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Vitamin E Loaded Nanoliposomes: Effects of Gammaoryzanol, Polyethylene Glycol and Lauric Acid on Physicochemical Properties

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ABSTRACT

Vitamin E is a sensitive compound that must be protected from peroxidant agents such as free radicals. In this study, the vitamin E loaded nanoliposomes containing different stabilizers such as gammaoryzanol (GO), polyethylene glycol 400 (PEG-400), and lauric acid (LA) were prepared by thermal method. The effects of these stabilizers on the particle size, zeta potential, turbidity and encapsulation efficiency stability of vitamin E loaded nanoliposomes were investigated during appropriate time intervals of 0, 20, and 40 days. Particle sizes ranges were about 72 to 302.7 nm with the polydispersity index around 0.190 to 0.381. Vitamin E and stabilizers increased particle size and decreased particle size distribution and GO showed the highest effect. In all samples, encapsulation efficiencies and encapsulation stability (ES) were more than 78% and the highest and lowest encapsulation efficiency were observed in the samples containing GO and LA, respectively.

1. Introduction

Consumers around the world are aware enough to have a healthy diet, especially foods with more health benefits which are called functional foods [1, 2]. Thus, one of the challenges in the food industry, in order to design functional foods, is the delivery of nutrients to consumers' diet to achieve their health benefits, while the basic properties of initial foods such as tastes and aromas are not influenced [2]. Direct adding of nutraceuticals to the foods could have many technical and physical defects which can make the fortified foods non acceptable. Due to the fact that many nutrients are insoluble in an aqueous media and have low chemical and physical stability when exposed to the food matrix, they cannot be added directly to the foods [3, 4]. Hence, the delivery systems such as liposomes are used to solve these types of problems.

Vitamin E as a nutraceutical is an essential vitamin for the human body that provides the health and stability of cells and cell membranes, and naturally can be found in beans, whole grains, and vegetable oils. Vitamin E has multiple isomers, including δ, γ, β, α- tocopherol, and tocotrienol. Activity and bioavailability of each of them depends on their structure. Among these isomers, α- tocopherol is the most biologically active and has more bioavailability than other forms [5]. Vitamin E is the body's most important fat-soluble natural antioxidants, which strengthen the immune system and prevent coronary heart diseases, but the food sources of vitamin E do not provide the body needs. Vitamin E in the form of α-tocopherol protects polyunsaturated fatty acids in cell membranes and reduces the stickiness of platelets in the blood [6]. α- tocopherol is a fat-soluble antioxidant and its oxidized form can be reduced by ascorbic acid. The encapsulation of it is necessary for increasing solubility in food and cell membrane, intestinal absorption and preventing from adverse effects of environmental conditions and unfavorable organoleptic changes in foods and beverages. Many delivery systems developed for the encapsulation of the vitamin E, depending on cost, ease of use, and biocompatibility such as liposome, noisome and NLC.

[7, 8].

Liposomes are lipid vesicles with bilayer membranes, which are composed of polar lipids and sometimes sterols, phospholipids such as lecithin (phosphatidylcholine) and cephalin (phosphatidyl ethanol amine) are polar lipids which mainly are used in formulation of liposomes [9]. The size of liposome particles is mostly from 10 nm to 10 μm, depend on production method. As their structures are similar to the cell

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membranes, they are very good candidates for transferring bioactive compounds into the cells. Furthermore, due to the presence of both lipid and aqueous phase in the structure of liposomal vesicles, they can be used in encapsulating amphiphilic, hydrophilic, and lipophilic bioactive compounds. They can encapsulate lipophilic bioactive compounds in the bilayer membrane and hydrophilic compounds in the inner core [10]. The liposomes are divided to small (unilamellar) and large (multilamellar) vesicles [9, 10].When the size of particles is reduced to a nanometer scale in the production of unilamellar nanoliposomes, the surface area is increased [10]. In this case, vesicles are absorbed with the cell membrane more easily than the pure compounds which enhance the bioavailability and solubility. The liposomes are prepared by different methods as film hydration, ethanol injection, and reverse phase evaporation. Nowadays, liposomes can produce by some methods without organic solvents such as thermal method [10].

Nanoliposomes has been used for encapsulation of different food bioactives and nutraceutical compounds such as vitamin C [11], vitamin E [12], vitamin A [9], DHA and EPA [13], nisin [14], carvacrol and thymol [15], and lipase [16], fish oil [17].

