng, Curcuma, Sand Ginger, and Ginger have been used to treat these conditions. This study aims to optimize the formulation of lozenges containing these plants using a combination of mannitol and sucrose as excipients through the SLD (Simple Lattice Design) method. Five formulations with varying ratios of mannitol and sucrose (FI = 75:25, FII = 25:75, FIII = 100:0, FIV = 0:100, FV = 50:50) were prepared using wet granulation. Granule physical properties were evaluated, and the optimum formulation was identified using statistical analysis including normality tests and one-sample t-tests. The results indicated that FI (mannitol 75%, sucrose 25%) provided the most desirable characteristics, with excellent granule flow, compressibility, and uniformity in lozenge quality. This research contributes to the development of herbal lozenges with optimized excipient combinations, enhancing the efficacy and quality of traditional medicine products.*

Keywords: *Lozenges; Mannitol-Sucrose; Optimization; SLD Method*; *Wet Granulation*

1. INTRODUCTION

Health issues such as reduced appetite, diarrhea, cough, and joint pain significantly affect the quality of life. These conditions, if not treated properly, can lead to further health complications and a decline in daily productivity. While synthetic drugs are commonly used to manage these symptoms, they often come with side effects, prompting many to seek alternative treatments. In this context, traditional medicinal plants offer promising therapeutic benefits with fewer adverse effects[1]. Among these health issues, diarrhea is particularly concerning as it is characterized by abnormal discharge of feces with increased volume, consistency, and frequency, sometimes accompanied by blood or mucus, which can lead to dehydration if left untreated[2] . Similarly, coughing is a natural reflex that helps clear the respiratory tract of mucus or foreign particles, playing an essential role in maintaining respiratory health across all age groups[3]. Joint pain, on the other hand, is often associated with inflammation, characterized by swelling, redness, heat, pain, and restricted movement, significantly impairing mobility and quality of life when multiple joints are affected[4]. These interconnected health problems highlight the need for comprehensive treatment approaches that address both symptoms and underlying causes.

In Central Java Province, the government has implemented measures to reduce stunting as outlined in Governor Regulation No. 34/2019 on Accelerating Stunting Prevention, focusing

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on eight convergence actions. One of these actions involves analyzing the stunting reduction program with specific nutritional interventions, particularly targeting the first 1,000 days of life[5].

The treatment of reduced appetite, diarrhea, cough, and joint pain involves both synthetic and herbal remedies. Synthetic drugs such as glucocorticoids, magesrol, and cyproheptadine are known to stimulate appetite[6], while ORS and norit are commonly used for diarrhea. Cough treatments include OBH and bromhexine[7]. and pain relief often involves paracetamol, methampyrone, and diclofenac sodium diclofenac sodium [8]. In addition, medicinal plants like Temu Ireng, Curcuma, Sand Ginger, and Ginger are widely used for these conditions.

Temu Ireng (*Curcuma aeruginosa* Roxb) contains essential oils that can stimulate appetite by enhancing peristaltic movement, which facilitates nutrient absorption and supports digestive health. This function complements the benefits of Curcuma longa (*Curcuma xanthorrhiza* Roxb), traditionally used to treat appetite loss, constipation, and joint pain, as it contains xanthorrhizol and curcumin—compounds known to act as appetite enhancers and anti-inflammatory agents that alleviate gastrointestinal discomfort and musculoskeletal inflammation [9]. Xanthorrizol is one of the components of essential oil in temulawak rhizome which gives an effect as an appetite enhancer[10]. Temulawak rhizomes generally have characteristics as pain relievers, because temulawak contains curcumin compounds [11]. urthermore, Sand Ginger (*Kaempferia galanga* L), rich in flavonoids, saponins, and essential oils, extends these therapeutic effects by addressing respiratory issues such as cough and nausea while also relieving joint pain through its anti-inflammatory properties.

