Lipid Nanospheres Containing Vitamin A or Vitamin E: Evaluation of Their Stabilities and In Vitro Skin Permeability

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Abstract: To encapsulate a fat-soluble vitamin, lecithin composed of several hydrogenated phospholipids obtained from soybean and an adjuvant were used. The resulting lipid nanospheres were about 200-300 nm in size and had a monodispersed-size distribution. Increasing the proportion of the oil phase produced large lipid droplets. The size and zeta-potential of a lipid nanosphere containing a 10 w/w% oil phase decreased with an increased proportion of lecithin and then leveled off with a lecithin content of about 1.2 w/w%. Furthermore, an attempt was made to improve the stability of a lipid nanosphere consisting of vitamin and lecithin by coating the surface of the lipid layer with several emulsifiers that had different hydrophilic-lipophilic balance (HLB) values and molecular weights. The lipid nanosphere emulsion prepared with only lecithin showed a significant coalescence over a storage period of 60 days. However, the size of the lipid nanosphere was smaller and its in vitro stability was significantly improved compared with other formula, when Tween 80 was used as the cosurfactant. In particularly, the lipid nanosphere with the minimum size and maximum stability had a 1:1 content ratio of lecithin to Tween 80. From in vitro permeation experiments using rat skin, it was found that the permeation of the vitamin from a lipid nanosphere was greater than that of free vitamin A or E, and varied depending on the composition and size of the lipid nanosphere.

Keywords: encapsulation, fat-soluble vitamin A and E, nanosphere, phospholipid, skin permeability

1. Introduction

Encapsulation techniques are used in pharmaceuticals, veterinary applications, food, copying systems, laundry products, agriculture, pigments, and other less known uses to control the delivery of encapsulated agents as well as to protect those agents from environmental degradation. In particular, the science and technology of microencapsulation has potential applications in the pharmaceutical industry. Many health care products including cosmetics, have been improved by microencapsulation techniques [1,2].

The present work attempts to deal with vitamin A and vitamin E as encapsulated materials. Vitamin A plays an essential role in the function of the retina, is necessary for the growth and differentiation of epithelial tissue, and is required for growth of bone, reproduction, and embryonic development. One of the important chemical features of vitamin E (tocopherols) is that it is an antioxidant. When acting as an antioxidant, vitamin E presumably prevents the oxidation of essential cellular constituents or prevents the formation of toxic oxidation products. However, vitamin A is very susceptible to oxidation, heat, light, moisture and catalysis, and oxidation and hydrolysis are accelerated at high temperature [3]. Vitamin E (tocopherols) also deteriorates slowly when exposed to air or ultra violet light [4]. Therefore, encapsulation techniques were used to attempt to control the delivery rate of these vitamins while also protecting them from environmental degradation.

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This paper focuses on hydrogenated soybean lecithin, since it is one of the most promising and useful agents capable of increasing skin permeation [5,6]. Even at high concentrations, lecithin is non-toxic and does not lead to dermatological concerns. Moreover, due to its amphiphilic molecular structure and physicochemical properties, lecithin is able to form polymeric structures such as direct and inverted micelles or hexagonal, cubic, and lamellar phases, offering the chance to produce innovative topical formulations [2,7].

Many studies on pharmaceutical devices have been carried out to develop suitable drug carriers for delivery using phospholipid. Davis and coworkers reported that commercial fat emulsions of vegetable oil in parenteral nutrition are stabilized by the lecithin (phospholipid mixtures) obtained from eggs or soybeans [8,9]. Lecithin forms a thick interfacial film at oil-water interface and this acts as a mechanical barrier to droplet coalescence. Furthermore, for drug or vaccine delivery, delivery systems with liposomes and polysaccharide-coated liposomes have also been studied [2,6]. Jeppsson and coworkers found that the elimination rate of emulsions stabilized with various Poloxamers (polyoxyethylene-polyoxypropylene block copolymer) is much lower than that of emulsions stabilized only with egg phosphatidylcholine (EPC) [10]. Kan and coworkers also reported on the potential of an other nonionic surfactant, Tween 80, for stabilizing emulsion through a synergistic effect with the combination of egg phosphatidylcholine [11]. A lipid microsphere was prepared by Yamaguchi for application in pharmaceutical devices such as prostataglandin delivery systems [12].