Different types of instability can be observed in nanoliposomes during production and storage time so that, different solutions can be used to overcome these issues and adding stabilizers can be one of these solutions. Various compounds for stabilizing of liposomal membrane have been used in liposome formulation which most important of them is sterols (cholesterol and phytosterols), saturated fatty acid and polyols. These compounds can improve size and encapsulation stability of vesicles during storage time [17]. The aim of this study was comparative study of some food grade compounds including gammaoryzanol, polyethylene glycol 400, and lauric acid on particle size and encapsulation stability of vitamin E loaded nanoliposomes.

2. Materials and Methods

2.1. Materials

Phosphatidylcholine (alpha- Phosphatidylcholine, PubChem CID: 45266626) with purity of more than 97% was provided from Acros Organics, Belgium. Vitamin E (PubChem CID: 2116) with 99% purity was purchased from ATA, Luxemburg. Polyethylenglycol 400 (PEG400, PubChem CID: 81248), Glycerol (PubChem CID: 753) with 99% purity and Lauric acid (PubChem CID: 3893) with 99% purity was obtained from Merck Chemical Co., Darmstadt, Germany. Gammaoryzanol (GO, PubChem CID: 5282164) was purchased from Tsuno Rice Chemicals, Japan. Other materials included deionized water and analytical grade of chloroform and methanol solvents.

2.2. Methods

2.2.1. Preparation of Liposomes

lecithin (250 mg lecithin) samples were fully hydrated (1 ml of deionized water) in an incubator shaker with 60 rpm at 60 °C for a day [18]. For preparation of liposomes without stabilizer and vitamin E (control sample) 250 mg of hydrated lecithin was mixed with 8 ml glycerol. For Preparation of vitamin E loaded liposomes, 50 mg of vitamin E was dissolved in 8 ml glycerol and then added to 250 mg of hydrated lecithin. For preparation of vitamin E loaded liposomes containing stabilizer, vitamin E, lauric acid and PEG400 with different ratios were dissolved in glycerol and then were added to 250 mg hydrated lecithin. In preparation of liposomes containing vitamin E and GO, first GO was dissolved in 5 ml PEG400 at the ratios of 1:5 and 1:10 v/v and was mixed with stirrer to achieve a clear solution then vitamin E was added to this solution. Then, 40 ml of twice-distilled water was added in all samples. All samples were poured in baffled glass vessel in order to create turbulent flow and were stirred with 1200 rpm at 65 °C for 1 h. To make stable liposomal solutions the samples stored at room temperature for 20 min and then they sonicated using probe sonicator (Hielscher UP200H, Germany) at cycle of 0.5 s and amplitude of 80% (200 W, 24 kHz) for 15 min at intervals of 1 min [19]. The prepared samples (without stabilizer, GO 25 mg, GO 50 mg, LA 25 mg, LA 50 mg, PEG-400 25 mg, and PEG-400 50 mg) were stored in a refrigerator at 4 °C for next evaluations.

2.2.2. Particle Size, Polydispersity, and Zeta Potential Analysis

The mean particle diameter (*Z*-average), polydispersity index (PDI) and zeta potential of samples was measured using a dynamic light scattering instrument (Zetasizer Nano ZS, Malvern Instruments, UK). To avoid multiple scattering effects, samples were diluted before the particle size measurements using deionized water. Zeta potential was measured at room temperature and pH of 4.7 [20]. All measurements were conducted in triplicate after overnight storage of samples.

2.2.3. Encapsulation Efficiency

To measure the amount of vitamin E encapsulated in liposome, UV-VIS spectrophotometer was used (Ultrospec 2000, England). The effect of the concentration and type of different stabilizers on the encapsulation efficiency of vitamin E was examined. A measurement of the amount of vitamin E encapsulated in liposome was carried out by the destruction method of liposome with chloroform-methanol (2:1). Chloroform-methanol, cause the dissolution of the liposomal membranes and therefore encapsulated vitamin E will be released. For this purpose, first, 0.5 ml of samples were taken and then centrifuged at 28*g* for 20 min. The supernatant contains free unloaded vitamin E. Then 0.4 ml of lower solution were taken and dumped in Falcon tubes. After that 2.4 ml chloroform-methanol (2:1) was added and stirred in a mixer for 5 min to completely break liposomes and release the encapsulated vitamin E. Due to opaque emulsion formation, the solution was centrifuged for 20 min once again until two-phase solution was completely achieved. Then absorbance of the lower solution was read at λ_{max} of vitamin E (285 nm) by spectrophotometer. The encapsulation efficiency and encapsulation stability were calculated by the following equations [21].

