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# Influence of Hydroxyethyl Cellulose and Glycerin Concentration Variations on the Physicochemical Stability of Niacinamide-Loaded Nanoparticle Serum Formulations

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***ABSTRACT***

***Introduction**: Niacinamide is widely used in cosmeceutical formulations for anti-aging and hyperpigmentation treatment. However, its instability and limited penetration through the stratum corneum reduce its efficacy. Nanoparticle-based facial serum systems incorporating hydroxyethyl cellulose and glycerin have the potential to improve niacinamide stability, control its release, and enhance skin penetration. **Objective**: This study aimed to evaluate the effect of hydroxyethyl cellulose and glycerin concentrations on the physicochemical stability of niacinamide-loaded nanoparticle serum using a factorial design. **Method**: Niacinamide nanoparticle serum was formulated by ionic gelation and optimized using a $2^2$ factorial design, yielding four formulations. Nanoparticles were prepared using chitosan and sodium alginate and incorporated into serum containing hydroxyethyl cellulose and glycerin, followed by evaluation of particle characteristics, physicochemical properties, and stability using cycling tests with pre- and post-test comparisons analyzed by a paired sample t-test. **Results**: All formulations produced nanoparticles within the nanometer range (134.7–152.2 nm) with acceptable size distribution (PDI 0.610–0.926) and zeta potential around –30 mV, and exhibited satisfactory physicochemical properties, including adhesion (>4 s), spreadability (5–7 cm), viscosity (273.33–1208.33 cP), and pH (4.72–5.55). **Conclusion**: All formulas meet the ideal characterization, and there is no significant difference between the before and after stability testing for the niacinamide nanoparticle serum, except viscosity result.*

***KEYWORDS**: Niacinamide, serum, nanoparticle, ionic gelation, stability*

## INTRODUCTION

An active ingredient that has become increasingly popular and widely used in cosmeceutical products is niacinamide or nicotinamide, as shown in Figure 1. It plays a vital role in the synthesis of nicotinamide adenine dinucleotide ($NAD^+$) which is an essential molecule involved in oxidation-reduction reactions and supports DNA repair processes and various dermatological conditions. It has met the Kligman Standard and well established over decades for its safety in cosmeceutical products (Marques et al., 2024). But,

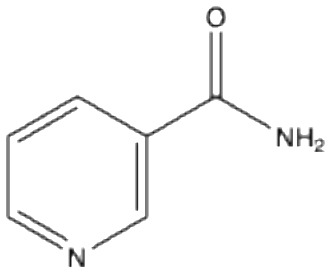


Figure 1. Molecular structure of niacinamide

niacinamide is less stable under certain environmental conditions, such as high heat and low pH. It has also limited skin penetration across the stratum corneum as a skin barrier (Basto et al., 2021; Somboon et al., 2025; Tiyaboonchai et al., 2025). Therefore, a novel approach is necessity to overcome these constrains through polymer-based nanoparticle delivery. This system not only enhances the stability of the active ingredient but also enables controlled delivery and improved penetration into the skin layers (Dikpati et al., 2024; Famielec & Flieger, 2022).

Facial serum is a popular cosmeceutical product that is designed to enhance the skin penetration of active ingredients and require essential components, such as a gelling agent and a humectant. These components determine the physical properties and the acceptability of product to the consument (Park et al., 2025). Hydroxyethyl cellulose (HEC) is a gelling agent commonly used in cosmetic formulations. It is known for its stability over a wide pH range and compatibility with a variety of active ingredients. Therefore, it is considered as an ideal excipient in topical product development by offering a pleasant texture and facilitating uniform application through the skin (Hartzke et al., 2022; Kaluku et al., 2022; Wijianto & Pratiwi, 2024). Hence, glycerin as humectant is essential in maintaining skin hydration by drawing and retaining water within the stratum corneum thereby enhancing its moisture content and preventing transepidermal water loss (Butarbutar & Chaerunisaa, 2020).. Glycerin can also increase the comfort of product use and support its effectiveness by enhancing transdermal absorption (Björklund et al., 2013; Nadya et al., 2020). This combination is considered to provide a synergistic effect (Arini & Wijayati, 2025; Nurleni et al., 2023; Purwanti et al., 2022; Wardhani et al., 2024).

