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Physicochemical Characteristics, Entrapment Efficiency, and Stability of Nanostructured Lipid Carriers Loaded Coenzyme Q10 with Different Lipid Ratios

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ABSTRACT: Nanostructured Lipid Carriers (NLC) could be a good choice for dermal or transdermal delivery. It could dissolve lipophilic drugs, solve the problem of low skin permeation, and also be photoprotective. The composition of constituent materials and the ratio between solid lipid and liquid lipid influence the characteristics and stability of NLC. Compritol 888 ATO and Miglyol 812 have been widely studied for the development of dermal or transdermal preparation, but this combination has not been studied for use in Coenzyme Q10 loaded NLC systems. Aim of this study is to determine the effect of different lipid ratios of Compritol 888 ATO as solid lipid and Miglyol 812 as liquid lipid on the physicochemical characteristics, entrapment efficiency, and stability of NLC loaded Coenzyme Q10 using the High Shear Homogenization method. Three different lipid ratios were used in the NLC formulation, in which the ratio of Compritol 888 ATO : Miglyol 812 were 70:30, 80:20, and 90:10, respectively. NLC was characterized with FTIR spectra, differential scanning calorimetry, organoleptic, particle size, polydispersity index, zeta potential, pH, viscosity, entrapment efficiency, and evaluated for stability using the real-time method for 1 month. The result showed that the polydispersity index, zeta potential, and pH value were not significantly impacted by the various ratios of lipid. On the other hand, it had a considerable impact on particle size, viscosity, and entrapment efficiency. Formula 1 shows highest entrapment efficiency and smallest particle size, so it was chosen as the best formula.

KEYWORDS: Coenzyme Q10; Nanostructured Lipid Carrier; characterization; entrapment efficiency; stability.

1. INTRODUCTION

The continuous exposure of human skin to environmental pollutants, UV radiation, and other mechanical or chemical stresses that could produce in reactive oxygen species and free radicals. These reactive compounds were involved in the etiopathogenesis of various skin diseases, the aging process, and skin cancer [1]. To inhibit the oxidation process and cell damage, we need antioxidants. The production of endogenous antioxidant compounds decreases with age [2]. Giving exogenous antioxidants could be an alternative to restore antioxidant deficiencies and also protect the skin from damage and premature aging due to excessive ultraviolet radiation.

One of the antioxidants that was often associated with the aging process and aging-related diseases of the skin is Coenzyme Q10 (CoQ10) [3]. CoQ10 must pass through the epidermis in order to be delivered to the skin. Because of its high molecular weight (863.3 g/mol) and practically insoluble in water, CoQ10 was difficult to penetrate the skin [4]. Also, CoQ10 was unstable and easily degrades when exposed to light [5]. Therefore, a special delivery system was needed to dissolve and solve the problem of low skin permeation and also photoprotective. To improve CoQ10's photostability, enhance stratum corneum penetration, and provide an extended-release profile, some formulation techniques, especially those utilizing nano-sized carriers, have been widely investigated [6].

Compared with various types of nanoparticle carrier systems, lipid nanoparticles have been widely developed because they were more biocompatible and more stable than polymer nanoparticles. The lipid components were non-irritating and non-toxic, making the system suitable for drug delivery applications through the skin. Furthermore, they also provided high drug entrapment efficiency for both lipophilic and hydrophilic drugs [7].

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The lipid base could help dissolve the drugs. So, it might provide better membrane permeation and improve drug bioavailability [5]. Lipid nanoparticle systems could facilitate drug targeting and protect loaded drugs from environmental factors like light and oxygen. For topical applications, nanosized particles caused more contact with the stratum corneum, so it could increase the number of drugs penetrated. Increased penetration by lipid-based carriers was influenced by lipid's ability to modify the stratum corneum's conformation through a variety of mechanisms, including lipid exchange, structure-loosening, polarity changes, and stratum corneum fluidization [8]. Lipid nanoparticles are colloidal dispersions consisting of a dispersed lipid phase stabilized by an emulsifier. If solid lipids are used, they are called Solid Lipid Nanoparticles (SLN), and if a mixture of liquid lipids is added, they are called Nanostructured Lipid Carriers (NLC). Several studies have stated that NLC was better than SLN in stability and loading efficiency. It was because the presence of liquid lipids in NLC might prevent crystal growth, hence preventing the crystallization of solid lipids [9].