$$\text{Encapsulation Efficiency (EE\%)} = \frac{\text{Encapsulated Vitamin E in liposomes}}{\text{Total vitamin E (Encapsulated + free vitamin E)}} \times 100 \quad (1)$$

$$\text{Encapsulation satbility (ES\%)} = \frac{\text{Rremained Vitamin E in liposomes during storage time}}{\text{Intial encapsulated amounts of vitamin E}} \times 100$$

2.2.4. The Measurement of Turbidity

Turbidity of liposomal samples with and without vitamin E was measured by uv-vis spectrophotometer (Ultrospec 2000) at 600 nm. For this purpose, 1 ml of samples were diluted with 2 ml of distilled water and were kept at room temperature for 30 min, then absorption was read on the wavelength of 600 nm by spectrophotometer.

2.2.5. Physical Stability of Liposomal Solutions

Physical stability of colloidal systems during storage is one of the main characteristics. To evaluate the physical stability, liposomal solutions prepared in 40 ml Falcon tubes and maintained at a temperature of 4 °C. Then the parameters such as encapsulation efficiency, particle size, polydispersity index and zeta potential were analyzed at the time intervals of 1, 20, and 40 days [22].

2.3. Statistical Analysis

Statistical analysis was carried out on a completely randomized design (CRD) using one-way ANOVA and Duncken's mean comparison tests at the 5% significance level using SPSS version 18.0. Time of storage (1, 20, 40 days) and types of stabilizers were independent

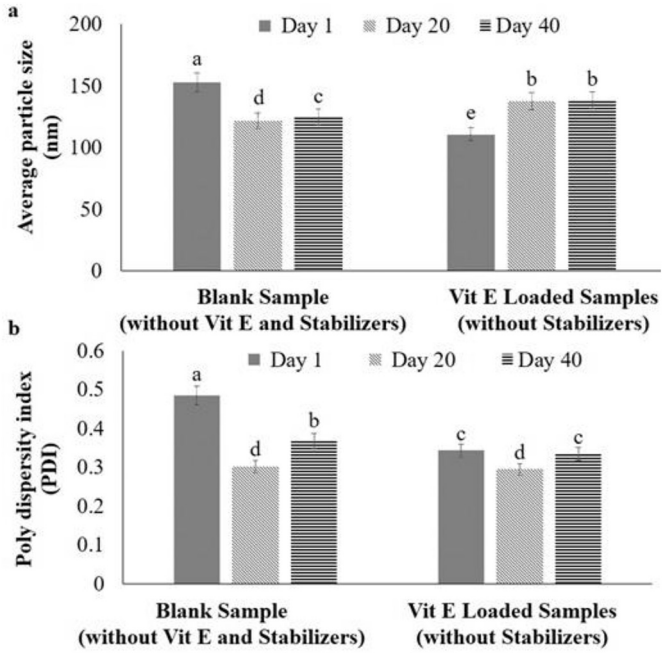

Fig. 1. Comparison particle size (a) and polydispersity index (b) of vitamin E loaded nanoliposomes (without stabilizers) with the blank sample (different words shows significant different at significant level of 5% Duncan-Test).

variables. The particle size, PDI, turbidity, zeta potential and encapsulation stability of liposome were dependent variables.

3. Results

3.1. Particle Size Analysis

3.1.1. Effect of Vitamin E Loading on Particle Size

Vitamin E is a terpenic hydrophobic compound and similar to cholesterol, is an important component of cell membranes. Phospholipid acyl chains create a suitable and safe environment for protecting vitamin E from oxidation and hydrolytic degradation.