Accelerated stability testing is performed to ensure the cosmeceutical formulation remains stable during storage. This research aims to develop a niacinamide nanoparticle serum with varying concentrations of hydroxyethyl cellulose and glycerin and evaluate stability using the cycling test method.

## METHODS

The tools used in this research were analytical balance, glass instruments (Pyrex, Iwaki), magnetic hotplate stirrer, dryer oven, refrigerator, pH meter, and viscometer Brookfield LV. The materials used in this research were niacinamide,

Table 1. Nanoparticle Serum Loaded Niacinamide

| Ingredients | Concentration (%) | | | | Function |
|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | |
| Niacinamide | 10 | 10 | 10 | 10 | Active pharmaceutical ingredients |
| Chitosan | 0,01 | 0,01 | 0,01 | 0,01 | *Biopolymer* |
| Sodium alginate | 0,1 | 0,1 | 0,1 | 0,1 | *Biopolymer* |
| Calcium chloride | 0,05 | 0,05 | 0,05 | 0,05 | Stabilizer |
| Hydroxyethyl cellulose | 0,75 | 0,75 | 1 | 1 | Gelling agent |
| Glycerine | 5 | 10 | 5 | 10 | Humectant |
| DMDM Hydantoin | 0,1 | 0,1 | 0,1 | 0,1 | Penetration enhancer |
| Ethoxydiglycol | 1 | 1 | 1 | 1 | Preservative |
| Oleum rosae | qs | qs | qs | qs | Fragrance |
| Aquadest ad | 100 | 100 | 100 | 100 | Sovent |

sodium alginate, calcium chloride, chitosan, hydroxethyl methylcellulose, DMDM hydantoin, ethoxydiglycol, glycerine, aqua destillata, and oleum rosae.

**Optimization of Nanoparticle Serum Loaded Niacinamide**

An amount of 100 mL nanoparticle serum loaded niaicinamide was carried out using ionic gelation method based on a previous study with a slight modification and used formula as shown in **Table 1** (Ahdyani et al., 2024; Stiani et al., 2024). Firstly, niacinamide, sodium alginate, and calcium chloride were dispersed each into distilled aqua separately as the medium. Meanwhile, chitosan was dispersed into distilled aqua containing glacial acetic acid 1%. These component were the base system of nanoparticle and to be mixed in ratio 1:1:1:1. Sodium alginate phase was mixed into the niacinamide phase and stirred for 30 seconds until homogeneous. Calcium chloride phase was added into the mixture and stirred for 30 seconds. Then, chitosan was added into the mixture and stirred for 30 seconds until homogeneous. Separately, a gelling agent hydroxyethyl cellulose was dispersed into distilled aqua and heated to temperature 70°C with continuous stirring until homogeneous gel base was obtained. Nanoparticle serum loaded niacinamide was prepared by mixing both the base system of nanoparticle and gel base of hydroxyethyl cellulose with continuous stirring until homogeneous. Subsequently, glycerine, DMDM hydantoin, and ethoxydiglycol were added into the mixture sequentially until homogenous system was obtained. Lastly, oleum rosae was added into the mixture as a fragrance and put in the serum bottle. The optimization of nanoparticle serum loaded niacianamide was performed in triplicates.

**Stability testing of Nanoparticle Serum Loaded Niacinamide**

Stability testing was carried out for 3 cycles based on the previous study through cycling test method (Stiani et al., 2024). Each formulation of nanoparticle serum loaded niacianamide was evaluated for its physical properties including organoleptic, homogeneity, pH, spreadability, and viscosity characteristic. These results were conducted as evaluation result before stability testing. Afterward, that sample was placed in the dryer oven at 40°C for 24 hours and transferred to chiller for another 24 hours. This process was defined as 1 cycle and repeated it for a total of 3 cycles. Then, the re-evaluation was carried out after completing 3 cycles of stability testing for the physical characteristic of each formulation. The result were recorded and analyzed.