The preparation process and the composition of the constituent materials influence the NLC system's properties. High shear homogenization was a common preparation technique since it was easy to scale up, did not use organic solvents, and required less time to produce than other techniques [10]. One of the solid lipids that were often used in several studies of lipid nanoparticles was glyceryl behenate (Compritol 888 ATO) because of its ability to dissolve CoQ10 and trapped it properly [7, 11, 12]. For liquid lipids, several studies used medium chain triglycerides (MCT / Miglyol 812) because of its ability to increase the solubility of hydrophilic materials thereby increasing drug loading capacity and minimizing drug expulsion during storage [13].

In addition, the ratio of solid and liquid lipids is another factor that influences the characteristics of NLC. Solid and liquid lipids can be combined in a ratio of 70:30 to 99.9:0.1 to produce the NLC system [14]. This study aimed to investigate the physicochemical characteristics, entrapment efficiency, and stability of NLC produced at various ratios (70:30, 80:20, and 90:10) of Compritol 888 ATO and Miglyol 812 with a total lipid of 10% of the formulations.

2. RESULTS AND DISCUSSION

2.1. Fourier Transforms Infra-Red (FTIR) spectroscopy

Drug interactions with excipients present in formulations were examined using FTIR. The FTIR spectrum profile of the NLC system loaded Coenzyme Q10 (NLC-CoQ10) between three different ratios of the lipid matrix concentration is similar (Figure 1). When compared to the FTIR spectra of CoQ10 and the lipids, the FTIR spectra of NLC-CoQ10 did not show any additional peaks. It was because there were no chemical reactions that would have occurred in the NLC-CoQ10 forming new functional groups. CoQ10 was only trapped in the lipid matrix and there was only a physical reaction [15, 16].

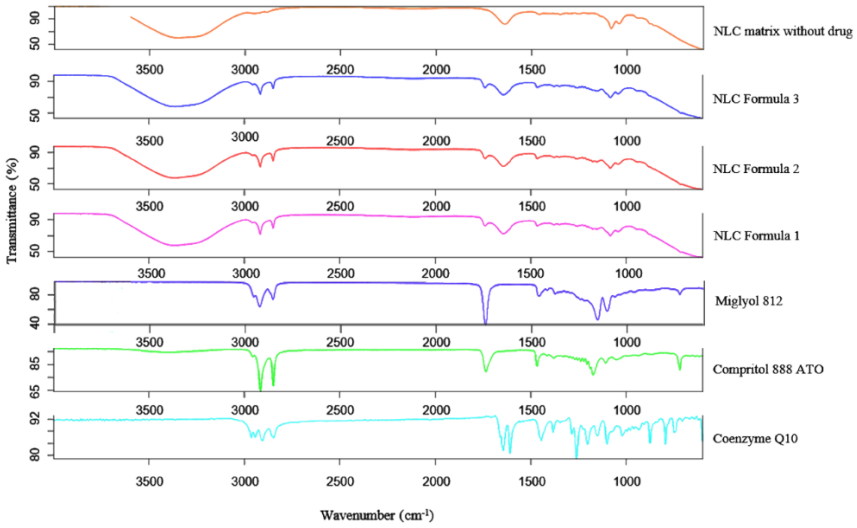

Figure 1. Infrared spectra of Coenzyme Q10, Compritol 888 ATO, Miglyol 812, NLC Formula 1, NLC Formula 2, NLC Formula 3, and NLC matrix at wave numbers 400-4000 cm^{-1}

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2.2. Differential Scanning Calorimetry (DSC)

The melting point of a sample can be determined using data from DSC analysis, such as a thermogram. As a function of temperature, DSC can identify heat changes brought on by physical or chemical changes in nanoparticles. Figure 2 shown the melting point of material component of NLC, whereas Figure 3 shown DSC thermogram for NLC formulas and physical mixture. In Figure 3, there were peak that higher melting point than the lipid in bulk. It may be an indication that a new bond formed, but it was not detected in the FTIR spectrum because it was no covalent bond. It might be a hydrophobic bond, which can occur from some hydrophobic material. It takes more energy to break a hydrophobic bond so that the melting point can be raised [17]. The melting point and enthalpy value of F2 are the lowest, probably because F2 forms a weaker bond than the others. Meanwhile, the melting point and enthalpy of F3 are the highest, because F3 has the highest ratio of solid lipids, so more effort is needed to break it down. The melting point of physical mixture was near with F1 but it has lower enthalpy value, it was because the physical mixture does not form bonds as strong as in NLC so it was easier to break.