According to Fig. 1a using vitamin E in the production of nanoliposomes caused reduction in the initial size of nanoliposomes and increases zeta potential during storage time (See section 3.4). Average particle size of nanoliposomes with and without vitamint E ranged from 110.7 to 138.5 nm and 121.7 to 152.7 nm, respectively. Lipophilic nature of vitamin E and its placement in nanoliposomes between two layers of phospholipids can change the properties of the membrane arrengement. The establishment of link between vitamin E and polar parts of membrane can change rearrangement of acyl chains in membrane which in turn lead to decrease in particle size. Furthermore, possible increase of the membrane rigidity and surface charge could cause less flocculation which lead to formation of smaller particles.

Vitamin E having a hydroxyl group in its structure which can form hydrogen bonds with choline group of phospholipid (having positive charge) and bring it inside the vesicle. This induces an increase in surface negative charge and consequently enhances the zeta potential of nanoliposomes. However, over the time, without presence of stabilizers, vitamin E has not been able to maintain the small size of particles (Fig. 1a). The incorporation of core material normally increase the particle size by being placed in the vesicles however, if the bioactive compound be able to cause more optimal packing in bilayer, a size reduction would be occurred. The results of this section are in a good match with previous works which have been shown the nanoliposomes containing vitamin E have smaller sizes than those without it [23]. They reported that their observations were due to interactions between cholesterol and vitamin E. They also stated that the zeta potential of

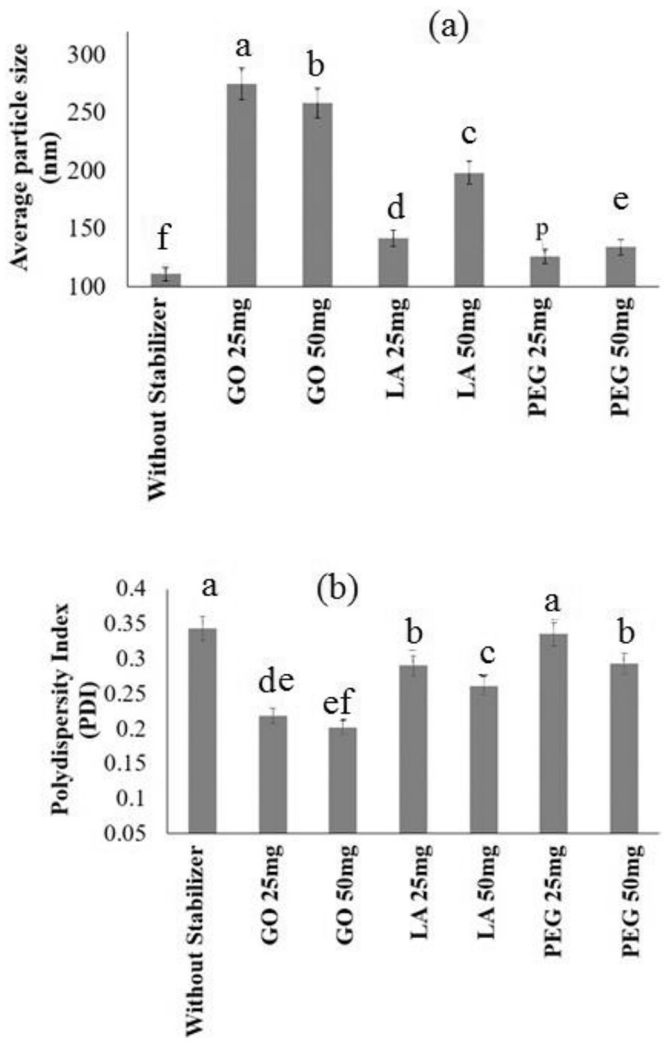

Fig. 2. Particle size (a) and size distribution (b) of nanoliposomal samples containing different stabilizers (GO: gammaoryzanol, LA: lauric acid and PEG: polyethylene glycol, different words shows significant different at significant level of 5% Duncan-Test).

nanoliposomes increased by loading them with vitamin E and the values of the zeta potential was high enough in the samples during storage in order to inhibit binding and flocculation [23].

As shown in Fig. 1b, vitamin E reduced the particle size distribution and the further decline was carried out over time. During storage time, molecular migration from small vesicles to large ones could be occurred which caused to decrease in polydispersity and increase in particle size.

