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Formulation and Characterization of Mucolytic Nanosuspension of Iler Leaf Extract (*Coleus atropurpureus L. benth.*) with Sodium Alginate as a Suspending Agent

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Abstract

Iter leaves (*Coleus atropurpureus L. Benth.*) are known for their mucolytic properties, which help to thin phlegm. However, poor absorption and bioavailability of some active components in herbal extracts, due to their large molecular size and inability to penetrate lipid membranes, limit their therapeutic potential. This research aimed to develop a nanosuspension formulation with fine particles to improve dissolution rate and bioavailability. An experimental method with a Non-Equivalent Control Group Design was used. Nanosuspensions were formulated using iler leaf extract with sodium alginate as the suspending agent. Characterization tests included organoleptic evaluation, pH, density, viscosity, redispersion, particle size distribution, zeta potential, and sedimentation volume. The results showed that all formulations met the required quality standards. pH ranged from 6.06 to 6.14 ($p < 0.001$), density ranged from 1.015 to 1.044 g/ml ($p < 0.01$), viscosity ranged from 38.2 to 93.8 cPs ($p < 0.001$), and redispersion testing confirmed 100% redispersion without clumping after three treatments. Particle size distribution ranged from 69.2 to 898.8 nm ($p < 0.001$), zeta potential ranged from -33.15 to -37.38 mV ($p = 0.35$), and sedimentation volume ranged from 0.95 to 0.98 ml. This research has implications implying that nanosuspensions of iler leaves, optimized with varying concentrations of sodium alginate, offer a promising strategy to improve the bioavailability and therapeutic efficacy of mucolytic herbal preparations. These results open up opportunities for further research regarding in vivo evaluation, development of combination therapies, and production scale-up to enable industrial application and commercialization in the pharmaceutical market.

Keywords: Iler Leaf Extract, Mucolytic, Nanosuspension, Sodium Alginate.

INTRODUCTION

The iler plant (*Coleus sp.*) is a medicinal plant which is also an ornamental plant that is quite popular with the people of Indonesia. From various studies that have been conducted, iler leaves (*Coleus atropurpureus L. benth.*) have properties as mucolytics or cough medicines that function to thin phlegm. In research conducted by (Herdaningsih & Kartikasari, 2022), iler leaf extract (*Coleus atropurpureus L. benth.*) at a concentration of 3-6% has mucolytic activity equivalent to the positive control (acetylcysteine 0.2%). Based on these results, iler leaf extract can be used as an alternative in the treatment of cough (Herdaningsih & Kartikasari, 2022). However, some of the active components present in herbal extracts are unable to pass through lipid membranes because they have a very high molecular size or poor water solubility, resulting in low absorption and poor bioavailability (Fadlilah & Gozali, 2022).

One of the important drug delivery systems to be developed today is nanosuspensions. Nanosuspensions are described as very fine particles, biphasic, solid particles separated in an aqueous carrier and stabilized by surfactants with reduced particle size, with the aim of making better dissolution rates and increasing bioavailability. In addition to increasing bioavailability, nanosuspensions can also increase absorption and biological action because nanosuspensions have good dissolution rates and drug saturation (Fadlilah & Gozali, 2022). The diameter of the suspended particles is less than 1 μm, which is 0.1 nm-1000 nm.

One thing that needs to be considered in developing a suspension dosage form is the suspending agent. Of the many types of suspending agents used for nanosuspension technology, sodium alginate is one of the anionic polymers that has been widely studied in the controlled release of pharmaceutical preparations with other polymers due to its low cost (Frent et al., 2022).

Despite the growing body of research on nanosuspensions, there remains a theoretical gap in understanding how variations in suspending agents, particularly sodium alginate, influence the physicochemical properties and stability of herbal-based nanosuspensions. Additionally, the mechanisms by which nanosuspensions enhance the bioavailability and therapeutic efficacy of high-molecular-weight herbal compounds require further exploration. Addressing these gaps is crucial to optimize the formulation and ensure effective drug delivery.

In practical terms, the development of nanosuspensions faces challenges in achieving consistent particle size reduction, ensuring stability during storage, and maintaining the desired physicochemical properties. Furthermore, scaling up nanosuspension production for commercial applications while retaining quality and efficacy remains a significant obstacle. These practical challenges underline the importance of systematic formulation studies and characterization to facilitate the successful implementation of nanosuspension technology in herbal medicine.