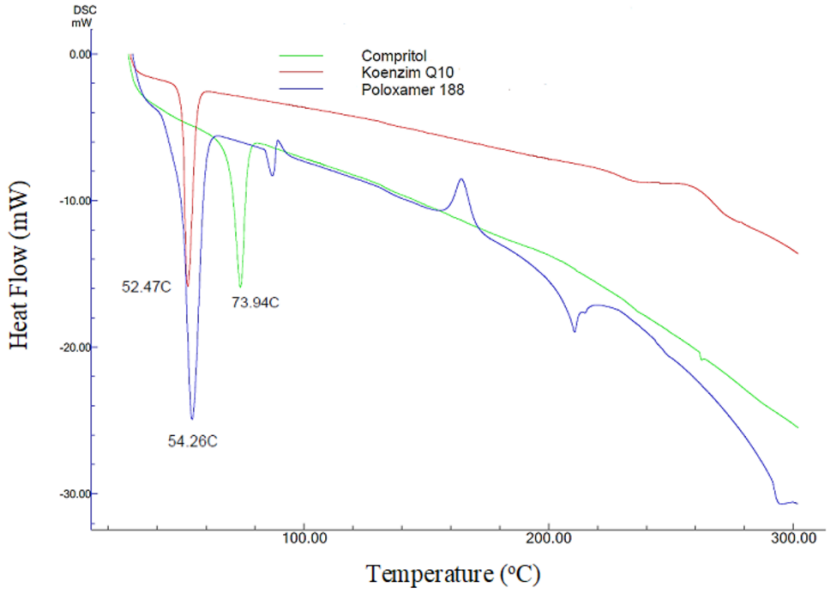

Figure 2. DSC examination results from Coenzyme Q10, Compritol 888 ATO, and Poloxamer 188

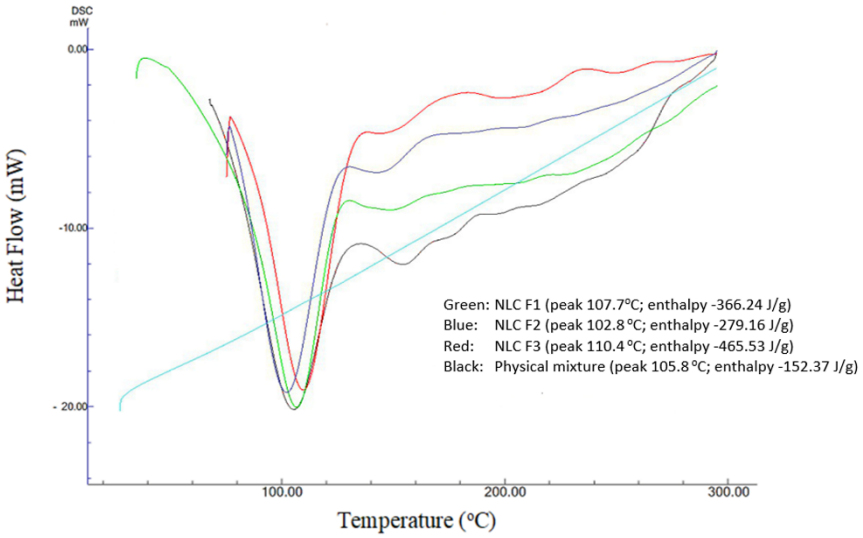

Figure 3. DSC examination results from NLC-CoQ10 formula 1, formula 2, formula 3, and physical mixture

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2.3. Organoleptic test

The organoleptic observation showed that the NLC-CoQ10 was yellow, specific odor, and had a semisolid form and soft texture, as shown in Figure 4.

