Review Article

Lipid nanoparticles (SLN & NLC) for delivery of vitamin E: a comprehensive review

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Abstract
The antioxidative and photoprotective properties of vitamin E have caused it to be included as an active agent in various pharmaceutical and cosmetic products. However, its lipophilicity, chemical instability and poor skin penetration have limited the effectiveness of these formulations. For that reason, many attempts to include it in different drug delivery systems have been made. In recent decades, lipid nanoparticles have received special attention due to their advantages of compatibility with the skin, ability to enhance penetration of drugs in the stratum corneum, protection of the encapsulated substance against degradation induced by the external medium and control of drug release. This work reviews the current status of the encapsulation of vitamin E in lipid nanoparticles. We describe the most important methods for obtaining and characterizing lipid nanoparticles containing vitamin E (LNP-VE), various techniques for the evaluation of vitamin E’s properties after encapsulation, the main in vitro and in vivo studies of the potential effectiveness or toxicity of LNP-VE, the formulations and stability studies of this delivery system, the commercial products based on LNP-VE and the regulatory aspects related to lipid nanoparticles. Finally, we discuss the most relevant advantages of encapsulating vitamin E in such particles and critical aspects that still demand attention to enhance the potential of solid lipid nanoparticles to deliver vitamin E.

Résumé
Les propriétés antioxydantes et photoprotectrices de la vitamine E ont fait que cette vitamine était incluse, en tant qu’agent actif, dans divers produits pharmaceutiques et cosmétiques. Cependant, son caractère hydrophobe (lipophile), son instabilité chimique et sa pauvre pénétration dans la peau ont limité l’efficacité de ces formulations. Pour cette raison, de nombreuses tentatives pour inclure la vitamine E dans différents systèmes de libération de médicaments ont été faites. Au cours des dernières décennies, les nanoparticules lipidiques ont reçu une attention particulière en raison de leurs avantages de compatibilité avec la peau, de leurs capacités d’augmenter la pénétration des médicaments dans la couche cornée (stratum corneum), de leurs facultés de protection de la substance encapsulée contre la dégradation induite par l’environnement externe et en raison du contrôle de la libération du médicament. Ce travail analyse l’état actuel de l’encapsulation de la vitamine E dans les nanoparticules lipidiques. Nous décrivons les méthodes les plus importantes pour obtenir et caractériser les nanoparticules lipidiques contenant de la vitamine E (TNL-VE), ainsi que les différentes techniques pour l’évaluation des propriétés de la vitamine E après encapsulation, les principales études in vitro et in vivo sur l’efficacité potentielle ou la toxicité des TNL-VE, les formulations et les études de stabilité de ce système de libération, les produits commerciaux contenant les TNL-VE et les aspects réglementaires liés aux nanoparticules lipidiques. Finalement, nous discutons des avantages les plus pertinents de l’encapsulation de vitamine E dans ces particules et les aspects critiques qui nécessitent encore de l’attention pour augmenter le potentiel des nanoparticules lipidiques solides pour la libération de la vitamine E.

Introduction
Vitamin E (VE) was discovered in 1922 and comprises a family of eight compounds: four tocopherols (α, β, γ and δ) and four tocotrienols (α, β, γ and δ). All of them are liposoluble compounds, and α-tocopherol is the most abundant in nature and the most active form since a pharmacological point of view [1–3]. Because of its antioxidative and photoprotective properties, vitamin E has been widely used as an active agent in pharmaceutical and cosmetic products [4]. Some experts have summarized the possible applications of vitamin E in recent decades. However, they also have agreed on the need for further research in the form of well-designed controlled trials to support the benefits of products containing vitamin E [4, 5]. In addition, several authors think that developing improved formulations of vitamin E could help obtain more relevant results after the application of this active compound. This idea is supported by the lipophilicity, chemical instability and poor skin penetration of vitamin E, which limits its effectiveness [2, 6, 7]. Therefore, several drug delivery systems have been used to administer vitamin E. Liposomes [8, 9], polymeric micro and nanoparticles [10–12], nanoemulsions [13, 14], transdermal devices [15, 16] and lipid nanoparticles (NPs) [17, 18] are some examples.