Since the physical stability of an emulsion system using a lipid is also a serious problem (e.g., during employment and storage), much effort has been made to improve the in vitro and in vivo stability. Moreira and coworkers developed a strategy where the liposomal surface is coated with a natural polysaccharide derivative, O-palmitoylpullulan [13].

This study focuses on the use of block polymeric nanospheres for a drug delivery system [14-16]. Based on the results of previous studies, this study reports on the optimum conditions for preparing nanospheres containing fat-soluble vitamins with long-term stability, and then systematically investigates the effect of several influencing factors. Aiming at the encapsulation of a fat-soluble vitamin series, a lipid nanosphere of soybean lecithin coated with a nonionic surfactant is prepared and its in vitro stability is evaluated. In addition, information on controlling factors that affect the size and stability of lipid nanospheres is also included. Finally, the influence of phospholipid formulations is evaluated based on the skin permeation of vitamins A and E.

2. Experimental Section

2.1. Materials

Lecinol (Nikkol lecinol S-10) is a lecithin obtained from soybean prepared by the addition of hydrogen to natural lecithin and was supplied by Nikko Chemicals Co., Ltd. (Tokyo, Japan). Vitamins A and E were kindly supplied by the Pacific Corporation R&D Center (Korea). The cosurfactants such as Tween 80 (polyoxyethylene (20) sorbitan monooleate, HLB: 15.0), HCO- 60 (polyoxyethylene hydrogenated castor oil, HLB: 14.0), Pluronic F-127 (polyoxyethylene-polypropylene block copolymer, HLB: 22.0) and Pluronic F-88 (polyoxyethylene-polypropylene block copolymer, HLB: 28.0) were obtained from Sigma Chem. Co. and kindly supplied by the BASF Corporation, respectively. All other ingredients used were of reagent grade. Deionized-distilled water was used by purifying with Milli-Q plus (Waters, Milipore, USA). Wistar rats, 200 to 250 g, were used for the in vitro release study.

2.2. Preparation of Lipid Nanosphere Containing Vitamin A or Vitamin E

Lipid nanospheres containing a fat-soluble vitamin were prepared by the emulsifying method. First, the emulsifier, such as soybean lecithin, and the emulsifier adjuvant in a particular formula were added to soybean oil as the oil phase. Then, the lecithin was stirred with heating to 80 °C until it was completely dissolved in oil phase. After the temperature of the mixture was cooled to room temperature, the fat-soluble vitamin was added and mixed homogeneously. The mixture was added dropwise into a 2.25% glycerol solution preheated at 40 °C as an isotonic agent for injection [17], and then homogenized for 10 min at 24000 rpm using a homogenizer (Heidolph, DIAx600, Germany). After the completion of the emulsification, the pH was adjusted to neutrality with NaOH.

2.3. Determination of Particle Size

To determine the mean size and size distribution of the lipid nanospheres containing a vitamin, dynamic light scattering (DLS) measurements were carried out using a dynamic light scattering spectrometer (Model 95 ION Lager, Lexel Laser Inc., USA) at a wavelength of 514 nm at 20 °C. The intensity of the scattered light was detected at 90° to the incident beam. After the lipid nanosphere emulsion was filtered using a microfilter with an average pore size of 0.8 µm (Milipore, USA), the size
and size distribution of the nanospheres were measured. The data analysis method used was based on the CONTIN programs of Provencher and coworkers [18].

2.4. Surface Morphology of Lipid Nanosphere
The size and surface morphology of the lipid nanospheres obtained by this procedure was examined using a field emission scanning electron microscopy (FE-SEM; Jeol 6340F) operated at 15 kV. The surface morphology of particles was observed with an atomic force microscopy (AFM) (Digital Instruments, Nanoscope III, USA).

2.5. Long-term Stability Tests
After production, the lipid nanospheres were stored at room temperature. During storage, the mean size of the lipid nanospheres was determined periodically by a DLS measurement. Three samples were drawn from one bath and measured in triplicate until 120 days after production.

2.6. Measurement of Zeta-potential
The zeta-potential of the particles was calculated from the mean electrophoretic mobility of the oil droplets using a zeta potential analyzer (Zetaplus, Brookhaven, USA).