Sand ginger (*Kaempferia galanga* L) is known to contain chemical compounds such as flavonoids, saponins, polyphenols, and essential oils. Empirically, sand ginger is used for coughing or itching in the throat, flatulence, feeling nauseous, catching a cold, muscle pain, and increasing appetit [12]. The content of essential oil Linoleoyl chloride and 2-propenoic acid, 3-(4-Methoxyphenyl) and ethyl-ester contained in sand ginger has carminative properties [13]. Active compounds in sand ginger that act as antibacterials that can cure diarrhea include ethyl p-methoxycinnamate and ethyl cinnamate sinamat [14]. Complementing these benefits, Ginger (*Zingiber officinale* Roxb) contains bioactive compounds like shogaol and gingerol, which not only provide antiemetic and antitussive effects but also enhance overall respiratory and digestive health, creating a synergistic effect when combined with the other medicinal plants.

Ginger (*Zingiber officinale* Roxb) is a plant that has a unique taste and distinctive aroma that is favored by all parties [15]. The components contained in ginger that function as

antiemetics are shogaol and gingerol [16]. The use of ginger plants used by the community serves to overcome respiratory problems such as dry cough and contributes as antitussive activity[17]. This study aims to optimize the formulation of lozenges containing these medicinal plants to enhance their therapeutic potential, improve patient compliance, and ensure product quality through the SLD method.

Preliminaries or Related Work or Literature Review

The formulation of lozenges containing traditional herbal ingredients has gained increasing attention due to the demand for natural remedies with enhanced palatability and consumer compliance. Various studies have focused on herbal-based formulations, particularly those incorporating Curcuma xanthorrhiza (temulawak), Curcuma aeruginosa (temu ireng), Kaempferia galanga (kencur), and Zingiber officinale (ginger), which are known for their pharmacological activities such as anti-inflammatory, antioxidant, and gastroprotective effects.

Purba et al. (2014) investigated lozenge formulations containing ginger extracts and emphasized the importance of sweetener selection in masking the pungency and enhancing organoleptic properties [18]. Prasetyo and Mufrod (2015) developed herbal lozenges using Curcuma species and suggested that the matrix composition significantly affects disintegration and hardness[19]. Youstina Dwi Rusita (2016) focused on the role of excipients in herbal tablet formulations, highlighting how sugar-based carriers influence both drug release and stability[20]. Similarly, Ernawati et al. (2017) examined lozenges containing Kaempferia galanga and reported that the combination of mannitol and sucrose can impact the mechanical and sensory characteristics of the final product[21].

However, most of these studies did not utilize a systematic design approach to optimize the sweetener composition. The application of a Simplex Lattice Design (SLD) for excipient optimization, particularly in the context of sweetener ratios such as mannitol and sucrose, remains underexplored. Moreover, previous research often focused on individual herbal extracts rather than a synergistic combination of multiple rhizomes with complementary health benefits.

The present study addresses this gap by applying the SLD method to optimize the ratio of mannitol and sucrose in lozenges containing a polyherbal blend of temu ireng, temulawak, kencur, and ginger. Unlike earlier formulations that used fixed sweetener concentrations, our study systematically investigates the impact of varying mannitol-sucrose proportions on key quality attributes such as hardness, friability, and taste acceptability. This integrated formulation strategy is expected to yield a more effective and consumer-friendly lozenge product.

2. PROPOSED METHOD

The materials used include mannitol, sucrose, PVP, magnesium stearate, talcum, temu ireng rhizome powder, temulawak, sand ginger and ginger. The equipment used includes analytical scales (Matrix), blender, oven (Memmert), measuring cup (Pyrex), beaker glass (Pyrex), glass funnel (HERMA), mesh sieve no 12 and 16 (ABM), mortar and stamper, hot plate / magnetic stirrer (Lab. Companion HP-30001). Companion HP-30001), porcelain cup, tapped density (Omron), manual tablet machine, friability tester (CS-2), hardness tester (YD -1) and disintegrator tester (Omron E5C4). The procedures carried out in the study include collecting materials and making rhizome squezee, formulating based on the SLD method, making granules, testing the physical properties of granules, confirming the optimum formulation, making lozenges, and finally testing the physical properties of lozenges.