**Evaluation of Nanoparticle Serum Loaded Niacinamide**

*Organoleptic*

The sample of nanoparticle serum loaded niacinamide was observed for its physical form, texture, color, and odor using the five senses. The result was recorded (Stiani et al., 2024).

*Homogeneity*

The sample of nanoparticle serum loaded niacianamide was weighted as amount of 0.1 gram, placed on the glass slide, and covered with another glass slide. Then, it was examined for homogeneity to ensure no coarse particle and recorded the result (Stiani et al., 2024).

*pH*

The sample of nanoparticle serum loaded niacianamide was examined its pH by using pH meter that was calibrated before. Then, it was observed the pH value that was presented in the pH monitor. The evaluation was carried out in triplicate and recorded the result (Stiani et al., 2024).

*Spreadability*

The sample of nanoparticle serum loaded niacinamide was weighed as amount of 0.5 gram and placed in the middle of glass plate. Then, it was covered with another glass plate, given a load of 50 grams, 100 grams, 150 grams, 200 gram, 250 grams and let it set for 1 minute. The diameter of the spread was measured using a ruler. The evaluation was carried out in triplicate and recorded the result (Stiani et al., 2024).

*Viscosity*

The sample of nanoparticle serum loaded niacinamide was carried out using Viscometer Brookfield LV. As amount of 100 grams sample was placed into the beaker glass and used spindle number 3 at 12 rpm. Read the value that presented in the monitor as dial reading in CentiPoise unit and converted in Poise unit. The evaluation was examined in triplicate and recorded the result (Stiani et al., 2024).

Figure 2. Niacinamide nanoparticle serum

*Adhesion*

The sample of nanoparticle serum loaded niacinamide was carried out using adhesion tester by weighing a 0.5 gram sample and placed another glass slide on top of that sample. An 1 kg load was applied to upper slide and left it for 5 minutes. Afterward, the time required to separate two slides was observed. The evaluation was examined in triplicate and recorded the result (Park et al., 2025).

**Particle Size, Polidispersity Index, and Zeta Potential**

The niacinamide nanoparticle was analyzed using a Particle Size Analyzer (Malvern, UK) based on the dynamic light scattering (DLS) method to determine the average particle size, particle size distribution, also known as the polydispersity index (PI) parameter, and Potential zeta. This instrument was controlled with Malvern software. Subsequently, the niacinamide nanoparticle sample was dispersed in 5 mL of distilled water and placed in a disposable cuvette. The graph of average particle size and particle size distribution was analyzed. Particle size and polydispersity index measurements were conducted in triplicate (Ahdyani et al., 2024).

**Analyze of Data**

Data were analyzed descriptively for organoleptic and homogeneity tests. Data were also analyzed statistically using SPSS software for pH, viscosity, adhesion, and spreadability tests. The data were examined normality to ensure either normal or non-normal distribution. If the data was distributed normally, continued using the Paired Sample t Test. Then, if the data was non normal distributed, continued using the Wilcoxon signed-rank test. The statistical test was performed to compare the physical evaluation of those formulations before and after stability testing with significance confidential of 95%.

**RESULTS AND DISCUSSION**

**Organoleptic**

Based on organoleptic testing of niacinamide nanoparticle serum, a clear color, rose fragrance and clear texture were obtained, with the results shown in Figure 2.

**Homogeneity**

Based on the observation results, all niacinamide nanoparticle serum formulas showed a homogeneous appearance and no coarse particles or clumps. After stability

Table 2. Result of pH Test of Niacinamide Nanoparticle Serum

| Formula | Before stability testing | After stability testing | *p value* | Description |
|---|---|---|---|---|
| F1 | 5.16 ± 0.116 | 5.09 ± 0.074 | 0.118 | No Difference significant |
| F2 | 5.55 ± 0.052 | 5.38 ± 0.030 | | |
| F3 | 4.79 ± 0.072 | 4.68 ± 0.044 | | |
| F4 | 4.80 ± 0.017 | 4.72 ± 0.020 | | |

*Data were presented as mean ± deviation standard (n=3) and analyze statistically using Paired Sample T Test.
F1 : Concentration of HEC : Gly (0.75:5)
F2 : Concentration of HEC : Gly (0.75:10)
F3 : Concentration of HEC : Gly (1:5)
F4 : Concentration of HEC : Gly (1:10)

testing, the serum preparation was still homogeneous and there was no phase separation or clumps. This indicates that the process of making the niacinamide nanoparticle serum formula produces a homogeneous and physically stable dispersion system. Similar results were also shown in a study (Sukor et al., 2024) which produced a homogeneous niacinamide facial serum with a fibrous silica nanocarrier system.