These drug delivery systems have been investigated to improve both oral and topical formulations of vitamin E. However, topical administration of this compound has been receiving more attention...
due to the potential impact that it could generate in increasing the number of pharmaceutical and cosmetic products available in the market. In this regard, lipid nanoparticles are one of the most promising delivery systems for the administration of liposoluble drugs such as vitamin E.

Lipid nanoparticles were introduced in the early years of the 1990s when their inventors published the first patents and papers [19]. They can be defined as particles composed of lipids stabilized by surfactants that are solid at body and ambient temperature [20] and are considered colloidal carriers based on effective lipids with sizes varying between 40-50 and 1000 nm [21, 22].

There are currently two generations of lipid nanoparticles. The first is called solid lipid nanoparticles (SLNs) and the second generation is named nanostructured lipid carriers (NLCs) [23]. The last one emerged as an improved system in relation to SLNs as the main difference, which is the inclusion of a liquid lipid in the structure, aims to solve the problems associated with the first generation of lipid particles. These limitations are the relatively low encapsulation efficiencies and the expulsion of the encapsulated substances during storage. Both are a consequence of the more organized structure due to the lipid crystallization process, which impedes the accommodation of other molecules inside the nanoparticles [6, 22].

In general, lipid nanoparticles have advantages over other systems used for topical administration:

- more compatibility with the skin, as lipids are normal components of its structures [21],
- enhanced penetration of active compounds in the stratum corneum [17, 24],
- low cost, and simple and easy-to-scale preparation [6, 25],
- excellent physical stability, with no leakage of encapsulated active substances [25, 26],
- chemical versatility and biodegradability [22, 27],
- controllable release profiles [17, 26],
- protection of the encapsulated substance against degradation processes induced by the external medium [17, 28].

Several authors have published interesting results about the inclusion of vitamin E in lipid nanoparticles for topical delivery. Some of them are focused on studying the properties of lipid nanoparticles prepared with vitamin E as a model molecule or an antioxidant additive [29–31]. However, there are many other articles centred on obtaining lipid nanoparticles loaded with vitamin E for pharmaceutical or cosmetic applications [17, 18, 32]. All of them supply valuable information for future investigations of these systems. Therefore, this work comprehensively reviews the key aspects of lipid nanoparticle technology that can be successfully adapted to prepare improved formulations of vitamin E.

**Preparation of lipid nanoparticles containing vitamin E**

Both types of solid lipid nanoparticles (SLNs and NLCs) are produced by the same methods. These are high-pressure homogenization, microemulsion, emulsification-solvent evaporation, emulsification-solvent diffusion, solvent injection (or solvent displacement), phase inversion, multiple emulsion, ultrasonication and membrane contractor technique. Many reviews describe all of them in detail [22, 33]. Of these techniques, only a few have been applied to prepare lipid nanoparticles with vitamin E. Here, we divide them into two groups, depending on the processes that transform the lipid phase into solid nanoparticles: (1) emulsion-solidification and (2) emulsion-solvent evaporation. Each group is then subdivided regarding the technique used to generate the emulsion: (a) high-pressure homogenization, (b) microfluidization, (c) ultrasonication, (d) microemulsion and (e) high-shear homogenization.

**Emulsion-solidification**

The principle of these methods is to form an emulsion by dispersing a molten lipid phase in an aqueous surfactant solution. The drug is usually a lipophilic compound which is dissolved in the molten lipid phase. When the nanoemulsion is formed, the system is cooled and the droplets solidify, generating the lipid nanoparticles loaded with the drug. The main advantage of these methods is to avoid the use of organic solvents [34, 35].

All five alternatives for generating the emulsion mentioned above can be used in this case. Each one of the resulting procedures has typical experimental factors that influence the final characteristics of the lipid nanoparticles.