Preparation of rhizome squeezed

The rhizomes used are fresh rhizomes, then the rhizomes are peeled and rinsed with water and cut with a thickness of 2-3 mm. Then mashed without adding water until smooth and then squeezed. After that, it was heated on a water bath for 15 minutes at 90ºC and stirred occasionally[7].

Formulation based on SLD method

The active ingredients used in this study were mannitol and sucrose as fillers. Comparison of the concentration of the two active ingredients from the design expert software version 13 and 5 formulations were taken. The results of the mannitol and sucrose concentration comparison obtained from SLD include :

FI = mannitol 75% : sucrose 25%

FII = mannitol 25% : sucrose 75%

FII = mannitol 100% : sucrose 0%

FIV = mannitol 0% : sucrose 100%

FV = mannitol 50% : sucrose 50%

Granule Preparation

In this study using the wet granulation method, where the tablet formulation has been determined, weighing the ingredients according to each formulation is carried out. Then mix mannitol and sucrose, after the ingredients are homogeneous added with PVP mucilago

dissolved with rhizome squezeed as a binder gradually until a moist mass is formed. The mass will be sifted with mesh sifted number 12, then the granule obtained is dried using an oven. The results of granule drying, then sieved again using mesh sieve number 16 and test the physical properties of granules.

Granule Physical Properties Test

The resulting granules were then subjected to granule evaluation including moisture content, flow time, stationary angle, as well as compressibility. The profile of the properties of the granule mixture can be determined through the SLD approach based on the equation Y = a (A) + b (B) + ab (A) (B), where :

Y = response (experiment result)

= part of the component (Mannitol)

= part of the component (Sucrose)

Confirmation of Optimum Formulation

The optimal formulation was confirmed by analyzing the data on the physical properties of the granules, after which the normality test was carried out using the Shapiro-Wilk method ($p>0.05$) and the results showed that the data was normally distributed. Confirmation of the optimum formulation is done using One Sample T-Test if the normality test produces normally distributed data [22].

Preparation of Lozenges

After the granule has tested the physical properties of the granule, talc and magnesium stearate lubricants are added and then forged with a manual tablet press. After the tablets had been forged, physical properties of lozenges were evaluated.

Tablet Physical Properties Test

The printed lozenges were then tested for physical properties of the tablets. To avoid other factors that may affect the evaluation results, tablets that have been molded can be immediately evaluated physically so as not to impact the evaluation results. Examination of physical lozenges includes organoleptic test, weight uniformity test, size uniformity test, hardness test, friability test and disintegration time test [23].

3. RESULTS AND DISCUSSION

This study was aims to determine the optimum formula for combination of mannitol and sucrose fillers in the preparation of temu ireng, temulawak, sand ginger and ginger squezee lozenges using the SLD method. The samples used were rhizomes from temu ireng, temulawak, sand ginger and ginger plants from Bedagas Village and Wlahar Village, Purbalingga Regency. The plants were determined to ensure the accuracy of the samples used. The determination was conducted in the biology laboratory of the Faculty of Pharmacy at Muhammadiyah Purwokerto University..

Preparation of Rhizome Squeezed, Mannitol-Sucrose Concentration Based on SLD Method, Examination of Granule Physical Properties Test, SLD Result Formulation Equation Approach, Optimum Formula Determination, Optimum Formula Confirmation Results, and Physical Properties Test of Lozenges

The first research procedure is making rhizome squeezed. The total weight of the rhizomes used was 54 grams of rhizomes that had been mashed and then squeezed to produce 26 ml of water squezee. The active ingredients used in this study were mannitol and sucrose as fillers. Comparison of the concentration of the two active ingredients from the design expert software version 13 and 5 formulations were taken.