**pH**

Based on the results, all niacinamide nanoparticle serum formulas showed pH values ranging from 4.72 to 5.55, as shown in Table 2, which meet the ideal skin requirements of 4.1 to 5.8 (Lukić et al., 2021). Skin pH plays a crucial role in influencing the surrounding normal flora. The skin maintains a slightly acidic pH of around 5.0, which facilitates the formation of an acid mantle. This acid mantle, also known as a protective layer, is responsible for protecting the skin from external pathogens while reducing excessive moisture loss (Janssens-Böcker dkk., 2025).The suitability of pH in cosmetic preparations is also important to avoid potential irritation if the pH is too acidic and dry and scaly skin if the pH is too alkaline (Tungadi et al., 2023).

Previous research reported similar pH results for facial serum formulations, ranging from 5.4 to 5.9 (Wijianto & Pratiwi, 2024). HEC concentrations were shown to influence the pH values of niacinamide nanoparticle serum. Higher HEC concentrations resulted in a decrease in pH, as demonstrated by F1 and F3, which contained 0.75% and 1% HEC, respectively. These results were also found for F2 and F4, which contained the same HEC concentration. Furthermore, the results showed that increasing the glycerin concentration in the formulas led to an increase in pH. This was seen in F1 and F2, which contained 5% and 10% glycerin, respectively, which showed higher pH values than formulas with lower glycerin concentrations. Similar results were also

Table 3. Result of Viscosity Test of Niacinamide Nanoparticle Serum

| Formula | Before stability testing (Poise) | After stability testing (Poise) | *p value* | Description |
|---|---|---|---|---|
| F1 | 283.33 ± 20.817 | 273.33 ± 15.275 | 0.004 | Difference significant |
| F2 | 290.00 ± 10.000 | 281.67 ± 2.887 | | |
| F3 | 703.33 ± 35.119 | 691.67 ± 29.297 | | |
| F4 | 1208.33 ± 52.042 | 1193.33 ± 55.752 | | |

*Data were presented as mean ± deviation standard (n=3) and analyze statistically using Paired Sample T Test.
F1 : Concentration of HEC : Gly (0.75:5)
F2 : Concentration of HEC : Gly (0.75:10)
F3 : Concentration of HEC : Gly (1:5)
F4 : Concentration of HEC : Gly (1:10)

shown in F3 and F4, which each contained the same glycerin concentration.

Data were statistically analyzed to compare the pH values of niacinamide nanoparticle serum before and after stability testing, and no significant differences were found with a p-value greater than 0.05. A decrease in pH occurred after stability testing, caused by the interaction of CO2 with the aqueous phase of the serum, resulting in the formation of acidic compounds. Despite the decrease in pH, all four facial serum formulations maintained their pH values within the acceptable range (Maya et al., 2024). pH stability is an important parameter that determines the stability of a product. Understanding the pH change profile of a product can provide an overview of its stability.

**Viscosity**

Viscosity is an important parameter in the development of drug/cosmetic formulations administered percutaneously or through the skin. The required viscosity value for facial serum preparations generally ranges from 230 to 3000 cPs, with an optimal value of around 1900 cPs. Viscosity values that are too low or too high within this range can negatively impact user comfort and reduce absorption efficiency in the skin (Alissa et al., 2023; Tort & Karakucuk, 2021). Based on the viscosity test results shown in Table 3, all niacinamide nanoparticle serum formulas met the required viscosity values.