**Emulsion-solvent evaporation**

This group of methods is based on dispersing a solution of the lipid components in an aqueous surfactant solution. The lipids and the lipophilic drug are commonly dissolved in an organic solvent such as dichloromethane, cyclohexane or chloroform [36]. When the nanoemulsion is formed, the solvent is extracted/evaporated and droplets start to solidify until the formation of the solid lipid nanoparticles carrying the drug. The emulsion can be formed by the same techniques already mentioned, and the solvent can be evaporated by simple agitation, rotoevaporation or spray-drying. The main disadvantage of these methods is the presence of residual solvent in the particles [34, 37]. Because of that, it is very important to eliminate the solvent, or at least ensure the amount is below the acceptable limit. However, these methods are useful for encapsulating drugs which are very poorly soluble in lipids and whose solubility is favoured with the addition of an organic solvent [19], and also for drugs that are sensitive to heat, because these methods do not need thermal stress [34, 37].

For all methods referred to above, it is common to make a coarse emulsion before supplying the high energy to the system [25, 31, 38]. This approach helps form a more homogeneous emulsion but means another step in the process of preparing the lipid nanoparticles. Consequently, the real need and/or advantage of introducing this step must be evaluated in each particular case.

As already mentioned, several techniques can be used to disperse the lipid phase in the continuous aqueous phase. These are discussed next.

**High-pressure homogenization**

This technique is quite good to form nanoemulsions composed of the lipid phase (melted or dissolved) and aqueous phase containing the surfactant previously heated at the same temperature. Generally, a pre-emulsion is prepared and then passed under high pressure (100–2000 bar) through a homogenizer valve. The fluid accelerates in a very short distance, reaching a high speed. Due to the high-shear stress forces, the lipid substances are divided into small droplets. The main disadvantage of this technique is the low encapsulation efficiency for hydrophilic substances. This is because the drug migrates to the external aqueous phase during the particle formation. However, it is recommended for lipophilic active...
agents such as vitamin E [21, 39]. Also, it is a proper technique to produce large quantities of sterile nanoparticles because there are industrial-scale high-pressure homogenizers that work in a closed regime [19]. Consequently, this technique is most widely used to prepare SLNs and NLCs containing drugs or cosmetics [34].

**Microfluidization**

Microfluidizers are high-pressure homogenizers that have, instead of a homogenizer valve, an interaction chamber in which the fluid is injected and homogenized by cutting, impact or cavitation. As in high-pressure homogenizers, the droplet size will depend on the number of cycles, pressure and temperature during processing [40].

**Ultrasonication**

Before ultrasonication, the active agent is added to the solid lipid previously melted or dissolved in a proper organic solvent. Then, the aqueous phase is mixed with the lipid phase using a probe or bath sonicator. For smaller particle size and more homogeneous particle size distribution, a combination of both ultrasonication and high-shear homogenization can be advantageous. This technique is simple and easy to perform but has some disadvantages, such as potential metal contamination, physical instability (e.g. particle growth during storage) and difficulties for scaling up [41].

**Microemulsion**

A microemulsion is formed when the lipid phase containing the drug is mixed with the aqueous phase, including the surfactant and almost always a co-surfactant. After producing the microemulsion, drastic cooling is performed to solidify the droplets and create the nanoparticles loaded with the active agent. This special type of emulsion does not require very much energy to form, and thus, it can offer some advantages if the drug is highly sensitive to shear forces or cavitation. Another advantage of this technique is the possibility of obtaining nanoparticles with a narrow size distribution due to the nature of the emulsion formation process, which is thermodynamically favoured [37]. The main disadvantages of this technique are the relatively high quantity of surfactant that is generally required to form such systems and the production of very diluted nanosuspensions that could hinder further scaling up [19, 41].

**High-shear homogenization**

The mixture of the lipid and the aqueous phase is emulsified by high-shear homogenizers such as the ultra-turrax devices. This procedure is easy to perform but the dispersion quality is often compromised by the presence of microparticles, the most important limitation [39, 41].

Tables I and II summarize the processes and ingredients used to prepare nanoparticles containing vitamin E, along with some key aspects and main conclusions derived from works published since 1999 to 2017. As can be observed, the most frequently used ingredients are stearic acid, glyceryl monostearate, glyceryl behenate and cetyl palmitate as solid lipids; medium chain triglycerides (TCM) and oleic acid as liquid lipids; and Tween 80, Tween 20, soy lecithin and Pluronic F-68 as emulsifiers. All of these excipients have been widely used to encapsulate other drugs and cosmetics, as has been thoroughly reviewed by different authors [19, 35, 42, 43]. The most utilized methods to prepare SLNs/NLCs containing vitamin E are emulsion-solidification using high-pressure homogenization or ultrasonication to form the emulsion. This also coincides with the most used procedures for other pharmaceutical or cosmetic agents [33].

