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FORMULATION OF A GEL CONTAINING ASIATICOSIDE FROM PEGAGAN (*CENTELLA ASIATICA L.*) AND CURCUMIN ISOLATE FROM TURMERIC (*CURCUMA LONGA L.*) AS A NANO MEDICINE PARTICLE DELIVERY SYSTEM

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Abstract

Background: Pegagan (*Centella asiatica*) and turmeric (*Curcuma longa*) have a chemical that has been identified and utilized for wound healing. **Purpose**: The study looked into how to make a gel with asiaticoside extract from Pegagan and curcumin isolate from turmeric and a nanoparticle delivery system to heal wounds caused by exercise and surgery. **Method**: The rhizomes of pegagan and turmeric were taken out to make a gel preparation with a nanoparticle delivery system. Also, the extract was standardized and turned into nanoparticles. Finally, the gel preparation formula was made. Asiaticoside and curcumin gel nanoparticles were made by adding chitosan to a 0.1% sodium tripolyphosphate solution. Furthermore, physical examination and gel stability testing were performed on the three gel formulations with varying concentrations of NaCMC, such as 5%, 3%, and 15%. **Result**: Asiaticoside nanoparticles had a size of 83.87 nm, while curcumin nanoparticles had a size of 62 nm, according to the results of the nanoparticle characterization. The viscous test for gel formulations employs gel viscosity standards of 80.000 (F1) cp, 34.000 cp (F2), and 3.600 cp (F3). The gel is stable for 30 days due to its organoleptic value and viscosity. **Conclusion:** Based on the results of a physical exam, Formula 3 is the best way to make a gel preparation with asiaticoside and curcumin nanoparticles.

Keywords: Nanomedicine; Gel; Pegagan (*Centella Asiatica*); Turmeric (*Curcuma Longa*); Particle Delivery System

1. INTRODUCTION

Nanoparticles are frequently employed to transport medications due to their numerous advantages. The ability to modify the size and surface qualities of the particles is an advantage of nanoparticle systems (Patra et al., 2018). Nanoparticles can control and slow the release of active substances while the drug is in transit and at the site where it works (Rizvi & Saleh, 2018). This makes the drug more effective and less likely to cause side effects. In the nanoparticle system, the release of drugs can be controlled by choosing the right matrix (Samavedi & Joy, 2020). This makes it possible to make different release systems. Nanoparticles can be given in many ways, such as orally, nasally, intravenously, intraocularly (Rowe et al., 2009).

The most common way to make nanoparticles is through a process called "ionic gelation" (Hoang et al., 2022). Mixing chitosan polymer with sodium tripolyphosphate polyanion is one example of the ionic gelation method (Thirupathi et al., 2022). This causes the positive charge on the amino group of the chitosan to interact with the negative charge of the tripolyphosphate (Kim et al., 2022).

Pegagan is an aromatic annual herb. Pegagan is useful as a medicinal plant that contains phytochemical components such as triterpenoids, saponins, flavonoids, tannins, steroids and glycosides (Vinolina & Sigalingging, 2022). The active substances contained in pegagan are asiaticoside, asiatic acid, madecassic acid and madecassoside (triterpenoid group), sitosterol and stigmasterol (steroid group) and vallerin, brahmoside (saponin group)(Vinolina & Sigalingging, 2022). Other chemical constituents found in pegagan are asiaticoside, thankuniside, isothankuniside, brahminoside, brahmic acid, mesoinositol, centelloside, carotenoids, hydrocotyle, vellarin, tannins and contain mineral salts such as potassium, sodium, magnesium, calcium and iron contain phosphorus, essential oils (1%), pectin (17.25%), amino acids and vitamins (Sutardi, 2017; Vinolina & Sigalingging, 2022).

Pegagan (*Centella asiatica*) has a cell revitalization function, namely accelerating wound healing. The saponins present inhibit the production of excessive scar tissue (inhibit the occurrence of keloids) (Arribas-López et al., 2022).