Based on the above considerations, this research aims to formulate and characterize mucolytic nanosuspensions from iler leaf extract (*Coleus atropurpureus L. Benth.*) using sodium alginate as a suspending agent. The goal is to develop an effective drug delivery system for phlegm thinners or mucolytics, addressing both theoretical and practical challenges in the field. So that the benefits in this research are to make a significant contribution in the pharmaceutical field, especially in the development of innovative and effective nanosuspension-based drug preparations. This research is expected to improve the efficacy of mucolytic drug delivery, extend the stability of the preparation, and optimize patient safety and comfort. In addition, another benefit is to open up opportunities for wider application of natural materials, such as iler leaf extract, as an alternative in modern pharmaceutical technology-based medicine. The results of this research are also expected to be a scientific reference for further research and have a positive impact on the pharmaceutical industry.

RESEARCH METHOD

The research method used in this research is the Quasy Experimental Design method with the Non Equivalent Control Group Design. The data collection instruments used in this research are a pH meter which is an instrument used to measure the pH of the preparation, a Stormer Viscometer is an instrument used to measure the viscosity or viscosity of the preparation, a Picnometer is an instrument used to measure density, then there are glassware such as test tubes and 10ml measuring cups used to conduct redispersion tests and

sedimentation volume, and the last is the Particle Size Analyzer (PSA) Malvern Zetasizer Pro (ZSU 300) is an instrument used to measure particle size distribution and zeta potential.

The types of qualitative data used in this research are organoleptic tests and redispersion tests. While the quantitative data used in this research are pH content test, density test, viscosity test, particle size distribution test, zeta potential, and sedimentation volume.

The tools used in this research are glassware (Pyrex, Herma), oven, blender, rotary evaporator (Dlab), analytical balance (ACIS AD-300i), Stormer Viscometer, Picnometer, pH meter, Particle Size Analyzer (PSA) Malvern Zetasizer Pro (ZSU 300), Overhead Stirrer, Hand Homogenizer, and Hotplate Stirrer (Thermo scientific). The materials used in this research are thick extract of iler leaf (Coleus atropurpureus L. benth.), phosphate-buffered saline solution pH 6, 70% ethanol, aspartame, sodium alginate, propylene glycol, propyl paraben, sodium thiosulfate, sodium chloride, distilled water.

Table. 1 Formulation of the preparation

Material	Formulation (%)			Material Function
	F1	F2	F3	
Iler Leaf Extract	6	6	6	Active Substance
Sodium Alginate	1	3	5	Stabilizer
Aspartame	1	1	1	Sweetener
Propylene glycol	15	15	15	Solvent
NaCl	0,05	0,05	0,05	Preservatives
Propyl Paraben	0,02	0,02	0,02	Preservatives
Sodium Thiosulfate	0,02	0,02	0,02	Thickener
Phosphate diluent pH6	0,8	0,8	0,8	pH regulator
Aquadest	Ad 100 ml	Ad 100 ml	Ad 100 ml	Solvent

a. Preparation of Iler Leaf Extract (*Coleus atropurpureus L. benth.*)

Collect 2 kg of iler leaves, then wet sorted by washing using running water until clean. The clean iler leaves are then dried using an oven. After drying, clean again from impurities that are still attached. The dried simplisia is then blended until it becomes powdered simplisia, then do the maceration process by putting all the powdered simplisia into a closed container and immersed in 300ml of 70% ethanol, then macerated for 3 days, after which every 24 hours the solvent is replaced by a new solvent. The filtrate was separated from the residue, then the residue was macerated again in 150 ml of solvent using the same method. This process is always carried out until the color of the resulting filtrate is constant. The filtrate is collected and evaporated using a rotary evaporator until it becomes a thick extract. (Utami et al., 2020).

b. Nanosuspension Formulation of Iler Leaf Extract (*Coleus atropurpureus L. benth.*)

