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Type of Cosurfactant Effects on Particle Size in Nanoemulsion Drug Delivery Systems

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A B S T R A C T

Nanoemulsions are thermodynamically or kinetically stable compared to conventional emulsions, and the particle size of nanoemulsions is around 5-200 nm. Until now, there has been no research comparing propylene glycol and PEG 400 cosurfactants for nanoemulsions, so it needs to be investigated. Laboratory experimental research with cosurfactant propylene glycol and PEG 400 Formula 1 and Formula 2 were repeated three times (n = 3) for each nanoemulsion formula. Parameters of physical properties (organoleptic, viscosity, particle size, index polydispersity) and chemical properties (pH). Evaluated and analyzed, <0.05 is considered significant. The results of formula 1 and formula 2 obtained the same clear organoleptic properties. The average particle size with cosurfactant propylene glycol was 10.41 ± 0.14 nm and PEG 400 was 12.32 ± 0.38 nm (p <0.05). The average viscosity, polydispersity index, and pH of propylene glycol were 8.72 ± 1.12; 0.03±0.02; 4.20 ± 0.04; and PEG 11.26 ± 1.80; 0.39 ± 0.58; 4.03±0.03. This shows that the type of cosurfactant has an effect on the size of the nanoemulsion particles.

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INTRODUCTION

The pharmaceutical industry develops more than 40% of new chemicals with practically insoluble solubility in water.[1] Drugs that are not water soluble are usually made into emulsion preparations. Emulsion preparations have poor stability compared to other dosage forms and have a short shelf life due to problems with the preparation such as precipitation.[2]

Until now, nanoemulsions do not have a reference formula regarding the choice of ingredients, especially cosurfactants.[15] Meanwhile, cosurfactants are ingredients that affect nanoemulsions to reduce surface tension. Inappropriate cosurfactant selection can affect the stability of nanoemulsion preparations. By considering the influence of cosurfactants in the formation of nanoemulsions but there is still no nanoemulsion reference formula with good physical and chemical properties, this research was conducted to compare the effect of cosurfactants on the physical and chemical properties of nanoemulsions.

THEORECTICAL REVIEW

Nanoemulsion has thermodynamic or kinetic stability and the nanoemulsion particle size is very small, around 5-200 nm.[3] Nanoemulsion can overcome damage to preparations due to long storage because the size of the nanoemulsion droplets is very small, making nanoemulsion kinetically stable.[4] Nanoemulsion is a development of emulsion but with greater stability. better.[2] Nanoemulsion can be used to overcome the solubility problem of drugs that are difficult to dissolve in water.[5] Nanoemulsion can increase drug penetration through the skin making it suitable for the topical route.[6]

Nanoemulsions are composed of oil, surfactant, cosurfactant and water components.[7] Surfactants and cosurfactants are components that make up nanoemulsions which play a role in reducing surface tension. Nanoemulsion has a small size. Based on the formula composition, cosurfactants are materials that influence the size of the nanoemulsion.[8] Cosurfactants that are often used include polyethylene glycol, propylene glycol, span, ethanol, ethylene glycol, and glycerin.[9]

Propylene glycol is a cosurfactant that is often used in topical preparations with a concentration of 1-10%.[10] Propylene glycol has hydrophilic and hydrophobic groups, which can reduce the intermolecular attraction of water.[11] Propylene glycol is a cosolvent with low toxicity.[12] PEG 400 is a cosurfactant with the ability to occupy the gaps between the particles of the nanoemulsion system so that the emulsification process is maximized.[13] Polyethylene glycol 400 (PEG 400) has chemical stability and a relatively low level of toxicity.[14]

METHODOLOGY

This research was carried out experimentally in a laboratory. Preparation preparation and testing were carried out at the Pharmaceutical Technology and Pharmaceutical Laboratory of the Pharmacy Study Program, Faculty of

Medicine, Islamic University of Malang. Research starts in December 2022 to June 2023.

The nanoemulsion formula tested was obtained from the nanoemulsion reference formula (**table 1**) which was modified in formula 1 and formula 2 (**table 2**).