Triterpenoid saponins are needed for plant growth and development which have an ecological role in regulating the interaction between plants and their environment, where the dominant group is derivative pentacyclic triterpenoid saponins (Moses et al., 2014). These triterpenoid saponins are secondary metabolites that can become defensive substances such as phytoanticipins, antifeedants, attractants, phytoalexins and pheromones (James & Dubery, 2009), antimicrobial chemicals in plants that are distinctive in their activity because they are generated prior to the onslaught of a pathogen or infection (Rahimi et al., 2022).

Turmeric contains compounds that have medicinal properties, called curcuminoids consisting of curcumin, desmethoxycumin and bisdemethoxycurcumin and other beneficial substances such as turmerin (a water-soluble peptide), essential oils (such as turmerone, atlantone, and zingiberene) (Sharifi-Rad et al., 2020).

2. METHOD

The research was carried out at the Laboratory of Solid and Semisolid Preparations of the Pharmaceutical Institute of the Indonesian Navy (Lafial) Drs. Mochamad Kamal, Central Jakarta and DKSH Laboratory, AIA Building.

This research was conducted in five stages, namely

1. Preparation of curcumin isolates and asiaticoside extracts

Curcumin is made from turmeric (*Curcuma longa* L.) and asiaticoside extract is made from Pegagan (*Centella asiatica* L.).

2. Nanoparticle Manufacturing

Sodium tripolyphosphate was dissolved in distilled water then curcumin and asiaticoside isolates were added. Furthermore, a chitosan solution was made. Chitosan was dissolved in acetic acid pH 5.5. The sodium tripolyphosphate-asiaticoside-curcumin solution was then added to the aqueous chitosan solution pH 5.5 drop by drop under a low-speed magnetic stirrer at room temperature (25°C). Then a suspension of nanoparticles is obtained. The resulting product is evaluated.

3. Nanoparticles Characterization

Determination of the amount of active substance, and determination of particle size distribution and zeta potential, Transmission electron microscopy was used to examine the morphology of nanoparticles (Avadi, 2009).

4. Gel dosage formulation

Na CMC was first developed in aqua demineralization (temperature 70°C) while stirring was carried out using a homogenizer until a temperature of 25°C was reached. The water used for the development of Na CMC is 20 times the weight of the Na CMC to be developed.

Asiaticoside-curcumin-tripolyphosphate suspension was added to the gel base after the developed gel base temperature was 25°C while stirring was carried out for 60 minutes using a homogenizer at 2000 rpm until a homogeneous gel was formed. Then check the pH and add NaOH to obtain a gel preparation whose pH is adjusted to the pH of human skin, namely in the pH range of 4.5-6.5.

5. Preparation Evaluation

Evaluation of the gel preparation was carried out, namely organoleptic observation, measurement of pH, viscosity, consistency, stability test.

3. RESULT

Table 1: Extraction Results and Extract Yield

Ingredients	Weight of simplicial (g)	Weight of extract (g)	Yield (%)
Turmeric	2000	275.70	13.78
Centella asiatica herb	2000	230.56	10.23

Extraction is carried out to extract the chemical components contained in the simplicial. The method used in this study was maceration using 70% ethanol for 2x24 hours with a new solvent replaced every 24 hours. As much as 2.5 kg of simplicial was extracted by dissolving it in 15 L of 70% ethanol.

The herb extracts of pegagan and turmeric rhizome were concentrated with a rotary evaporator at 50^{o}C to obtain a concentrated extract. Each evaporation product was evaporated over a water bath at a temperature of 40^{o}-50^{o}C to obtain a thick extract with a stable weight.

Table 2: Secondary Metabolite Content Test Results

Group of Chemical Content	Turmeric	Centella asiatica herb
Alkaloids	-	-
Flavonoids	+	+
Polyphenols	+	+
Tannins	-	-
Monoterpenoids/Sesquiterpenoids	+	+
Triterpenoids	+	-
Steroids	-	-
Quinone	+	+
Saponins	+	-

Note: (+) detected to contain compounds and (-) not detected to contain compounds

Phytochemical screening was carried out to determine the secondary metabolites contained in extracts of pegagan and turmeric rhizome. The results of the phytochemical screening of the two types of extracts can be seen in the Table 2.