Weigh all ingredients, dissolve sodium alginate powder with water as much as 7 times its weight in a mortar and allowed to expand. Tiler leaf extract was added little by little with the addition of water and propylene glycol, stirred until homogeneous. Sodium chloride and sodium thiosulfate were dissolved in water, then mixed into sodium alginate and iler leaf extract and stirred until homogeneous. Propyl paraben is dissolved in propylene glycol, mixed into sodium alginate which has been mixed with iler leaf extract, water, sodium chloride and sodium thiosulfate and stirred until homogeneous. Aspartame is dissolved into enough water by heating until homogeneous, after which it is mixed into the sodium alginate mixture of iler leaf extract and stirred until homogeneous. The remaining propylene glycol and phosphate dapar solution pH 6 were added to the

suspension preparation that had been mixed until homogeneous, (Muthmainnah, 2020). Add water up to 100%, then dispersed with a magnetic stirrer at 1000 rpm for 20 minutes, stirred with a homogenizer at 15,000 rpm for 10 minutes, after which it was put into a container. (Pınar et al., 2022). Then the evaluation and characterization of nanosuspension of iler leaf extract (*Coleus atropurpureus L. benth.*) (Dzakwan, 2020).

c. Organoleptic Test
   Organoleptic testing aims to assess and identify iler leaf extract nanosuspension preparations. Identification of iler leaf extract nanosuspension includes odor, color, and taste (Budiati et al., 2023).
d. pH Level Test
   pH testing is carried out using a pH Meter, which aims to determine the amount of acidity level in a preparation, whether it is in accordance with the provisions or not in accordance with the provisions (Wijaya & Lina, 2021)
e. Density Test
   The density test was conducted using a dry and clean empty 50 ml piconometer. (a). Then add distilled water into the pycnometer and measure the weight. (b) Nanosuspension of extract combination was put into the pycnometer and measured the weight. (c) The density of the extract formulation nanosuspension is determined using the following formula (Wijaya & Lina, 2021).

$$\rho \frac{c - a}{b - a} \, x \, \rho$$

f. Viscosity Test
   The viscosity test was carried out using a Stormer viscometer at a rotation speed of 30 rpm spindle no.1.
g. Redispersion Test
   The redispersion test is done manually with care, the bottle containing the formulation is shaken 10-13 times (Budiati et al., 2023).
h. Particle Size Distribution
   Each formulation was evaluated by optical microscope analysis using a 100x (10x10) ocular lens equipped with a camera. Particle size determination was done by measuring 100 particles from each formulation and categorizing the particle size (Muthmainnah, 2020).
i. Zeta Potential
   The zeta potential test of nanoparticles was carried out using a PSA (particle size analyzer) tool at 25°C. Zeta potential is a charge parameter between nanoparticles. Higher zeta potential values prevent aggregation (formation of larger colloids from smaller colloids). The requirement of zeta potential is ± 30 mV (Ambarwati & Rustiani, 2022).
j. Sedimentation Volume Test
   The extract nanosuspension was placed in a 10ml measuring cup and stored at room temperature protected from direct sunlight. The volume of extract nanosuspension introduced was the initial volume (Vo).

RESULTS AND DISCUSSION

Organoleptical Test

Table 2. Organoleptical Test Results

Formulation	Organoleptical Test		
	Smell	Color	Taste
1	Distinctive of iler leaf extract	Chocolate	Sweet
2	Distinctive of iler leaf extract	Chocolate	Sweet
3	Distinctive of iler leaf extract	Chocolate	Sweet

From the organoleptical test results above, the four formulas show the same results in terms of smell, color, and taste, namely having a distinctive smell of iler leaf extract (*Coleus atropurpureus L. benth*.), brown color, and sweet taste.

pH test

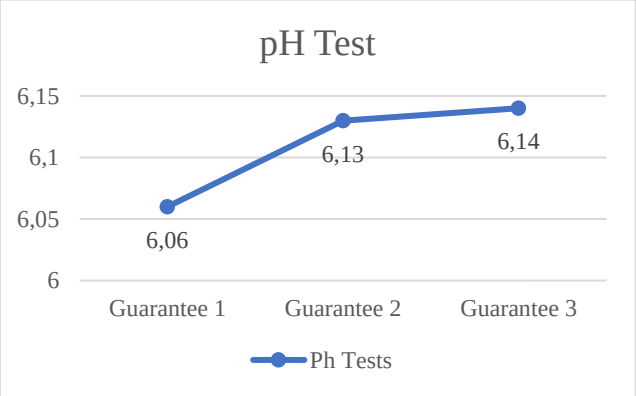

Figure 1. pH test graph

Table 3. pH Test Results

Formulation	Mean±SD	Specifications	Description
I	6,06±0,15	The optimum suspension pH is 5-6	Meet
II	6,13±0,01		Meet
III	6,14±0		Meet
p-Value	0,001[a]		