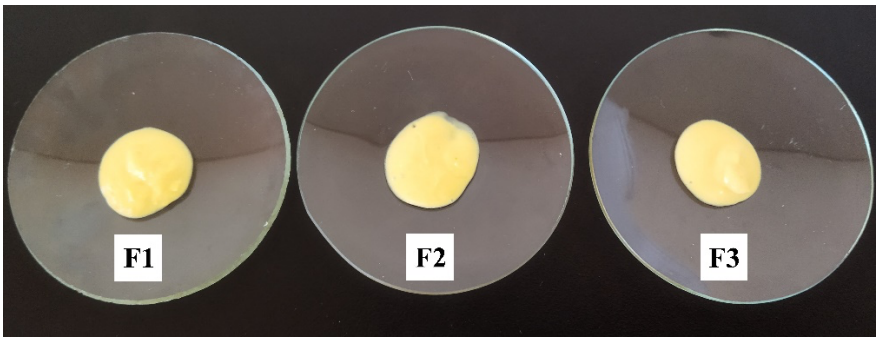

Figure 4. NLC-CoQ10 systems for Formula 1 (F1), Formula 2 (F2), and Formula 3 (F3)

2.4. Particle size and polydispersity index evaluation

A carrier system's ability to penetrate the bio-membrane is determined by the average particle size. Particle size is influenced by some factors i.e the type of surfactant, concentration of surfactant, manufacture method, concentration, and ratio of liquid lipids and solid lipids [18]. This study found that increasing liquid lipid ratio contributed to smaller particle size (Table 1). Statistically, it showed a significant difference in at least one pair between the groups of formulas F1, F2, and F3 at $\alpha = 0.05$. The results of the post hoc test using Tukey HSD showed that the significantly different groups for particle size are F1 with F3, and F2 with F3. However, the particle size values show that there was a tendency for average particle size F1 < F2 < F3. Smaller particle size was obtained when the ratio of liquid lipids in the formula was increased. Liquid lipid helps to dissolve the drugs thereby allowing the system particle size to be smaller [19].

The particle size distribution can be seen from the polydispersity index. The polydispersity index indicates the uniformity of particle sizes within the sample population [20]. A polydispersity index that is lower than 0.5 indicates homogeneity and mono-dispersity formulation. If polydispersity index > 0.5 indicates a less homogeneous size variation or polydispersity in the formulation. The polydispersity index obtained from this study shows an average result of < 0.5, it indicates a homogenous particle size distribution in the system. The statistical analysis of polydispersity index found no significant differences between all the formulas.

2.5. Zeta potential evaluation

The stability of the colloidal dispersion is indicated by the zeta potential. Generally, the zeta potential of the nano-dispersions outside the 30 mV range indicates particle aggregation can be avoided due to electrical repulsion. Although several studies with lower zeta potential values still give a stable form during storage [21]. The average result of zeta potential in this study was under -10 mV. The statistical analysis of zeta potential found no significant differences between all the formulas.

2.6. pH evaluation

The average pH of all formulas demonstrated that NLC systems can be used for topical administration in accordance with normal skin pH of 4 - 6 [22]. The statistical analysis of pH found no significant differences between all the formulas.

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Table 1. Physicochemical characterization of NLC-CoQ10 systems

Formula	Particle Size (nm)	Polydispersity Index	Zeta Potential (mV)	pH	Viscosity (cps)
1	205.2 ± 14.5	0.354 ± 0.042	-9.7 ± 1.0	6.06 ± 0.07	40.51 ± 0.48
2	234.4 ± 10.5	0.378 ± 0.046	-9.5 ± 1.7	5.99 ± 0.25	41.86 ± 0.45
3	280.6 ± 18.3	0.426 ± 0.109	-8.6 ± 1.8	5.94 ± 0.19	43.55 ± 0.48

2.7. Viscosity test

The parameter that also affects the acceptability for topical administration is viscosity. The proper viscosity is required for NLC to adhere to the skin surface, thereby increasing drug penetration and residence time [20]. Viscosity can describe the ease of preparation when applied and predict the ease of moving molecules associated with drug release. Statistically, the three groups of formulas showed significant differences in viscosity. This viscosity value decreases as the amount of liquid lipid in the formula increases. This is consistent with the theory that a higher liquid lipid ratio can reduce the viscosity and reduce particle size, consequently resulting in a greater release of the drug and improved penetration ability [19].