The phytochemical screening revealed that both extracts included flavonoids, polyphenols, and quinones, which are secondary metabolites with varied pharmacological actions, including anti-inflammatory properties. Pegagan includes saponins with wound-healing properties as well as asiaticoside, which promotes the repair and strengthening of skin tissue cells. Tannins were not detected in any of the two studied extracts, and neither pegagan nor turmeric rhizome contained saponins. However, monoterpenoids and sesquiterpenes were detected in both pegagan and turmeric rhizome. The concentration and composition of chemicals in plants might vary from one plant species to another. Numerous variables, including as the site of growth, the regional climate, the harvest time, the portion of the plant used, and the extraction procedure, affect this. Curcumin extract was followed by the procedure of isolating curcumin using Thin-Layer Chromatography to separate curcumin and its derivatives.

Table 3: Nanoparticle Formulation

Nanoparticles	Ingredients	Quantity	Size (nm)	Zeta Potential	Polydispersity Index
Asiaticoside	Centella asiatica extract	5 grams	83,87	201,5	0,382
	Chitosan Solution	100 ml			
	STTP solution	100 ml			
Curcumin	Curcumin Isolate	5 grams	62,89	308,6	0,367
	Chitosan Solution	100 ml			
	STTP solution	100 ml			

Note: STTP= Sodium Tripolyphosphate

Manufacture of curcumin nanoparticles (nanocurcumin) is expected to improve the bioavailability of curcumin. It is anticipated that the production of asiaticoside nanoparticles will optimize the function of asiaticoside in enhancing the repair and fortification of skin tissue cells during wound healing.

4. DISCUSSION

The results of nanoparticle measurements (Table 3) indicate that asiaticoside nanoparticles are 83.87 nm in size and curcumin nanoparticles are 62.89 nm in size. Due to the usage of curcumin isolate in the nanoparticle synthesis, the nanocurcumin size was reduced. The particle size is the most significant aspect of nanoparticle systems since it directly affects the nanoparticles' distinctive properties. The asiaticoside nanoparticles and curcumin nanoparticles met the size requirements for a nanoparticle based on the nanoparticle measurement results, which yielded diameters of less than 100 nm for both types of nanoparticles. The therapeutic efficacy of medications with nanoparticle delivery methods will be enhanced due to their increased absorption.

Zeta potential is a parameter that describes the electric charge between colloidal particles. The higher the zeta potential value, the stronger the flocculation prevention. The zeta potential of asiaticoside nanoparticles is 201.5 whereas the zeta potential of curcumin nanoparticles is 308.6.

The polydispersity index is a measure of the distribution of molecular masses in a particular sample. The smaller the polydispersity index value, the more stable the formula of a preparation made, this is because the greater the polydispersity index value indicates that the particles formed are not uniform.

The polydispersity index values obtained in this study can be said to be good because they fall into the range of 0.08 – 0.7 which is the mean value of the polydispersity index in general. The polydispersity index is said to be poor if it has a size > 0.7 because it is very polydispersity and shows a very wide distribution of particle sizes, so that sedimentation is likely to occur.

Table 4: Gel Preparation Formulation

Ingredients	%	Formula 1	Formula 2	Formula 3
Asiaticoside and Curcumin Nanoparticles	50 %	100 ml	100 ml	100 ml
CMC sodium	1, 5 – 5%	10 grams	6 grams	3 grams
Methyl Paraben	0, 2 %	0, 4 gram	0, 4 gram	0, 4 gram
Propylene glycol	15 ml	30 ml	30 ml	30 ml
Butyl Hydroxy Toluene	0, 1 %	0, 2 gram	0, 2 gram	0, 2 gram
Alcohol 96%	2 %	4 ml	4 ml	4 ml
Aqua demineralization	Ad 100 ml	55, 4 ml	59, 4 ml	62, 4 ml

Organoleptic tests of the three Gel preparation formulas with the active ingredients of curcumin nanoparticles and pegagan using the organs of sight and smell from the researcher.

Organoleptic test results for the three gel preparation formulas gave different results for the gel form, where formula 1 gave very thick results, formula 2 gave thick results and formula 3 gave dilute results. This is because the CMC sodium concentration used in formula 1 is the highest, namely 5%, so the gel that is formed is too thick.

Meanwhile, the organoleptic results for odor and color gave the same results for the three formulas, where for the odor it produced a distinctive odor from acetate buffer and the color formed in the three gel preparation formulas was a typical curcumin orange color.