2.7. In vitro Penetration Study
The in vitro penetration study was performed using a two chambers diffusion cell. Briefly, rat skin including subcutaneous tissue was settled between two chambers. The skin membrane surface area exposed to the fluid was 233.7 mm² (17.25 mm diameter). The receptor side (subcutaneous tissue side) was filled with 25 mL of the release medium and the donor side (stratum corneum side) was filled with the vitamin-encapsulated lipid emulsion. Since fat-soluble vitamins exhibit highly lipophilic properties, methanol was used as the release medium for determining the amount of vitamin released. The two chambers cell was agitated with magnetic stirrers and kept at 37 °C. At predetermined time intervals, aliquots were withdrawn from the release medium and equivalent amounts of fresh release medium were added immediately to maintain the initial volume. The concentrations of the vitamin released were analyzed spectrophotometrically (UV-2101PC, Shimatzu, Japan). Vitamin A and vitamin E were detected at 326 nm and 298 nm in the UV wavelengths, respectively. All experiments were carried out in triplicate then the mean and standard deviation were calculated. The permeability coefficients of the vitamins released from lipid thin nanosphere through the rat skin were calculated using the following equation.

\[
\ln \left(1 - \frac{2C_t}{C_0}\right) = -\frac{2A}{V\delta}P_t
\]

Here, \(C_t\) is the vitamin concentration in the receptor cell at time \(t\), \(C_0\) the initial vitamin concentration in the donor cell, \(A\) the surface area, \(V\) the volume of each cell, \(\delta\) the thickness of the rat skin, and \(P\) the permeability coefficient.

3. Results and Discussion

3.1. Preparation of Lipid Nanosphere Containing Vitamins A and E
O/w emulsion type lipid nanospheres prepared had a white and milky appearance. Since the polar head groups in phospholipids have an affinity toward water, and their hydrocarbon tails avoid water, these preferences can be satisfied by the formation of a micelle, a globular structure in which the polar head groups are sequestered inside. Therefore, lipid nanospheres containing a lipophilic solution can be maintained inside the oil phase due to the difference in polarity between the inside and the outside of the interfacial membrane layer.

The lipid emulsion droplets had a uniform spherical shape and sub-micron size, as shown in the FE-SEM picture of Figure 1. To prepare the sample for the FE-SEM measurement, the lipid nanospheres were placed onto a metal mount, then the external solution was slowly evaporated and coated with gold. Accordingly, the FE-SEM image in Figure 1 (E-0.5 sample in Table 2, average size determined by DLS: 146.6 nm) can be viewed as a coagulant composed of nanospheres, and the size of the nanospheres after the pre-treatment procedure seems to be smaller.
Table 1. Composition and Size of Lipid Nanospheres Containing Fat-soluble Vitamin

<table>
<thead>
<tr>
<th>Sample</th>
<th>Lecithin (wt %)</th>
<th>Oil phase (wt %)</th>
<th>Cosurfactant (wt %)</th>
<th>Avg. S.D.</th>
<th>Size (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-12</td>
<td>1.2</td>
<td>10% vitamin E 5.0</td>
<td>-</td>
<td>314.4</td>
<td>0.299</td>
</tr>
<tr>
<td>PT-12</td>
<td>1.2</td>
<td>10% vitamin E 5.0</td>
<td>Pluronic F127 1.2</td>
<td>289.7</td>
<td>0.170</td>
</tr>
<tr>
<td>P2-12</td>
<td>1.2</td>
<td>10% vitamin E 5.0</td>
<td>Pluronic F88 1.2</td>
<td>303.2</td>
<td>0.183</td>
</tr>
<tr>
<td>HCO-12</td>
<td>1.2</td>
<td>10% vitamin E 5.0</td>
<td>HCO-60 1.2</td>
<td>277.1</td>
<td>0.167</td>
</tr>
<tr>
<td>T-08</td>
<td>1.2</td>
<td>10% vitamin E 5.0</td>
<td>Tween 80 0.3</td>
<td>221.6</td>
<td>0.184</td>
</tr>
<tr>
<td>T-06</td>
<td>1.2</td>
<td>10% vitamin E 5.0</td>
<td>Tween 80 0.6</td>
<td>208.5</td>
<td>0.121</td>
</tr>
<tr>
<td>T-12</td>
<td>1.2</td>
<td>10% vitamin E 5.0</td>
<td>Tween 80 0.2</td>
<td>198.5</td>
<td>0.103</td>
</tr>
<tr>
<td>T-18</td>
<td>1.2</td>
<td>10% vitamin E 5.0</td>
<td>Tween 80 0.8</td>
<td>201.0</td>
<td>0.120</td>
</tr>
<tr>
<td>T-21</td>
<td>1.2</td>
<td>10% vitamin E 5.0</td>
<td>Tween 80 0.1</td>
<td>212.8</td>
<td>0.122</td>
</tr>
<tr>
<td>A-12</td>
<td>1.2</td>
<td>10% vitamin A 5.0</td>
<td>Tween 80 0.2</td>
<td>256.0</td>
<td>0.169</td>
</tr>
</tbody>
</table>