2.8. Entrapment efficiency test

The results of the entrapment efficiency test showed a significant difference among all formulas (Table 2). The entrapment was increased with an increasing liquid lipid ratio. This is consistent with the theory that an increase in the liquid lipid ratio will improve the flexibility of the NLC core by influencing the imperfections in the crystal lattice, causing numerous drugs to be trapped in the system during the solidification of the lipid phase. This increase in the flexibility of the NLC core is also useful for preventing expulsion [19].

Table 2. The entrapment efficiency of NLC-CoQ10 systems

Formula	Entrapment Efficiency (%)
1	92.73 ± 0.93
2	87.90 ± 0.90
3	84.60 ± 0.69

2.9. Stability test

The stability test result of the NLC-CoQ10 with various ratios of solid lipid and liquid lipid can be seen in Table 3. There was no change in organoleptic observation during storage for all formulas. The NLC-CoQ10 systems did not significantly change pH and polydispersity index values, but statistically significantly changed particle size and viscosity. There were increments in the particle size and viscosity, which indicates the incorporation of small particles or coalescence. It is shows that the system is not stable enough so optimization is still needed to obtain the best system that has a long shelf life.

Table 3. Stability test results of NLC-CoQ10 systems in real-time method

Formula	Days	Parameters				
		Organoleptic	Particle Size (nm)	Polydispersity index	pH	Viscosity (cP)
1	1	Conform	205.2 ± 14.5	0.354 ± 0.042	6.13 ± 0.07	40.51 ± 0.48
	15	Conform*	282.9 ± 45.5	0.341 ± 0.101	6.23 ± 0.02	40.17 ± 0.11
	30	Conform*	299.2 ± 44.1	0.373 ± 0.101	6.10 ± 0.03	39.86 ± 0.48
2	1	Conform	234.4 ± 10.5	0.378 ± 0.046	5.99 ± 0.25	41.86 ± 0.45
	15	Conform*	310.2 ± 63.2	0.406 ± 0.058	6.21 ± 0.04	40.92 ± 0.53
	30	Conform*	325.4 ± 57.9	0.399 ± 0.035	6.06 ± 0.02	40.83 ± 0.56
3	1	Conform	280.6 ± 18.3	0.426 ± 0.109	5.94 ± 0.19	43.55 ± 0.48
	15	Conform*	340.0 ± 47.5	0.414 ± 0.214	6.18 ± 0.04	41.72 ± 1.15
	30	Conform*	359.9 ± 38.0	0.392 ± 0.041	6.04 ± 0.03	41.20 ± 0.85

Conform: Semisolid form, yellow color, and characteristic odor
* : There were no discoloration, odor change, and phase separation

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3. CONCLUSION

The lipid carriers Compritol 888 ATO and Miglyol 812 for the NLC-CoQ10 system have been successfully developed. Small particle size, low crystallinity, and good Coenzyme Q10 entrapment efficiency were all characteristics of the NLC that were generated. This study showed that the entrapment efficiency of the NLC system and some physicochemical characteristic parameters were affected by the different ratios of Compritol 888 ATO and Miglyol 812. The polydispersity index, zeta potential, and pH value were unaffected significantly. However, the entrapment efficiency, particle size, and viscosity from three various formulas showed a considerable difference. Based on physicochemical characteristics and entrapment efficiency, Formula 1 shows highest entrapment efficiency and smallest particle size, so it was chosen as the best formula.

4. MATERIALS AND METHODS

4.1. Materials

Coenzyme Q10 (Kangcare Bioindustry - China), Compritol 888 ATO (Gattefosse - France), Miglyol 812 (Sigma Aldrich - USA), Poloxamer 188 (BASF - Germany), and propylene glycol (Dow Chemical Pacific - Singapore). All of these substances were pharmaceutical grade, unless otherwise noted.

4.2. Tools

High Shear Homogenizer (T25 Ultra-Turrax IKA®), Fourier Transform Infrared (Bruker Alpha-II), Differential Scanning Calorimetry (Shimadzu DSC-60 plus), Centrifuge (Hettich Rotofix 32), Double Beam Spectrophotometer UV-vis (Shimadzu UH5300), Particle Size Analyzer (Delsa™ Nano), Zetasizer Nano (Microtrac Nanotrac Wave II), pH Meter (Transinstrument WalkLAB HP9010), Viscometer Cone and Plate (Brookfield).