The homogeneity test results showed that all gel preparations did not show any coarse grains when the preparations were smeared on transparent glass. The absence of separation between the gel base and the asiaticoside and curcumin nanoparticles as well as the other components of the gel indicated that the preparations made had a homogeneous composition.

Determination of the pH of the gel preparation was carried out using a Hanna pH meter. From the examination it was found that formula 1 had a pH of 7.3; formula 2 has a pH of 6.7; Formula 3 has a pH of 7.1. The difference in the pH of the preparations was caused by differences in the concentration of Na CMC, but the pH of this gel preparation still met the requirements of the physiological pH of the skin, namely 4-7 (Rowe et al., 2009).

Viscosity testing is an important factor because it affects the parameters of spread ability and release of active substances from gel preparations. The results of the Viscosity Test on the three formulas gave different results, where formula 1 gave a result of 80,000 cPs, formula 2 gave a result of 34,000 cPs and formula 3 gave a result of 3,600 cPs.

Formula 1 gives the highest viscosity value of the gel preparation because the concentration of CMC sodium used is the largest, namely 5%. It is known that the requirements for a good gel preparation are expected to be in the range of 2000 – 4000 cPs viscosity values. From the results of the viscosity test in table 4.10 it can be seen that the viscosity value of formula 3 meets the requirements for a good gel preparation viscosity. Therefore, the formula is declared as the best gel preparation formula.

From the results of the Stability Test (Table 5) for 30 days for the three formulas, there was a change in form in formula 3 to become more viscous at cold temperatures, this can be seen from the results of the Viscosity test for formula 3 at cold temperatures showing a result of 7200 cPs which indicates an effect of storage temperature ± 2 – 8o C on the viscosity of the gel preparation. Then the preparation experienced a decrease in viscosity value which could be caused by long storage time, so that old preparations were affected by the environment such as exposure to air.

Table 5: Gel Stability Test Results

Day	Parameter	Room Temperature			Cold Temperature			Hot Temperature		
		F1	F2	F3	F1	F2	F3	F1	F2	F3
0	Form	Very Viscous	Condensed	Dilute	Very Viscous	Condensed	Condensed	Very viscous	condensed	condensed
	Smell	typical	typical	typical	typical	typical	typical	typical	typical	typical
	Color	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange
	Viscosity	80000	34000	3600	80000	34000	3600	80000	34000	3600
	pH	7,3	6,7	7.1	-	-	-	-	-	-
30	Form	Very Viscous	Condensed	Dilute	Very Viscous	Condensed	Condensed	Very viscous	condensed	watery
	Smell	typical	typical	typical	typical	typical	typical	typical	typical	typical
	Color	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange	Orange
	Viscosity	80000	35000	3650	80000	38000	7200	80000	26000	4080
	pH	7	6,5	6.8	-	-	-	-	-	-

Note: F= Formula

After storage for 30 days, the pH obtained decreased slightly compared to the pH after it was made. Even though there is a decrease in pH, the preparation is still safe to use. Where the pH of this preparation is still in the physiological pH of the skin, namely 4-7 (Rowe et al., 2009).

5. CONCLUSION

A gel preparation can be formulated containing asiaticoside extract from Centella asiatica L. and curcumin isolate from turmeric (*Curcuma longa L*.), with the best formula based on the results of physical evaluation is formula 3. Furthermore, can apply chitosan and sodium tripolyphosphate as a nanoparticle delivery system using the ionic gelation method and characterize the preparations obtained, then provide particle size results that meet the requirements, namely asiaticoside nanoparticles 83.87 nm and 62.89 nm curcumin nanoparticles. We look forward conducting pre-clinical evaluation of the 3rd formula gel preparation produced from this study; conducting accelerated stability test and on-going stability test on the best gel preparation formula; and apply the design of packaging design and product use in healing soldiers' wounds during operations and war training.

COMPETING INTERESTS

The authors declare no conflict of interest.

Authors' Contributions

Conceptualization, AA, ST; methodology, AA and ST; writing-review and editing, ST; project administration, AA; funding acquisition, AA. All authors have read and agreed to the published version of the manuscript.

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