The pH test results obtained in formulation I amounted to 6.06, formulation II amounted to 6.13, and formulation III amounted to 6.14. In the results tested, the highest pH value was in formulation III of 6.14 and the lowest pH value in formulation I of 6.06. The above data were analyzed using the One-Way ANOVA test obtained a significance value of 0.001a ($p < 0.05$).

Density Test

Table 4. Density Test Results

Formulation	Mean (g/ml) ±SD	Specifications	Description
I	6,06±0,15	The optimum suspension pH is 5-6	Meet
I	1,015±0,11	The specific gravity of the preparation with water carrier should be more than 1.00 g/mL	Meet
II	1,025±6,03		Meet
p-Value	0,01[a]		

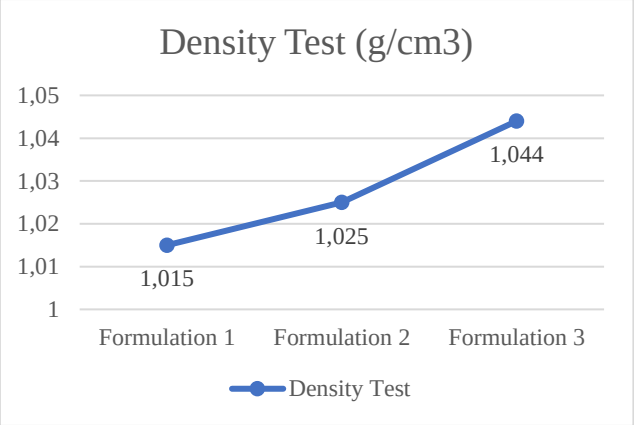

Figure 2. Density Test Chart

The density test results obtained in formulation I amounted to 1.015 g/ml, formulation II amounted to 1.025 g/ml, and formulation III amounted to 1.044 g/ml. In the results tested, the highest density test value was found in formulation III at 1.044g/ml and the lowest pH value in formulation I at 1.015g/ml. The above data was obtained by analyzing the One-Way ANOVA test with a significance value of 0.10a (p>0.05).

Viscosity Test

Table 5. Viscosity Test Results

Formulation	Average (cps)±SD	Specifications	Description
I	6,06±0,15	The optimum suspension pH is 5-6	Meet
I	38,2±1,44	The viscosity value of the suspension according to SNI is 37cP-396 cP.	Meet
II	63,0±1		Meet
p-Value	0,01[a]		

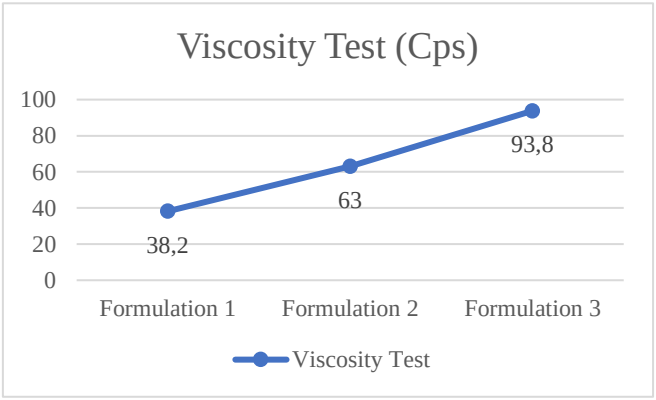

Figure 3. Viscosity Test Chart

The viscosity test results obtained in formulation I amounted to 38.2 cps, formulation II amounted to 63.0cps, and formulation III amounted to 93.8cps. In the results tested, the highest viscosity value was in formulation III of 93.8cPs and the lowest pH value in formulation I of 38.2cPs. The above data was obtained by analyzing the One-Way ANOVA test with a significance value of 0.001a (p <0.05).