Table 1. Nanoemulsion Reference Formula

Ingredient	Function	Concentration (%)
Virgin Coconut Oil (VCO)	Oil Phase	2
Extract	Active substance	1
Polysorbate 80	Surfactant	13,5
Propylene glycol	Cosurfactant	4,5
Water	Water phase	Ad 100 ml

Table 2. Nanoemulsion Formulation

Ingredient	Concentration (%)	
	F1	F2
Salicylic acid	1	1
VCO	1,5	1,5
Polysorbat 80	10	10
Propylene glycol	5	0
PEG 400	0	5
Methyl Paraben	0,2	0,2
Propyl Paraben	0,2	0,2
Aquadest	Ad 100	Ad 100

Making Nanoemulsion

The nanoemulsion formulation was made by weighing salicylic acid, Tween 80, VCO, propylene glycol, PEG 400, propyl paraben, methylparaben, and distilled water. All materials are heated to a temperature of 50^{o}C. The oil phase was made by mixing salicylic acid, VCO, and propylparaben in a glass beaker until homogeneous. The water phase was made by mixing methylparaben and distilled water in a beaker until homogeneous. Surfactant and cosurfactant are mixed until homogeneous. The oil phase was added to the surfactant and the cosurfactant was mixed until homogeneous, then the water phase was added little by little while continuing to stir using a magnetic stirrer at 1500 rpm for 60 minutes until a nanoemulsion was formed.

Organoleptic

Organoleptic testing can be carried out by observing the color, odor and form of the dosage using the five senses.

Viscosity

A total of 50 mL of sample was put into the cup. The viscosity results of the nanoemulsion can be seen in the analysis results displayed on the viscometer screen.[16]

Particle Size

A total of 10 ml of the preparation was put into the cuvette. The sample will be analyzed by the instrument. The data obtained are particle size and polydispersity index value.[17]

Polydispersity Index

A total of 10 ml of the preparation was put into the cuvette. The sample will be analyzed by the instrument. The data obtained are particle size and polydispersity index value.[17]

pH

The sample was taken in 10 ml. The solution is measured by inserting an electrode. The pH value that appears on the screen is the pH of the preparation being measured.[18]

Statistical Analysis

The data obtained are expressed as mean ± SD. The data obtained was subjected to a T-test to determine the comparison between formula 1 propylene glycol and formula 2 PEG 400.

RESULT

Organoleptic

The organoleptic test results of nanoemulsion formula 1 and formula 2 can be seen in **Figure 1, Figure 2, and Table 3** which show that formula 1 using propylene glycol and formula 2 using PEG 400 have the same organoleptic results. The preparation is in liquid form, clear in color, and has a distinctive surfactant odor.

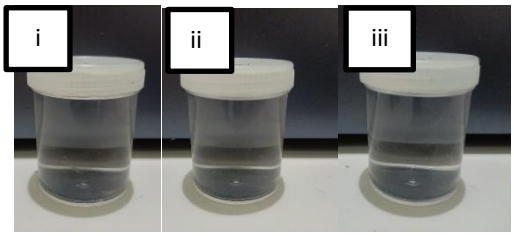

Figure 1. Organoleptic Results of Nanoemulsion Formula 1
Description: i. Replication 1; ii. Replication 2; iii. Replication 3

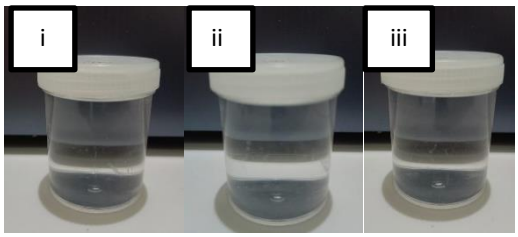

Figure 2. Organoleptic Results of Nanoemulsion Formula 2
Description: i. Replication 1; ii. Replication 2; iii. Replication 3

Table 3. Organoleptic

Formula	Shape	Color	Smell
1	Clear	Liquid	Typical surfactant
2	Clear	Liquid	Typical surfactant

Table 4. Viscosity Test Results, Particle Size, Polydispersity Index, pH of Nanoemulsion

Formula	Parameter (mean ± SD)				
	n	Viscosity	Particle Size	Polydispersity Index	pH
1	3	8,72±1,12	10,41±0,14	0,03±0,02	4,20±0,04
2	3	11,26±1,80	12,32±0,38	0,39± 0,58	4,03±0,03
Sig.		0,249	0,017	0,381	0,051

Test Results for Viscosity, Particle Size, Polydispersity Index, and pH

The nanoemulsion test results can be seen in **Table 4**. In formula 1 (8.72 ± 1.12 mPa.S) the viscosity was lower than formula 2 (11.26 ± 1.80 mPa.S). There was no significant difference ($p>0.05$) in the use of different cosurfactants.