3.1.2. Effect of Stabilizers on Particle Size

Particle size and particle size distribution are important in the stability of colloidal carrier systems, solubility, appearance and bioavailability of encapsulated ingredient. In this research, the effects of different stabilizers such as GO, LA and PEG-400 at two stabilizers to lecithin ratios (10% and 20%) w/w on the particle size and polydispersity of vitamin E loaded nanoliposomes were investigated. According to the Fig. 2a, average particle size of different samples varies from 110.7 to 274.85 nm which indicates that thermal method with sonication treatment can produce sub-micron and nanometeric size particles. All stabilizers caused to increase in particle size of vesicles and the samples containing GO and PEG showed maximum and minimum size, respectively. Stabilizers may cause to change in the position and orientation of the lipid acyl chains in the bilayer. These changes can lead to increase of regularity and fill of void spaces by

encapsulated material which in turn decreases in size or increase of irregularity which lead to increase of vesicle size.

GO is a mixture of phytosterol which has similar structure with cholesterol. Cholesterol potentially is responsible for high strength and integrity in bilayer membrane however, is not desired from dietary aspect. Both GO and vitamin E is lipophilic compounds and hence, probably is placed in liposomal double layer (hydrophobic region) with different orientations which in turn increase particle size. This result conformed to previous studies that showed the adding of plant sterols to liposome formulations containing vitamin C, increases particle size [17, 24]. In contrast, some researchers suggested that the addition of GO to liposomes reduced particle size [21]. The effect of cholesterol on liposome formulation prepared by thin layer method was studied and the results showed that cholesterol increased stiffness of liposomal double layer and size of the vesicles. Adding cholesterol to liposomes produced by extrusion method increased stiffness and particle size however, there was no change in particle size distribution [25]. The difference in the results of different researchers may be related to the method of preparation or type of encapsulated material. PEG is a long chain hydrophilic polymer which more interest to place on the liposomes surface and less in bilayer. This probably causes to less interfere of PEG in orientation of acyl group and increase steric hindrance among vesicles. This potentially decreases flocculation of vesicles during storage time which in turn increase stability of particle size. Lower polydispersity index represents narrower particle size distribution and a homogeneous colloidal system. Samples with a narrow size distribution are more resistant to the instability phenomenon called Oswald ripening. In this study according to Fig. 2b, size distribution of nanoliposomes was in the range of 0.2 to 0.4 which can be considered relatively narrow particle size distribution. The highest PDI was observed in the samples without stabilizers and samples containing polyethylene glycol 400 (10%). The samples containing GO (50 mg), had lowest PDI. The results of this study were compatible with the results of [17]. They reported that, adding phytosterols caused narrow particle size and mono modal distribution.

Overall, particle size of liposomal colloidal system depends on several factors such as type and concentration of stabilizer and encapsulated active material, liposome preparation method and processing conditions (temperature, agitation rate and time). This parameter should be monitored in liposome preparation.

3.2. Turbidity Evaluations

The turbidity of a colloidal system is originated form light scattering by particles and depends on nature, size and number of dispersed particles. According to the Fig. 3, the highest level of turbidity could be observed in the liposome stabilized by GO 10% which could be attributed to maximum particle size of this sample in comparison to other liposomal formulations. As well as, the lowest level of turbidity was related to the nanoliposomes containing PEG-400, which could be related to the both lowest particle size and nature of stabilizer. It was reported that liposomes above 200 nm affect the turbidity of colloidal systems, which conforms to the results obtained in this study [26]. This result was also approved by considering the samples without stabilizers, which had the lowest particle sizes.

3.3. Zeta Potential Stability

Zeta potential is an important parameter in the stability of the charged particles such as liposomes and its measurement is useful in controlling of aggregation [27]. Furthermore, it is effective parameter in binding of liposomes to cell membrane and binding of active materials to liposomes and release rate. According to the Fig. 4, zeta potential of nanoliposomes varied from −36.95 to −78.42 which indicate high electrostatic stability of the nanoliposomes prepared by thermal method and the strong effects of the selected stabilizers on zeta