Viscosity values increased in F1, F2, F3, and F4 with increasing concentrations of HEC and glycerin in the niacinamide nanoparticle serum formulation. This is due to increased interactions between polymer chains, which form a more compact and rigid three-dimensional network structure. As structural rigidity increases, the system's flowability decreases, resulting in a significant increase in viscosity (Kokol, 2022). This finding aligns with research conducted by Stolz et al., (2021) which reported an increase in viscosity with increasing concentrations of HEC in cellulose nanoparticle formulations.

Table 4. Result of Spreadability Test of Niacinamide Nanoparticle Serum

| Formula | Before stability testing (cm) | After stability testing (cm) | *p value* | Description |
|---|---|---|---|---|
| F1 | 6.83 ± 0.058 | 6.89 ± 0.036 | | |
| F2 | 6.73 ± 0.029 | 6.77 ± 0.029 | 0.014 | Difference significant |
| F3 | 6.32 ± 0.126 | 6.38 ± 0.104 | | |
| F4 | 5.65 ± 0.050 | 5.75 ± 0.050 | | |

*Data were presented as mean ± deviation standard (n=3) and analyze statistically using Paired Sample T Test.
F1 : Concentration of HEC : Gly (0.75:5)
F2 : Concentration of HEC : Gly (0.75:10)
F3 : Concentration of HEC : Gly (1:5)
F4 : Concentration of HEC : Gly (1:10)

The serum viscosity test data of niacinamide nanoparticles were statistically analyzed to compare the values before and after the stability test. The analysis results showed a statistically significant difference with a p value of less than 0.05. The decrease in viscosity after the stability test is thought to be caused by an increase in temperature and humidity during storage, which can accelerate the absorption of water vapor from the environment into the preparation, resulting in an increase in water content in the formulation and causing a decrease in viscosity (Maya et al., 2024). The study reported by Saputra et al., (2023) also mentioned changes in viscosity observed after stability testing using the freeze-thaw or cycling test method. This is due to the possibility that the serum preparation absorbs water from the external environment, increasing the water volume and decreasing viscosity.

**Spreadability**

Based on the results shown in Table 4, it is known that the niacinamide nanoparticle serum has met the required spreadability test value with a range of 5-7 cm (Iskandar et al., 2023). There was a decrease in the spreadability value along with increasing concentrations of HEC and glycerin used, as shown in F1, F2, F3, and F4, respectively. Similar results were also shown in previous studies that reported a decrease in the spreadability value.

The data were statistically analyzed to compare the results of the niacinamide nanoparticle serum spreadability test before and after stability testing, and there was a significant difference with a p-value of less than 0.05. Based on the results of the study, the spreadability test value increased after stability testing. Similar results were shown in the study (Maya et al., 2024) which reported an increase in the spreadability value of serum preparations after stability testing associated with a decrease in viscosity values.

Table 5. Result of Adhesion Test of Niacinamide Nanoparticle Serum

| Formula | Before stability testing (s) | After stability testing (s) | *p value* | Description |
|---|---|---|---|---|
| F1 | 6.33 ± 0.577 | 6.00 ± 0.00 | | |
| F2 | 6.67 ± 0.577 | 6.33 ± 0.577 | 0.016 | Difference significant |
| F3 | 7.67 ± 0.577 | 7.00 ± 0.000 | | |
| F4 | 10.00 ± 0.000 | 9.67 ± 0.577 | | |

*Data were presented as mean ± deviation standard (n=3) and analyze statistically using Paired Sample T Test.
F1 : Concentration of HEC : Gly (0.75:5)
F2 : Concentration of HEC : Gly (0.75:10)
F3 : Concentration of HEC : Gly (1:5)
F4 : Concentration of HEC : Gly (1:10)

**Adhesion**

Based on the results shown in Table 5, all niacinamide nanoparticle serum formulas met the adhesion test requirements, namely more than 4 seconds. The data were statistically analyzed to compare the results of the serum adhesion test of niacinamide nanoparticles before and after the stability test, and there was a significant difference with a p value of less than 0.05.