Redispersion Test

Table 6. Redispersion Test

Formulation	Number of Treatments	%Redispersion	*Caking*
I	6,06±0,15	The optimum suspension pH is 5-6	Meet
I	3 times	100%	No *caking*
II	3 times	100%	No *caking*

The redispersion test results obtained with the number of revolutions to redisperse are 1x rotation (180º), the redispersion results of all preparations in sequence starting from Formulations I, II, and III are obtained 100% and there is no caking in the preparation when cornered.

Particle Size Distribution

Table 7. Particle size distribution results

Formulation	Average (nm)±SD	Specifications	Description
I	69,2±10,4	Nanosuspensions are colloidal dispersion systems containing drugs with particle sizes of 10-1000 nm.	Meet
II	146,9±21,7		Meet
III	898,8±137,0		Meet
p-Value	0,001[a]		

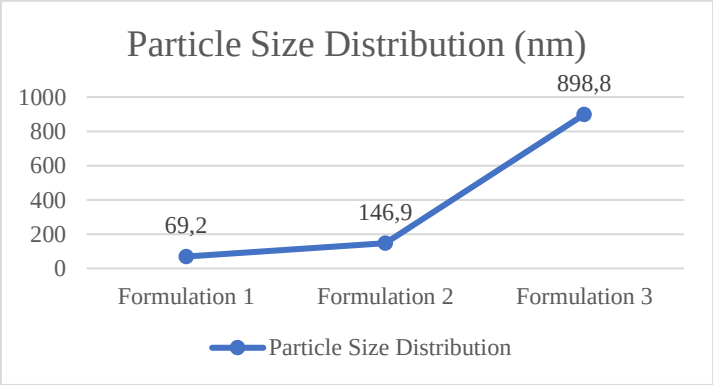

Figure 4. Particle size distribution graph

The results of the particle size distribution test obtained data on formulation I of 69.2nm, on formulation II of 146.9nm, and on formulation III of 898.8nm. In the results tested, the highest particle size distribution value was in formulation III of 898.8nm and the lowest particle size distribution value in formulation I of 69.2nm. Based on the results that have been tested, the three formulations all meet the requirements of the Nanosuspension preparation. The above data was obtained by analyzing the One-Way ANOVA test with a significance value of 0.001a ($p < 0.05$).

Zeta Potential

Table 8. Zeta Potential Results

Formulation	Average (-mV)±SD	Specifications	Description
I	-33,15±3,5	Nanoparticles with zeta potential values smaller than -30 mV and greater than +30 mV have higher stability.	Meet
II	-37,38±3,5		Meet
III	-36,59±3,5		Meet
p-Value	0,35[a]		

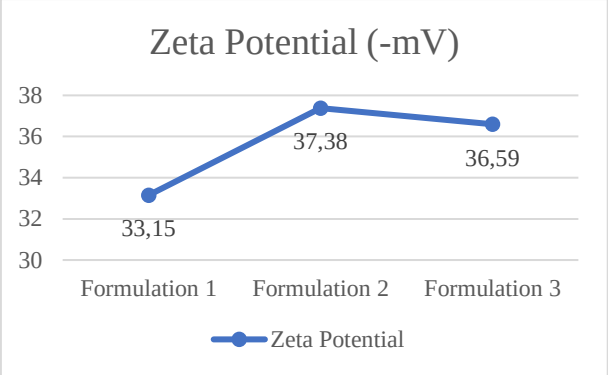

Figure 5. Zeta potential graph

The zeta potential test results obtained data on formulation I amounted to -28.53mV, on formulation II -37.38mV, and on formulation III -36.59mV. In the results tested, the highest potential zeta value is in formulation II of -37.38mV and the lowest potential zeta value in formulation I of -33.15mV. Based on the results that have been tested in a row into the requirements but almost meet the requirements, and in formulation II and formulation III the results obtained are in accordance with the existing requirements. The above data was obtained by analyzing the One-Way ANOVA test with a significance value of 0.35a (p>0.05).