* Aqueous phase: glycerol 2.25% solution
* Measured by dynamic light scattering
* Weight ratio of vitamin: soybean oil = 1:1
* Tween 80: polyethylene(20) sorbitan monooleate
Pluronic F-127, F-88: polyoxyethylene-polypropylene block copolymer, HCO-60: polyethylene hydrogenated castor oil

Table 2. Permeation Coefficients of Vitamin A or E from the Stratum Corneum Side Through Rat Skin

<table>
<thead>
<tr>
<th>Sample</th>
<th>Formulation*</th>
<th>Weight ratio</th>
<th>Size (nm)</th>
<th>Permeability coefficient**</th>
</tr>
</thead>
<tbody>
<tr>
<td>FE</td>
<td>free vitamin E</td>
<td>-</td>
<td>-</td>
<td>0.146</td>
</tr>
<tr>
<td>E-0.5</td>
<td>vitamin E 0.5%</td>
<td>24</td>
<td>146.6</td>
<td>0.086</td>
</tr>
<tr>
<td>E-1.25</td>
<td>vitamin E 1.25%</td>
<td>9.6</td>
<td>179.9</td>
<td>0.145</td>
</tr>
<tr>
<td>E-5.0</td>
<td>vitamin E 5.0%</td>
<td>2.4</td>
<td>294.5</td>
<td>0.121</td>
</tr>
<tr>
<td>FA</td>
<td>free vitamin A</td>
<td>-</td>
<td>-</td>
<td>0.086</td>
</tr>
<tr>
<td>A-2.5</td>
<td>vitamin A 2.5%</td>
<td>4.8</td>
<td>207.0</td>
<td>0.129</td>
</tr>
</tbody>
</table>

* Lecithin 1.2%, cosurfactant: Tween 80 0.6%, oil phase: vitamin
soybean oil = 1:1
** Determined by equation (1)
* Concentration of free vitamin E: 1.25%
** Concentration of free vitamin A: 2.5%

Figure 2. Surface morphology and characteristics of lipid nanosphere containing 5% vitamin E measured by atomic force microscopy (AFM): (a) scan size 436 nm, (b) scan size 4.640 μm.

Figure 3. Typical size distribution profile of lipid nanosphere (T-12) according to dynamic light scattering measurement with an invariable spherical shape and smooth surface had been prepared.

Also, the mean size of the lipid nanospheres was determined by DLS measurements. A typical and representative example of the DLS measurement results is shown in Figure 3. Most of the lipid nanospheres prepared were about 200 nm in size and their size distributions exhibited a unimodal distribution with no standard deviations over 0.2 except for the data of the sample prepared without a cosurfactant, as shown in Table 1. A detailed explanation about the sizes will be included later.

3.2. Effect of Composition on Lipid Nanosphere Size and Size Distribution

Table 1 presents the composition and size of the lipid nanospheres prepared. To encapsulate a fat-soluble vitamin, soybean oil and a fat-soluble vitamin...
were used as the oil phase, with hydrogenated lecithin obtained from soybeans as the emulsifier and an emulsifier adjuvant.