Tabel 1. Granule formulation with mannitol-sucrose mixture based on SLD

Formulation component	Weight of ingredients in formula (mg)				
	I	II	III	IV	V
Fresh rhizome	54	54	54	54	54
Mannitol	982,5	327,5	1310	0	655
Sucrose	327,5	982,5	0	1310	655
PVP	30	30	30	30	30
Mg Stearat : Talk	45	45	45	45	45
Weight of each tablet	1439	1439	1439	1439	1439

Description :

FI = mannitol 75% : sucrose 25%

FII = mannitol 25% : sucrose 75%

FII = mannitol 100% : sucrose 0%

FIV = mannitol 0% : sucrose 100%

FV = mannitol 50% : sucrose 50%

Data from the physical properties test of rhizome squezeed granules from the five formulas are shown in the following **table 2**.

Tabel 2. Physical properties of rhizome squeezed granule

No	Inspection	F I	F II	F III	F IV	F V	Standar
	Humidity Content (%)	1,13	1,0	1,4	0,73	1,2	≤5
	Flow Time (gr/detik)	7,7	6,98	8,43	6,17	7,71	<10
	Angle of Silence (º)	31,2	29,38	32,69	29,55	31,15	25-40
	Compressibility (%)	5,10	3,36	13,94	3,02	7,69	<20

From the test results of granule moisture content based on the SLD approach, the equation is obtained, namely: Y = 1.4 (A) + 0.73 (B) + 0.54 (AB). For the flow time test based on SLD, the equation is obtained, namely = Y = 8.43 (A) + 6.17 (B) + 2 (AB). The results of the granule dwell angle test equation based on SLD obtained the equation, namely = Y = 32.69 (A) + 29.55 (B) + 0.12 (AB). For the granule compressibility test based on the SLD approach, the compressibility equation is obtained, namely = Y = 13.94 (A) + 3.02 (B) - 3.16 (AB). From the equation approach based on the SLD of each component, it will be known the amount of response that will be generated.

The optimum formula was selected based on the largest response value. In the calculations carried out formulas with a ratio of mannitol 75%: sucrose 25% is the optimum formula. In normality testing, a significant value was obtained, where the moisture content test had a value of 0.298, flow properties 0.584, angle of repose 0.203 and compressibility 0.879 ($p>0.05$). From the available data, it can be concluded that the test data for the physical properties of the optimum granule formulation are normally distributed. The results of the One Sample T (T-Test) test obtained mean that there is no significant difference between the results of the optimum formulation granule physical properties test and the SLD prediction results.

Tabel 3 Results of inspection of physical properties of lozenges

No	Inspection	Replication I	Replication II	Replication III
	Weight Uniformity Average (mg)	615	614,5	613, 5
	Size Uniformity (cm) (Diameter ± Thickness)	0,79 ± 0,96	0,79 ± 0,96	0,79 ± 0,96
	Hardness (kg)	1,52	1,54	1,55
	Friability (%)	0,23	0,24	0,25
	Disintegration Time (minutes)	8,08	7,53	7,65

Inspection of the physical properties of the optimum formulation lozenges in each replication produces lozenges with an elongated round shape, yellowish white in color, a

distinctive aromatic odor and has a sweet and cold taste in the mouth. Uniform weight uniformity, in the size uniformity test of replication 3 produced uniform size uniformity with a diameter of 0.79 cm and a tablet thickness of 0.96 cm, in the inspection of tablet hardness produced an unfavorable hardness value of less than 4kg, in the inspection of the smallest suction tablet fragility contained in replication I of 0.23%, while in the inspection of the fastest suction tablet destruction time in replication II with a time of 7.53 minutes.

Compound content in rhizome samples that can improve appetite, diarrhea, cough, and joint pain

The temu ireng plant has properties as an appetite enhancer, because it contains essential oils which have the potential to reduce fat so that it can increase appetite [24]. In addition, the curcumin content in temu ireng plays a role in relaxing the intestinal muscles in the gastrointestinal tract, thereby supporting the process of food digestion by increasing gastric performance. This causes the stomach to feel empty which will then send signals to the brain, having an impact on increasing or causing hunger [25].