In formula 1 (10.41 ± 0.14 nm) the particle size was lower than formula 2 (12.32 ± 0.38 nm). There was a significant difference ($p<0.05$) in the use of different cosurfactants.

In formula 1 (0.03 ± 0.02), the polydispersity index was lower than in formula 2 (0.39 ± 0.58). There was no significant difference ($p>0.05$) in the use of different cosurfactants.

In formula 1 (4.20 ± 0.04), the pH was higher than formula 2 (4.03 ± 0.03). There was no significant difference ($p>0.05$) in the use of different cosurfactants.

DISCUSSION

In this research, nanoemulsion was formulated with Tween 80 as a surfactant to reduce the surface tension of VCO and distilled water. Due to the small size of the nanoemulsion, it is necessary to add a cosurfactant because it can help the surfactant in reducing surface tension. Propylene glycol cosurfactant was used for formula 1 and PEG 400 for formula 2.

Propylene glycol is a cosurfactant that is often used in topical preparations.[10] Propylene glycol has hydrophilic and hydrophobic groups,

which can reduce the intermolecular attraction of water.[11] Propylene glycol is a cosolvent with low toxicity.[12]

PEG 400 is a cosurfactant with the ability to occupy the gaps between the particles of the nanoemulsion system so that the emulsification process is maximized.[13]

Polyethylene glycol (PEG) 400 has good chemical stability and a relatively low level of toxicity.[14]

The selection of propylene glycol and PEG 400 concentrations used was based on the optimization that had been carried out before the research in the preliminary test. The evaluations carried out were organoleptic, viscosity, particle size, polydispersity index and pH.

Effect of Cosurfactants on Organoleptic Physical Properties

Organoleptic testing is a test based on a sensing process that aims to implement the quality of nanoemulsion preparations. Nanoemulsion has clear visuals. This indicates the formation of nanoemulsion with a small particle size.[19]

Based on the results of organoleptic testing, nanoemulsion preparations with 1 and 2-color formulas were produced clear with a distinctive surfactant aroma. This is because the initial color of propylene glycol and PEG 400 is clear with a slightly thick liquid form. Propylene glycol and PEG 400 do not have a distinctive aroma. The shape and aroma of nanoemulsion are influenced by the active ingredients, surfactant and cosurfactant.[20] Formula 1 and Formula 2 produce a clear color, so this clear color can be a sign that the nanoemulsion preparation made is suitable and has a nano size. However, organoleptic test results need to be confirmed by particle size testing.

Based on the observation results, the consistency of nanoemulsion formulas 1 and 2 has a liquid consistency. This is because the water composition is high.

Effect of Cosurfactants on the Physical Properties of Viscosity

Viscosity testing was carried out to measure the viscosity of the nanoemulsion. It is known that the viscosity of nanoemulsions affects the release of active substances from nanoemulsions. The higher the viscosity of the preparation, the longer the release of the active substance will be.[17]

The viscosity test results for nanoemulsion formula 1 had an average viscosity of 8.72 ± 1.12 mPa.S and formula 2 had an average viscosity of 11.26 ± 1.80 mPa.S. Based on these results, it is known that formula 2 has a greater viscosity value, compared to formula 1. This is because PEG 400 has a viscosity of 114.5 mPa.S, which is a higher value than propylene glycol which is only 58.1 mPa.S. Based on statistical tests using SPSS 29, the results were sig. 0.249 ($p>0.05$) which shows that there is no difference in viscosity caused by propylene glycol and PEG 400.

The increase in viscosity is influenced by the concentration and type of material used in this research, different types of cosurfactant. The greater the

concentration and viscosity of the material, the more viscosity of the nanoemulsion will increase. Based on the research results, it is known that each formula has good viscosity results. These results are by the viscosity range of nanoemulsion preparations because they are in the range of 1-100 mPa.S.