Sedimentation Volume Test

Table 9. Sedimentation Volume Test Results

Formulation	Mean±SD	Specifications	Description
I	0,95±5,77	A good suspension sedimentation volume test has a price < 1 or > 1.	Meet
II	0,97±5,77		Meet
III	0,98±5,77		Meet
p-Value	0,033[a]		

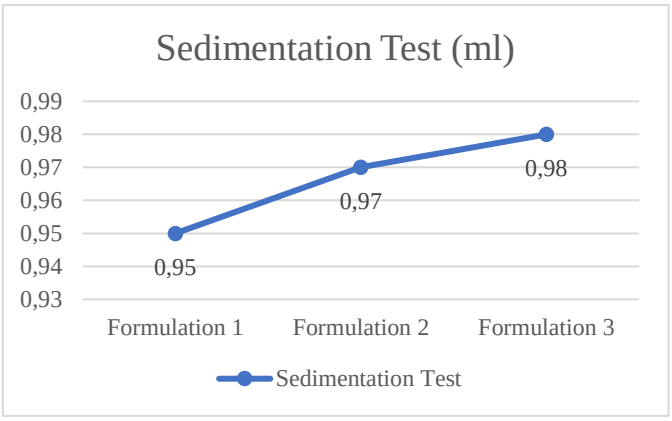

Figure 6. Sedimentation Test Chart

Discussion

This research begins with the extraction process of iler leaf (*Coleus atropurpureus L. benth.*) using the maceration method which is carried out for 3 days by soaking iler leaf powder (*Coleus atropurpureus L. benth*.). Then proceed with the formulation of Nanosuspension of iler leaf extract (Coleus atropurpureus L. benth.) using sodium alginate as a suspending agent which varies in different concentrations in each formula. The variation of sodium alginate concentration in formula I is 1g, formulation II is 3g, and formulation III is 5g.

Organoleptical Test

The results of testing the preparation of Nanosuspension of Iler Leaf Extract (*Coleus atropurpureus L. benth.*) in the three formulations obtained brown results and a distinctive odor of Iler leaves (*Coleus atropurpureus L. benth.*) in the preparation which is the result of Iler leaf extract (*Coleus atropurpureus L. benth.*), while the sweet taste in the preparation is obtained from the sweetener used in the formulation, namely aspartame.

From the results of the research that has been obtained, it shows that the three formulations are in accordance with the organoleptical provisions despite the different concentrations of sodium alginate used, this is because the difference in sodium alginate concentration from low to high does not significantly affect the color, odor, and taste of the Nanosuspension preparation of Iler Leaf Extract (*Coleus atropurpureus L. benth.*).

pH Level Test

In general, sodium alginate has a pH of 9-10, and pH values greater than 7 indicate alkaline properties (Putriyana et al., 2018). The pH test that has been carried out obtained suitable results at pH 6, this is due to the influence of the addition of phosphate dapar pH 6 in the formulation of making Nanosuspension of Iler Leaf Extract (*Coleus atropurpureus L. benth*.). However, in the preparations that have been tested there is a slight pH difference that is not significant but there is still a difference, and it can be seen that the higher the concentration of sodium alginate, the higher the pH value obtained, this result is in accordance with the statement that says that the pH properties of sodium alginate are alkaline (Abka-Khajouei et al., 2022)..

Density Test

Based on the results of density measurements, the average result obtained in formulation I was 1.015g/ml, formulation II was 1.025g/ml, and in formulation III was 1.044g/ml. Judging from the results obtained, it meets the requirements, which say that the density or specific gravity of a preparation with a water carrier must be> 1.00g / ml, this is because water has a specific gravity of 1.00g / ml (Ulfah & Slamet, 2020).

Viscosity Test

Based on the results of viscosity testing that has been carried out, the results of formulation I with an average of 38.2cPs, formulation II of 63.0cPs, and formulation III of 93.8cPs were obtained. Therefore, the average results obtained by each formulation tested ranged from 38.2cPs-93.8cPs, and these results of each formulation tested met the range of viscosity requirements of the Mucolytic Nanosuspension preparation of iler leaf extract (*Coleus atropurpureus L. benth*.). These results are in accordance with the theory that the higher the concentration of sodium alginate used, the higher the viscosity of the preparation (Jayanudin et al., 2014).