4.3. Preparation Method of NLC

NLC loaded Coenzyme Q10 (NLC-CoQ10) was prepared using the High Shear Homogenization (HSH) method. The method has been adopted from the previously reported studies in the literature with slight modification [23]. The composition of the NLC-CoQ10 with various ratios of solid lipid and liquid lipid can be seen in Table 4. Using a hot plate set to 80 °C, Compritol 888 ATO and Miglyol 812 were placed in a beaker glass and melted. Then put some CoQ10 into the mixture. Separately prepared surfactant solution (Poloxamer 188) in phosphate buffer solution (pH 6.0) and heated using a hot plate at 80 °C. The water phase is added gradually into the oil phase. A high-speed homogenizer was then used to stir this mixture for 2 minutes at 3400 rpm. Then slowly added the mixture of propylene glycol and phosphate buffer solution (pH 6.0) which has been heated at 80 °C using a hot plate. The mixture was homogenized by high shear homogenizer at 20,000 rpm for 5 minutes in three cycles with constant heating at 80 °C after all the ingredients had been added. The result was cooled while stirring at 500 rpm until room temperature and the best NLC system was obtained.

Table 4. The composition of NLC formulas (% w/w)

Composition	Formula 1 (F1)	Formula 2 (F2)	Formula 3 (F3)
Coenzyme Q10	2.4	2.4	2.4
Compritol 888 ATO	7	8	9
Miglyol 812	3	2	1
Poloxamer 188	8	8	8
Propylene glycol	8	8	8
Phosphate buffer solution (pH 6.0)	q.s	q.s	q.s

4.4. Fourier Transforms Infra-Red (FTIR) spectroscopy

Amounts of samples were placed in the sample holder on the instrument, then pressed with a hydraulic press, and then scanned at a wave number of 400-4000 cm^{-1}.

4.5. Differential Scanning Calorimetry (DSC)

The material was placed into an aluminum pan after being weighed at 2-8 mg. A temperature rise of 10°C per minute was used to heat this pan to a temperature between 30 and 300 °C.

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4.6. Organoleptic test

Organoleptic tests were carried out by visually determining the form, color, and odor of NLC systems.

4.7. Particle size and polydispersity index evaluation

In 50 ml of distilled water, approximately 50 mg of NLC system were dispersed. Then put 2 ml of solution and added by distilled water up to 10 ml. The sample was placed in the cuvette and perform a measurement.

4.8. Zeta potential evaluation

Approximately 3 ml sample was diluted in 10 ml distilled water. After that, the sample was kept in the sample holder until the measurement result was stable. The dilution rate in zeta potential measurements is different compared to particle size measurements because it uses different instrument so that it follows a procedures that have been validated for each instrument.

4.9. pH evaluation

In 20 ml of distilled water, approximately 1 g of NLC system was dispersed, then immersed the electrode into the sample. A digital pH meter was used to measure the pH value of the NLC preparations, which were already calibrated.

4.10. Viscosity test

A viscometer was used to determine the viscosity of the samples. About 2 ml samples were poured into the container, and the spindle had to be sunk into it.

4.11. Entrapment efficiency test

The centrifugation technique was used to measure drug entrapment efficiency. The amount of free drug was measured to estimated amount of drug trapped, then the entrapment efficiency was calculated using the ratio of the amount of drug trapped to the total amount of drug added. About 2 g of NLC systems were centrifuged for 60 minutes at 3000 rpm. After phase separation, the supernatant was collected and 10.0 ml of ethanol was added. About 1 ml solution was taken and added with ethanol again up to 10.0 ml. The amount of drug was measured at 274 nm by spectrophotometry.

4.12. Stability test

A stability test was performed using real-time conditions at room temperature (25 ± 2 °C). The organoleptic, particle size, polydispersity index, pH, and viscosity properties were evaluated on 1, 15, and 30 days.

4.13. Statistical analysis

To statistically analyze the characterization, which includes particle size, polydispersity index, zeta potential, pH, viscosity, and entrapment efficiency, a one-way Analysis of Variance (ANOVA) technique was utilized. On the other hand, to statistically analyze the stability of each formula during storage, a repeated measure ANOVA technique was utilized.

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