The use of temulawak plants in this study because temulawak contains xanthorrizol to be a source of appetite enhancing supplements due to choleretic properties. This occurs by accelerating the process of gastric emptying and increasing the digestion and absorption of fat in the intestine. In addition, xanthorrizol also stimulates the secretion of various hormones that play a role in increasing appetite [26] In general, temulawak has characteristics as a pain reliever or pain because it contains curcumin compounds. One of the benefits of curcumin compounds serves to relieve pain in the joints. Curcumin can minimize pain by blocking cyclooxygenase activity which results in the formation of prostaglandins[27].

Sand ginger can be used to restore energy to a tired body, functions as a tonic, and has carminative properties to overcome flatulence. Substances such as essential oils, Linoleoyl chloride, 2-propenoic acid, 3-(4-methoxyphenyl), and ethyl esters found in sand ginger rhizomes function as carminatives, which help remove gas from the intestines [28]. In addition, these compounds have analgesic and anti-inflammatory effects, so they can prevent inflammation in the digestive system and support better food digestion. Active compounds contained in sand ginger include ethyl p-methoxycinnamate and ethyl cinnamate, which have antibacterial activity that can inhibit the growth of microbes *S. aureus, B. subtilis, E. coli, and P. Aureugenosa* [29].

Gingerol and shogaol compounds contained in ginger have anti-nausea properties. 6-gingerol and 6-shogaol compounds are able to inhibit the reaction of 5-HT3 receptors that

contribute to nausea and vomiting [30]. e use of ginger plants is used by the community to overcome respiratory problems, such as dry cough and acts as a cough inhibitor. Gingerol and shagaol compounds are spicy compounds in ginger that function through a common group of nerve receptor cells, namely vanilloid receptors [31].

Comparison

Most existing studies on herbal lozenge formulations have employed conventional trial-and-error methods in determining excipient composition, especially sweeteners. For example, Purba et al. (2014) and Ernawati et al. (2017) used fixed ratios of mannitol and sucrose without exploring the interaction effects between these components[18] [32]. While their research demonstrated that sweeteners influence sensory and mechanical properties, the optimization process was neither systematic nor statistically validated. In contrast, this study applies a Simplex Lattice Design (SLD) approach, which allows for the modeling of mixture interactions and the identification of an optimal sweetener ratio based on multiple response variables. The use of SLD enables more precise control and prediction of formulation outcomes, providing stronger statistical confidence compared to prior empirical approaches. Furthermore, previous studies such as Prasetyo & Mufrod (2015) and Rusita (2016) primarily focused on single herbal extracts or limited binary combinations, whereas our formulation integrates four synergistic rhizome-based ingredients (temu ireng, temulawak, kencur, and ginger), enhancing both therapeutic potential and formulation complexity [19], [20]. This multi-component herbal system, coupled with a design of experiment (DoE) methodology, distinguishes our work from existing literature. Our contribution lies not only in the novelty of ingredient combination but also in the application of an optimization framework that ensures reproducibility, scalability, and product quality in herbal lozenge development.

CONCLUSIONS

From the results of the research conducted, it is concluded that the formula optimization with SLD prediction obtained the most optimum formulation is formulation I with a ratio of mannitol 75% and sucrose 25%, as evidenced by the results of the granule physical properties test including moisture content test 1.13 ° C, flow time 6.98 grams / second, dwell angle 31.5° and compressibility 5.1% which meet the requirements of good granule physical properties. And in the data analysis, the optimum formulation has a significant normality test value, namely with a value> 0.05, which means that the test data for the physical properties of the optimum formulation granules are normally distributed and the One Sample T-Test test

produces a value that is not significantly different between the test of the physical properties of the granules and the predicted value of SLD.

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