**Stability Testing**

The stability testing of the niacinamide nanoparticle serum preparation was carried out using the cycling test method for 3 cycles by placing all formulas into a drying oven at 40°C for 24 hours and then transferred to a refrigerator for 24 hours. This process is counted as 1 cycle. At the end of the third cycle, the physical properties of the niacinamide nanoparticle serum preparation were re-observed. A paired sample *t*-test was used to compare the niacinamide nanoparticle serum formulations before and after stability testing. The results are presented in the evaluation tables, including pH, viscosity, spreadability, and adhesion. Statistically significant differences (<0.05) were observed in viscosity, spreadability, and adhesion, whereas no significant difference was found in pH (>0.05).

**Particle Size and Polidispersity Index**

Particle size is the most crucial factor which may affect the ability and skin penetration. An increase in particle size has been reported to reduce the permeability coefficient (Nafisi & Maibach, 2018). Particle size is particularly important for overcoming the stratum corneum, the outermost layer and primary barrier of the skin in percutaneous drug delivery systems. Moreover, penetration depth is a key determinant in the effective application of nanoparticles, especially in transdermal drug delivery (xMaeda et al., 2025; Mok, 2024). All formulations yielded average particle sizes within the nanometer range 134.7 – 152.2 nm, specifically from that

Table 6. Result of average particle size and polidispersity index of niacinamide nanoparticle serum

| Formula | Particle Size (nm) | Polidispersity Index | Zeta Potential (mV) |
|---|---|---|---|
| F1 | 134.7 | 0.610 | -10.3 |
| F2 | 139.9 | 0.624 | -11.8 |
| F3 | 141.6 | 0.825 | -12.2 |
| F4 | 152.2 | 0.926 | -13.0 |

F1 : Concentration of HEC : Gly (0.75:5)
F2 : Concentration of HEC : Gly (0.75:10)
F3 : Concentration of HEC : Gly (1:5)
F4 : Concentration of HEC : Gly (1:10)

presented in Table 6. These results were consistent with a previous study by Ahdyani et al., (2024) that reported average particles sizes for niacinamide nanoparticle gel ranging 217- 428 nm. Variations in HEC concentration were obtained to influence the particle size of niacinamide-loaded nanoparticles significantly with increasing HEC concentrations leading to larger particle sizes. This result is consistent with previous findings reporting size variations in synthesized silica nanoparticles prepared using different HEC concentrations. Larger aggregates were observed in formulations containing higher HEC concentrations (Clogston & Patri, 2011).

Particle size distribution is commonly used to describe the size range of nanocarrier systems and is expressed as the polydispersity index (PDI). Polydispersity (or dispersity, as recommended by IUPAC) refers to the degree of non-uniformity in particle size distribution. The PDI that also known as the heterogeneity index, is a dimensionless parameter obtained from cumulant analysis through a two-parameter fit of correlation data. Lower PDI values indicate a more uniform particle population, which values below 0.5 are generally considered relatively monodisperse, whereas values exceeding 0.7 reflect a broad size distribution. Overall, the PDI provides a quantitative representation of particle size populations within a sample, ranging from 0.610 – 0.926. The F1 and F2 showed monodisperse system, except for F3 and F4 showed for a highly polydisperse system with multiple particle size population (Danaei et al., 2018).

The Zeta potential is an indirect measure of surface charge and significantly influences colloidal stability and interfacial interactions. It depends on surface charge, which is crucial for the stability of nanoparticles in colloidal systems. Zeta potential is also a key factor in the initial adsorption of nanoparticles onto the cell membrane (Nafisi & Maibach, 2018; Ramalingam et al., 2010). All formula showed good zeta potential that presented

in Table 6. Nanoparticles with a Zeta potential below −30 mV are considered strongly anionic, which can influence their ability to permeate negatively charged cellular membranes (Nafisi & Maibach, 2018).

## CONCLUSION

All niacinamide nanoparticle serum formulas showed particle size within nanorange and has good Zeta potential. The results also met the requirements for viscosity, spreadability, adhesion, and pH values. Based on the results of the Paired sample t Test statistical analysis, there was a significant difference ($p<0.05$) in the results of the physical properties test of niacinamide nanoparticle serum preparations before and after stability testing with the cycling test method for 3 cycles, except for the pH test results.

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