After the preparation, the nanoparticles can be stored as a nanosuspension in the medium where they were formed or they can be ultratitrated in order to change that medium to another more favorable depending on the final purpose [49]. Some authors have used filtration to recover the particles [47], but this procedure can affect the final yield of the process because a part of the material is lost in the filter. Other researchers have preferred to dry the particles by lyophilization without previous treatment [32]. However, aggregation of particles can occur as a consequence of the freeze-drying process and the removal of water. The addition of an adequate amount of cryoprotectant and/or lyoprotectant can prevent or minimize the aggregation of nanoparticles during this process [21].

All the methods used to prepare SLNs/NLCs involve a great number of experimental parameters that modify the final properties of nanoparticles. Lipid proportion, type and concentration of surfactant, temperature, ultrasonication time, pressure and cycles of homogenization when the emulsion is obtained with a high-pressure homogenizer are only some of them. Many papers contain studies focused on determining the most relevant factors for each system and their specific effect on the final product. However, there are only a few works that have used statistical experimental designs for that purpose. To the best of our knowledge, there is only one paper about lipid nanoparticles containing vitamin E that employs this tool [47]. De Carvalho and co-workers first used a fractional factorial design to determine the most influential factors in the particle size, recovery of α-tocopherol and zeta potential. They identified the concentration of three components of the system (active agent, lipophilic surfactant and hydrophilic surfactant) as the factors to include in the optimizing step, which was performed by the response surface methodology. These important tools should be more exploited because they allow obtaining more complete information with the lowest number of experiments.

**Characterization of SLNs/NLCs loaded with vitamin E**

Adequate characterization of the particles is a prerequisite for the quality control of products based on SLNs and NLCs. Some parameters receive more attention because they have a direct impact on particles’ stability and release kinetics. They are particle size, zeta potential, particle morphology, degree of crystallinity and modification of lipids [42].

Table III summarizes the general parameters used to characterize SLNs/NLCs containing vitamin E, the specific measurements associated with these parameters, and the common techniques utilized to determine them.

**Morphology**

The morphological properties of lipid nanoparticles are often evaluated after the preparation in order to determine the shape of the particles and to visualize possible agglomeration. Particularly, Dingler et al. [44] concluded that surfactants used in the preparation of SLN-VE distorted the crystal formation, leading to more spherical shapes than the ones of SLNs made without the drug. The last ones had platelet-like shapes typical of the β-modification present in the crystalline structure of pure lipids. Using transmission electron microscopy, Carvalho et al. [47] observed some agglomeration between the lipid nanoparticles and signals of lipid crystals around...
Table 1 Main preparation methods for obtaining SLNs loaded with vitamin E and most important findings