In a colloidal system, the size and size distribution of the particles are the most important physicochemical characteristics associated with good stability during storage [20,21]. Figure 4 (a) shows that the concentration of lecithin as an emulsifier influenced the size of the lipid nanospheres containing the vitamins. The size of the lipid nanospheres containing a constant volume of 10 w/w% in the oil phase in a total volume prepared using a constant amount of Tween 80 decreased as the lecithin concentration increased, and then leveled off at a concentration of more than 1.2 w/w%. However, the excessive addition (more than the critical amount) of lecithin eventually increased the size of the lipid nanospheres. This indicates that a nanosphere system containing 10 w/w% of vitamin and soybean oil as

**Figure 4.** Effect of lecithin content and oil phase on size of lipid nanosphere; (a) containing 5 w/w% vitamin E prepared with 0.6 w/w% Tween 80, and (b) prepared with 1.2 w/w% lecithin, 0.6 w/w% Tween 80.

the oil phase was completely emulsified using 1.2 w/w% of lecithin which can, therefore, be regarded as the optimal condition for stable emulsion. The size was also affected by the amount of the oil phase. As shown in Figure 4(b), the size of the lipid nanospheres increased with an increased vitamin and soybean oil content as an oil phase with the constant amount of 1.2 w/w% of lecithin.

3.3. Zeta-potential Measurements of Surface of Lipid Nanospheres

The surface potentials of the droplets play an important role in the stability of lipid emulsion through electrostatic repulsion [2,22]. Figure 5 shows the change of the zeta-potential of the oil droplets in the emulsions stabilized by soybean lecithin at various concentrations. Hydrogenated soybean phospholipid, a mixture of neutral and/or polar lipids was used. Natural phospholipids usually exhibit neutral or negative charges at a neutral pH, and one or more charges depending on the polar head group. Accordingly, in the neutral pH region, the emulsion showed negative charges due to minor components such as phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, etc.

As the concentration of lecithin increased, the zeta-potential of the surface of emulsion droplets decreased and then leveled off at a lecithin content of more than 1.2 w/w%, as shown in Figure 5. This dependency of the zeta-potential relative to the amount of the lecithin was similar to the effect of the lecithin content on the particle size as seen in Figure 4 (a). These results clearly indicated that an o/w type emulsion containing a 10 w/w% oil phase composed of vitamin and soybean oil is completely coated by lecithin molecules with a lecithin content of more than 1.2 w/w% and is sufficiently stabilized. These results on the content of lecithin versus the size of the lipid nanospheres coincide well with those
reported by Ishii and coworkers [22], and Davis and coworkers [8,9]. They also demonstrated that 1.2 w/w% of lecithin was necessary to produce the stable parenteral fat emulsions.

3.4. Influence of Cosurfactant on the Size of Lipid Nanosphere

This study attempt to improve the stability of lipid emulsion consisting of a vitamin and lecithin (emulsifier) by coating the surface of the lipid layer with several emulsifiers that have different HLB values and molecular weights. Accordingly, Tween 80, Pluronic F-127, Pluronic F-88, and HCO-60 were used as they are known to be biologically safe hydrophilic surfactants [23-25].

As shown in Table 1, the size of the lipid nanospheres stabilized with nonionic cosurfactants was smaller than that of the lipid nanospheres prepared without cosurfactants. Smaller and more stable lipid nanospheres were produced based on the steric hindrance to repel other oil droplets due to the the polyethyalted chains of the polysorbate oriented to the aqueous medium. It should be noted that the size of the lipid nanospheres, stabilized by Tween 80 was smaller than those of lipid nanospheres stabilized with Pluronic F-127 or HCO-60. In addition, the size of the lipid nanospheres decreased as the concentration of Tween 80 increased and then gradually increased with a concentration higher than 1.2 w/w%. These results will be discussed later under long-term stability.

Pluronic F-127 and HCO-60 may also include steric hindrance with long polyethyalted chains. However, the influence of the molecular weight of these cosurfactants overwhelmed the effect of steric hindrance on the size of the lipid nanospheres. The molecular weights of Pluronic F-127, HCO-60, and Tween 80 are 12600, 3578 and 428.6, respectively. If the lipid nanospheres stabilized with Pluronic F-127 and Pluronic F-88 (Mw = 11400), which have similar molecular weights and different HLB values of 22.0 and 28.0, respectively, are compared the size of the lipid nanospheres stabilized with Pluronic F-88 was larger than that of the lipid nanospheres stabilized with Pluronic F-127 even though Pluronic F-127 has a higher molecular weight.

From these size measurement result, it was found that the HLB value and molecular weight of a cosurfactant significantly affects the size and stability of a lipid nanosphere containing a fat-soluble vitamin.