Effect of Cosurfactants on Physical Properties of Particle Size

Particle size testing is a test carried out to measure the size of nanoemulsion particles. Nanoemulsion has a particle size of 5-200 nm. Nanoemulsion can overcome damage to preparations due to long storage because the size of the nanoemulsion droplets is very small making the nanoemulsion kinetically stable. 4 This test can be carried out using a Particle Size Analyzer (PSA).

The results of nanoemulsion particle size testing for formula 1 had an average particle size of 10.41 ± 0.14 nm and formula 2 had an average particle size of 12.32 ± 0.38 nm. Based on statistical tests using SPSS 29, the results were sig. 0.017 ($p<0.05$) which shows that there is a difference in particle size caused by propylene glycol and PEG 400.

Based on the results obtained, it is known that formula 2 has a larger particle size, compared to formula 1. This is because propylene glycol has hydrophilic and hydrophobic groups, which can reduce the intermolecular attraction of water so that the particle size becomes smaller.[11] Meanwhile, PEG 400 only can occupy the gaps between the particles of the nanoemulsion system so that the emulsification process can be maximized. But it does not help reduce particle size.[13]

The formation of nanoemulsion is influenced by stirring speed, temperature, surfactant and cosurfactant chosen. These results show that each formula has a good particle size. These results are by the particle size range of nanoemulsion preparations, namely around 5-200 nm.[3]

Effect of Cosurfactants on the Physical Properties of Polydispersity Index

Polydispersity Index (PDI) is a value that shows the distribution of particle sizes. If the PDI value is >1, the preparation is categorized as heterogeneous. Heterogeneous preparations have many particles that aggregate so that the preparation is unstable.

The polydispersity index test results for the nanoemulsion formulation 1 had an average polydispersity index of 0.03 ± 0.02 and formula 2 had an average polydispersity index of 0.39 ± 0.58. Based on the data obtained, it is known that formula 2 has a greater polydispersity index, compared to formula 1. This is because propylene glycol has hydrophilic and hydrophobic groups, which can reduce the intermolecular attraction force of water.[11] Meanwhile, PEG 400 can only occupy gaps in between the particles of the nanoemulsion system so that the emulsification process can be maximized. But it doesn't help reduce PDI.[13] Based on statistical tests using SPSS 29, the results were sig. 0.381

(p>0.05) which shows that there is no difference in PDI caused by propylene glycol and peg 400.

Based on these results, it is known that all formulas have good polydispersity index results. These results are by the range for the polydispersity index value, namely <1.[21] A PDI value that is closer to zero means the stability and distribution are better.[22] Because formula 1 has a PDI that is close to 0, formula 1 has a better PDI.

Effect of Cosurfactants on pH Chemical Properties

pH testing is a test to determine the acidity of nanoemulsion. The pH of the preparation must be the same as the pH of the skin, with a range of 4–7.5 because a pH that is too high can cause the skin to become scaly. If the pH of the nanoemulsion is too low it can cause skin irritation.[23]

Based on the pH test results, the two formulas have almost the same pH. This is thought to be caused by the pH of the two cosurfactants being almost the same. Popylenglycol has a pH range of 3-6 and PEG 400 has a pH range of 4-7.5. Based on statistical tests using SPSS 29, the results were sig. 0.051 (p>0.05) which shows that there is no significant difference for pH testing.

The pH value that increases or decreases during storage can affect the effect when applied. This could indicate that the constituent components in the preparation are damaged. This damage indicates the chemical instability of the preparation. To determine the chemical stability of a preparation by knowing its charge. Zeta potential with a value more positive than +30 mV or more negative than -30mV indicates good stability.[24]

The weakness of this research is that the repetition was only carried out 3 times at the same time so the results of testing the physical and chemical properties at different times are not known. The only chemical properties testing carried out was pH testing.

CONCLUSION AND RECOMM ENDATIONS

Based on the research results, it can be concluded that:

1. The nanoemulsion particle size differs significantly when using propylene glycol and PEG 400 cosurfactants.
2. The use of propylene glycol and PEG 400 cosurfactants did not change the pH, viscosity and polydispersity index of the nanoemulsion

FURTHER STUDY

Based on the research results, it can be recommended to:

1. Increase the number of repetitions at different times.
2. Evaluate the effect of cosurfactants on nanoemulsion chemistry using zeta potential testing.

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