<table>
<thead>
<tr>
<th>Method for preparation</th>
<th>Solid lipids</th>
<th>Surfactants</th>
<th>NPs characteristics and main conclusions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsion—solidification</td>
<td>Cetyl palmitate</td>
<td>Polyglycerol methylglucose</td>
<td>Particles of 270–280 nm (PDI = 0.07) had good physical stability as a dispersion or in a cream. The encapsulation of VE in the NPs increased their diameter and enhanced VE chemical stability.</td>
<td>Dingler et al. [44]</td>
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<td>Cetyl palmitate</td>
<td>PMD</td>
<td>NPs having 200 nm were physically stable during a year.</td>
<td>Wissing and Müller [45]</td>
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<td></td>
<td>Glyceryl monostearate</td>
<td>NI</td>
<td>NPs with 300–500 nm were obtained. The inclusion of vitamin E increased the stability of NPs containing a UV blocker. With optimized conditions, the NPs had 214.5 nm, yield = 75.4%, ZP = –41.9 mV, EE = 98% and 21 days of stability.</td>
<td>Song and Liu [46]</td>
</tr>
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<td></td>
<td>Glyceryl behenate</td>
<td>Soy lecithin, Pluronic F-68</td>
<td>NPs having 74–80 nm (PDI &lt; 0.25) and zeta potential between –27 and –32 mV were obtained. Co-loading of VE increased the cytotoxicity in cancer cells of SLNs containing doxorubicin.</td>
<td>De Carvalho et al. [47]</td>
</tr>
<tr>
<td>Sonication</td>
<td>Glyceryl behenate</td>
<td>Tween 80</td>
<td>Spherical or ellipsoid NPs with 200 nm (PDI = 0.2), EE = 100% and ZP = –30 mV were stable in suspension during 15 weeks at 25°C. These NPs were also stable in gastrointestinal fluid.</td>
<td>Oliveira et al. [28]</td>
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<td>Glyceryl tristearate,</td>
<td>Tween 20, Sucrose stearate</td>
<td>Nanoparticles with a size smaller than 1000 nm, EE = 75.77–98.67% were obtained. Some of the evaluated formulations released vitamin E in 8 h and were stable for 60 days.</td>
<td>Shylaja and Mathew [25]</td>
</tr>
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<td></td>
<td>Soybean lecithin</td>
<td></td>
<td>The size of NPs and the EE depended on the lipid used. SF NPs had 175 nm and particles prepared with SA showed 195 nm. EE was 58.7% for SF and 19.4% for SA. Size of NPs increased while EE decreased after 3 months of storage. SF better stabilized the SLNs containing α-tocopherol and diminished its degradation.</td>
<td>Trombin et al. [49]</td>
</tr>
<tr>
<td>High-shear homogenization</td>
<td>Stearic acid</td>
<td>Tween 80</td>
<td>Autoclaving increased particle size from 100 to 350 nm and modified the crystalline structure of the lipid matrix.</td>
<td>Worle et al. [38]</td>
</tr>
<tr>
<td>Microfluidization</td>
<td>Monoolein</td>
<td>Poloxamer 407</td>
<td>NPs had 175 nm and particles prepared with SA showed 195 nm. EE was 58.7% for SF and 19.4% for SA. Size of NPs increased while EE decreased after 3 months of storage. SF better stabilized the SLNs containing α-tocopherol and diminished its degradation.</td>
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<tr>
<td>Microemulsion</td>
<td>Stearic acid (SA),</td>
<td>Tween 20, Sodium taurocholate,</td>
<td>NPs had 175 nm and particles prepared with SA showed 195 nm. EE was 58.7% for SF and 19.4% for SA. Size of NPs increased while EE decreased after 3 months of storage. SF better stabilized the SLNs containing α-tocopherol and diminished its degradation.</td>
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<td></td>
<td>Stearyl ferulate (SF)</td>
<td>Butanol (co-surfactant)</td>
<td>Ni, not informed; PDI, polydispersity index; EE, encapsulation efficiency; ZP, zeta potential.</td>
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<tr>
<td>Method of preparation</td>
<td>Lipids</td>
<td>Surfactant</td>
<td>NPs characteristics and main conclusions</td>
<td>References</td>
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<tr>
<td>Emulsion-solidification</td>
<td>High-pressure homogenization</td>
<td>SL-glyceryl monostearate, stearic acid LL-soybean oil</td>
<td>Lechithin, Polyoxyethylene stearate (S-40)</td>
<td>NPs with 121 nm (PDI = 0.172), ZP = −45.5 mV were stable for 560 days. Higher levels of liquid lipid led to smaller NPs with higher stability. More cycles in HPH reduced size of particles</td>
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<td>SL-glyceryl tripalmitate LL-oleic acid</td>
<td>Tween 80, Pluronic F-68, SDS</td>
<td>Particles of 67 nm (PDI = 0.2), ZP = −32 mV and EE = 87% released 75% of the drug in 24 h. The preparation was non-irritant and protected vitamin E against photodegradation.</td>
</tr>
<tr>
<td>Sonication</td>
<td>SL-stearic acid LL-rambutan seed</td>
<td>Tween 20</td>
<td>Poloxamer 188</td>
<td>An increase in Tween content reduced particle size and PDI while increasing zeta potential. The best results were obtained with 5% (w/w): 139.43 nm, PDI = 0.165 and ZP = −30.93 mV</td>
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<td></td>
<td>SL-stearic triglyceride LL-MCT</td>
<td>Tween 20 or 80, Phosphatidyl-choline, Poloxamer</td>
<td>Ovoidal NPs with 203 nm (PDI = 0.26), EE = 82.6% and DL = 4.13 mg mL−1 were stable for 6 months at room temperature. Release profile followed dissolution kinetics</td>
</tr>
<tr>
<td>High-shear homogenization</td>
<td>SL-n-hexadecyl palmitate, glyceryl stearate LL-MCT</td>
<td>Tween 20 or 80, Poloxamer</td>
<td>NPs made with Tween 20 had 180 nm (PDI = 0.2), ZP = −47 mV, more imperfections in the crystalline structure, and hence higher physical stability. Co-encapsulation of α-tocopherol protected the UVA filter against photodegradation</td>
<td>Nicules et al. [32]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SL-stearic acid LL-oleic acid</td>
<td>Tween 80, Lechithin</td>
<td>Spherical NPs with 200 nm (PDI = 0.2), ZP = 30 mV and EE &gt;90% were included in a gel that had the slowest release profile</td>
</tr>
<tr>
<td>Microfluidization</td>
<td>SL-oleyl palmitate LL-sesame oil</td>
<td>Tween 80</td>
<td>Higher levels of LL increased the NPs size while more microfluidization cycles, surfactant and pressure formed smaller NPs (86-169 nm) that provided photoprotection to vitamin E</td>
<td>Chen et al. [17]</td>
</tr>
<tr>
<td>Emulsion-solvent evaporation</td>
<td>NI</td>
<td>SL-glyceryl monostearate (SL) LL-MCT</td>
<td>NI</td>
<td>Particles had mean particle size of 400 nm. Quantities of liquid lipid lower than 15% did not affect the particle size but more than 25% caused a decreasing in mean diameter. Encapsulation efficiency increased with higher content of liquid lipid.</td>
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</table>