Redispersion Test

In this test, the redispersion test was carried out by rotating the preparation 1x (180º), the results of this test were that each consecutive formulation from formulation I, formulation II, and formulation III could be dispersed 100% without any caking at the time of cornering, so that from the redispersion tests that have been carried out on formulation I, formulation II, and formulation III including Nanosuspension preparations that have a flocculation system as expected.

Particle Size Distribution

The results that have been obtained are certainly influenced by several factors, starting from the method of making Mucolytic Nanosuspension preparations of iler leaf extract (*Coleus atropurpureus L. benth.*) using the Top-Down technique of High Pressure Homogenization type, which technique consists of three steps in the manufacturing method, the first step of the active substance is dispersed in a stabilizer solution to form a prasuspensi, then the prasuspensi that has been formed is homogenized using a high pressure homogenizer at high pressure premilling, which is finally homogenized at high voltage for 10 to 25 cycles until the expected nanosuspension size is formed (Fadlilah & Gozali, 2022).

Factors that affect the particle size distribution in the Mucolytic Nanosuspension preparation of iler leaf extract (*Coleus atropurpureus L. benth.*) are in the suspending agent used, namely sodium alginate. Sodium alginate itself is a substance that has soft viscoelastic properties, which means that the substance has flowing and elastic properties at the same time, because of this, sodium alginate particles can easily change shape when getting external stimuli caused by water and its gel network (Abka-Khajouei et al., 2022).. Based on this, it can be concluded that viscosity and density weight have a relationship with the neatness of a preparation, which will certainly have an influence on the particle size distribution of Mucolytic Nanosuspension preparation of iler leaf extract (*Coleus atropurpureus L. benth*.).

Zeta Potential

Zeta potential is a measure of the potential difference between the bulk liquid in which a particle is dispersed and the liquid layer containing oppositely charged ions associated with the nanoparticle surface (Selvamani, 2019). In addition, zeta potential will also provide an overview of the repulsive forces between particles and cause the greater the zeta potential so that the dispersion system will be more stable (Noval & Malahayati, 2021).

Based on the results of zeta potential testing that has been done, the results of formulation I with an average of -33.15mV, formulation II of -37.38mV, and formulation III of -36.59mV are obtained. Therefore the average results obtained for each formulation tested ranged from -33.15mV-37.38mV, consecutively the smallest particle size distribution results were in formulation I with a value of -33.15mV and the largest particle size distribution was in formulation II with a value of -37.38mV. From these results, each formulation tested has met the range of requirements for the value of the requirements of a good zeta potential test, which is at least -30mV (Koca et al., 2022).

Sedimentation Volume Test

Based on the test results that have been carried out, the average sedimentation volume in formulation I is 0.95, formulation II is 0.97, and in formulation III is 0.98. So judging from the results that have been obtained in all formulas in a row ranging from 0.95-0.98, the results have met the existing requirements, namely a good sedimentation volume <1. From the results that have been obtained, it can be concluded that the viscosity or viscosity of the preparation will affect the speed of the sedimentation process, the greater the level of viscosity or viscosity in Nanosuspension, the slower the sedimentation process will be, this is due to the resistance provided by the suspending agent or suspending material.

CONCLUSION

This research successfully addressed the problem of formulating and characterizing mucolytic nanosuspensions from iler leaf extract (Coleus atropurpureus L. Benth.) using sodium alginate as the suspending agent. The research demonstrated that sodium alginate concentration significantly influenced key physicochemical properties of the nanosuspensions, including viscosity, pH, particle size distribution, zeta potential, and sedimentation volume. All formulations adhered to the quality standards for nanosuspensions, featuring particle size distributions in the nanometer range and high stability as indicated by zeta potential measurements. These results underscore the potential of iler leaf nanosuspensions to improve the bioavailability and therapeutic efficacy of mucolytic herbal extracts, thereby contributing to the advancement of plant-based pharmaceutical applications.

The research's contributions establish a solid groundwork for the further development of nanosuspensions derived from natural materials. Future research should prioritize in vivo evaluations of bioavailability and pharmacological efficacy, development of combination formulations with complementary active ingredients, and integration with advanced drug delivery technologies such as controlled release systems. Additionally, investigations into long-term stability and scalability for industrial production are essential for enabling the commercialization of nanosuspension-based herbal therapies.

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