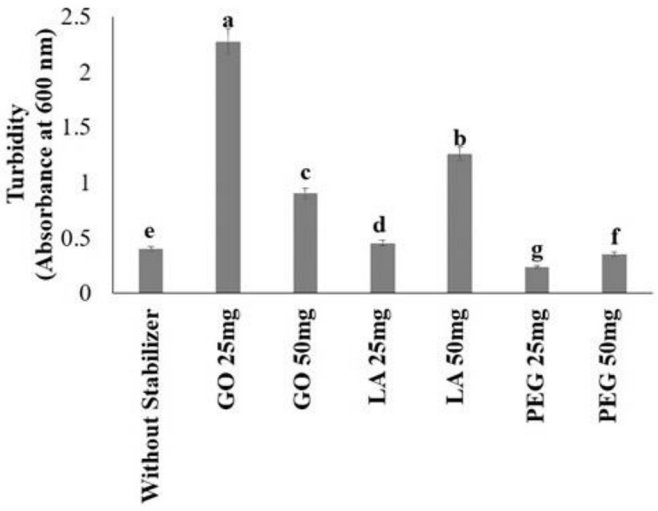

Fig. 3. Turbidity of nanoliposomal solutions containing different stabilizers (different words shows significant different at significant level of 5% Duncan-Test).

potential of vesicles. All the samples maintained high zeta potential during storage time and samples containing GO have more zeta potential stability than other liposomal formulations. In general, if the zeta potential of particles be more than −30 mV, high colloidal stability will be obtained due to strong repulsion force between the particles [22]. Various parameters are effective on zeta potential of liposomes such as type and concentration of phospholipid, encapsulated compound and stabilizer, ion strength of medium and temperature. Sterols can form hydrogen bond with choline groups (with positive charge) which can probably cause to repel of them to surface and pull the phosphate group (with negative charge) to bilayer. This leads to increase of zeta potential in vesicles. Another reason for providing stable nanoliposomes during 40 days can be attributed to the low storage temperature (4 °C) and keeping them in dark place. Exposing to high temperatures and light, can lead to changes in the crystal structure of membrane lipids and may soften and reduction in zeta potential which in turn lead to reduced repulsion force and then particles are prone to aggregate.

3.4. Encapsulation Efficiency and Stability

As can be seen in Fig. 5a, the added stabilizer has been show different effects on encapsulation efficiency (EE%) of vitamin E loaded liposome. All samples showed EE% more than 75%. GO and PEG increased the EE% and lauric acid decreased it in comparison to the sample without stabilizer. The liposomes containing GO and lauric acid showed the highest and lowest %, respectively. Encapsulation stability (ES%) of different samples showed similar trends (Fig. 5a). Stabilizers with modifying acyl chain arrangement, cohesiveness and permeability of membrane can cause to change in active material diffusion and coalescence rate which in turn changes encapsulation stability. In samples containing PEG, ES% increased during storage which could be attributed to bonding unloaded vitamin E to the hydrophilic surface vesicles [28]. Liposomes are thermodynamically unstable systems and tend to flocculation and release during storage time. Active substance's tendency to leave the liposomal structure can be decreased by modifying the structure of the membrane [29]. According to previous study, the use of lipophilic phytosterols like GO in liposomes, can increase the encapsulation stability during storage time [17]. In this research, the amount of ES% in all samples remained almost constant during storage time which can be attributed to the lipophilic nature of the vitamin E and its tendency to remain in the phospholipid bilayer. Vitamin E also has the OH groups in its structure, which can interact with lecithin by

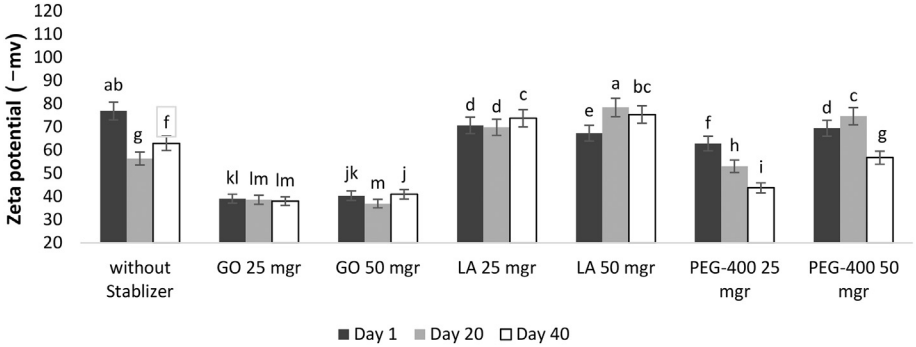

Fig. 4. Zeta potential of nanoliposomes containing different stabilizers (different words shows significant different at significant level of 5% Duncan-Test).

hydrogen bonds and increase the stability of liposomal membrane and remain in the bilayer membrane. On the other hand, glycerol used in this study as a co-solvent of vitamin E, having free hydroxyl groups which can be interact with choline in phosphatidylcholine and hence probably increases stiffness and stability of the membrane which in turn increases the stability of the encapsulation. Rasti et al. [13]. reported slight changes were seen in particle size and encapsulation efficiency of omega 3 loaded liposome during 7 days at 4 °C [13]. Encapsulation efficiency and stability depends on different factors such as hydrophobicity and molecular weight of encapsulant, type (saturation) and concentration of phospholipid and stabilizer, method of liposome preparation and temperature (17,18, 28).