3.5. Long-term Stability Test of Lipid Nanosphere Containing Fat-soluble Vitamin

To evaluate the long-term stability of a lipid nanosphere containing vitamin A or E, the size changes were measured frequently as shown in Figure 6. The stored samples exhibited distinct characteristics between the different formulations. N-12, which was stabilized by only lecithin without any cosurfactant, showed a large increase in size within 60 days of storage. This was in contrast to the cosurfactant formulations which did not undergo any significant size change.

As shown in Table 1, the size of the lipid nanospheres decreased as the concentration of Tween 80 increased and then gradually increased with a content of more than 1.2 w/w%. It is speculated that a lipid nanosphere has a minimum size and maximum stability when the weight ratio of lecithin to Tween 80 is 1:1. In general, a surfactant will form good mechanical and/or electrical barriers to emulsion droplet coalescence. Accordingly long-term stability induced by the incorporation of surfactants can be explained by steric-stability and electrostatic-stability. As the concentration of a cosurfactant (Tween 80) increases, the steric-stability action increases due to the long polyoxyethylated chain of the polysorbate oriented to the aqueous medium. However, the size of the lipid nanosphere gradually increased when the weight ratio of Tween 80 to lecithin was higher than 1:1. This implies that the electrostatic-stability of the negatively charged lipid droplets was reduced due to the coating of the lipid droplets by Tween 80. Namely, the zeta-potential of lipid nanospheres stabilized by an excessive amount of Tween 80 is low since Tween 80 confers stability by a sterility rather than by electrostatic repulsion. Therefore, it was established that a highly stable lipid nanosphere can be produced by a formula that contains both lecithin and a nonionic surfactant (Tween 80). These results are similar to the synergistic effect of lecithin.


3.6. In vitro Permeation studies of Vitamin through Rat Skin Including Subcutaneous Tissue

The permeation kinetics of vitamins through rat skin were examined. The permeation of the free vitamin without any treatment through the skin was poor. However, the application of lipid nanospheres containing the vitamin in the core increased the permeation of the vitamin. The vitamin permeation varied depending on the composition and size of the lipid nanospheres. In the permeation experiments of vitamins through were rat skin, the permeability coefficients (P) were calculated using equation (1) and are listed in Table 2.

Stratum corneum is known to be the main barrier limiting passive transdermal diffusion. The most commonly accepted structure of stratum corneum consists of some 20 layers of flattened keratin-filled cells (corneocytes) surrounded by lipid lamellae containing cholesterol, fatty acids, and ceramide [5,6]. This structure can be described as a ‘brick and mortar’ model where the keratinized cells represent the bricks and the interstitial spaces between the cells behave like pores through which solution flux can take place [27-30].

Therefore, it would appear that the process of the permeation of a vitamin consist of an initial the interaction (or sorption) between the lipid in the stratum corneum and the phospholipid surrounding the lipid nanosphere, then the diffusion of the vitamin out of the vehicle, and finally the penetration of the vitamin through the stratum corneum.

As shown in Table 2, the permeability coefficient of vitamin E depend on the formulation of the component. Briefly, as the weight ratio of the phospholipid and cosurfactant to the vitamin in the total lipid nanosphere increased and the size of the lipid nanosphere decreased, the permeability coefficient of vitamin A or E through the rat skin increased.

In drug permeation, the most important issue in this complex membrane is the stratum corneum or horny layer, which is usually the rate-limiting or slowest step in the penetration process. Anatomically, the possible micro routes comprise the transepidermal pathway across the horny layer (either intracellularly or intercellularly) or via the hair follicles and sweat glands. The intercellular spaces are filled with compact lamellae composed of lipids, and the intracellular volume is primarily filled with cross-linked proteins.

For penetration-enhancer activity, in most situations,
a nonionic surfactant was used as the cosurfactant, the size of the lipid nanoparticles was smaller and the in vitro stability was significantly improved compared with the lipid nanosphere emulsion prepared with only lecithin. In particular, when Tween 80 was used as the cosurfactant along with lecithin, the lipid nanospheres exhibited the minimum size and maximum stability. In vitro permeation experiments of vitamins A and E through rat skin were performed. The permeation of the vitamin from lipid nanospheres through rat skin was greater than that of free vitamin A or E, and varied depending on the composition and size of the lipid nanosphere. These results clearly indicate that a lipid nanosphere containing a vitamin is a useful vehicle for a variety of dermally-active compounds, particularly due to its ability to produce a sub-micron size emulsion, long term stability, and nontoxic penetration enhancers.

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References