4. Conclusion

The using of hydrophobic stabilizers (Gamma orizanol and lauric acid) in liposome formulation caused to increase of particle size However, hydrophilic one (PEG 400) had not considerable effect on mean size. On the other hand, hydrophobic stabilizers caused to decrease of particle size distribution (PDI) in colloidal system which showed they have benefit stabilizing effect during storage time however, PEG had little effect on PDI. This suggests that hydrophobic stabilizers probably with increasing of integrity and stiffness in membrane bilayer cause to decreasing of coalescence and increasing of physical stability. Vitamin E showed behavior similar to other hydrophobic stabilizers so that using of it in liposome formulation can have

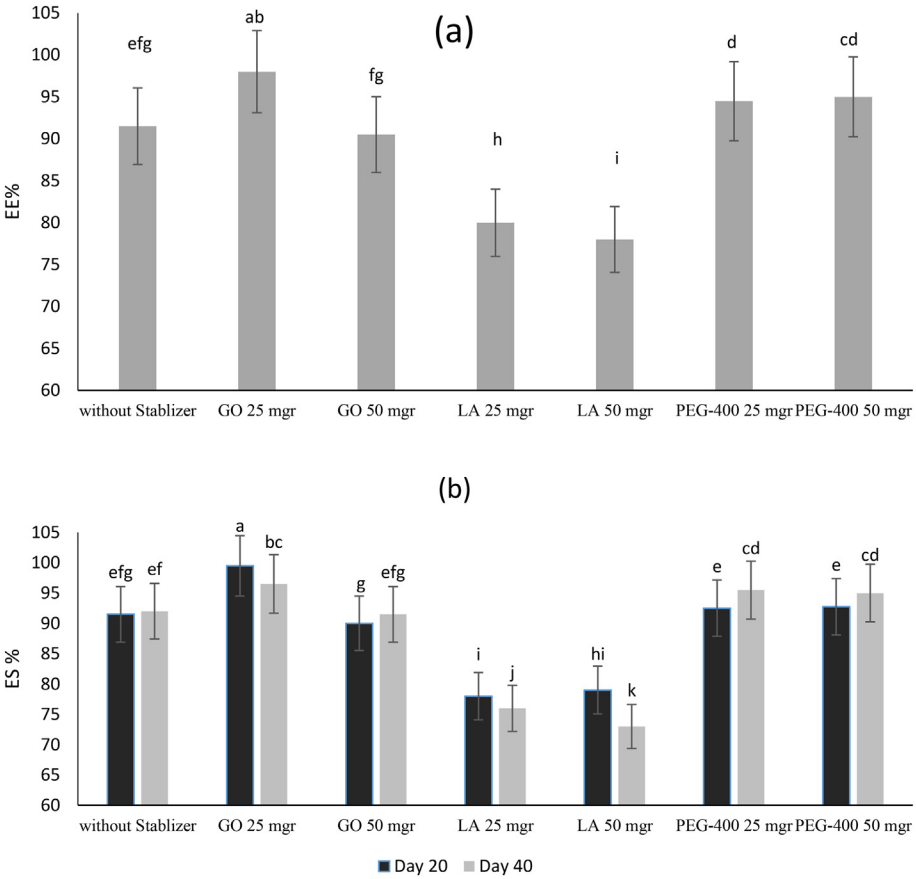

Fig. 5. Encapsulation efficiency (a) and stability (b) of nanoliposomes containing different stabilizers (different words shows significant different at significant level of 5% Duncan-Test).

stabilizing effect beside to its nutritional and antioxidant effects. Also, some of stabilizer such as GO can improves encapsulation efficiency and stability which probably related to their ability in modifying of membrane permeability and stiffness.

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