SL, solid lipid, LL, liquid lipid, MCT, medium chain triglycerides, NI, not informed, PDI, polydispersity index, EE, encapsulation efficiency, DL, drug loading, ZP, zeta potential, HPH, high-pressure homogenization.
the particles. Recently, Yin and Misran [51] observed that NLCs prepared with stearic acid as solid lipid, oleic acid as liquid lipid and Tween 80/lecithin as surfactants exhibited potent aggregation when they were loaded with a high amount of alpha-tocopherol.

Particle size

The mean particle diameter and size distribution can be determined by several techniques, but only a few are frequently used to characterize solid lipid particles. The most exploited techniques have been photon correlation spectroscopy (PCS) or dynamic light scattering (DLS) and laser diffraction (LD) [54]. PCS measures the fluctuation of the intensity of the scattered light that is caused by the movement of the particles and analyses diameters between 3 and 3000 nm [54]. The LD method is based on the dependence of the diffraction angle on particle size (Fraunhofer spectra) and can measure sizes between 40 nm and 2000 μm [33].

There are many experimental conditions that directly affect the particle size: composition of SLNs, formulation variables such as surfactant or surfactant mixture, amount of drug incorporated, structural properties of lipid and drug, production methods and technological parameters [55]. Therefore, it is really difficult to make comparisons between the results of different works. However, it is worth mentioning some results about the particular effect of some experimental conditions on the size of lipid nanoparticles.

Table III Parameters used to characterize lipid nanoparticles (SLNs and NLCs) containing vitamin E

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measurements</th>
<th>Techniques [References]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Scanning electron microscopy [25, 30, 45]</td>
<td>Photon correlation spectroscopy [17, 18, 28-32, 44, 47, 49-51]</td>
</tr>
<tr>
<td>Zeta potential</td>
<td>Transmission electron microscopy [46]</td>
<td>Sedimentation field flow fractionation analysis [31]</td>
</tr>
<tr>
<td>Vitamin E loading and</td>
<td>Reversed-phase high-performance liquid chromatography of samples treated with methanol or ethanol [17, 18, 30, 31, 44, 47-49]</td>
<td>Static light scattering [48]</td>
</tr>
<tr>
<td>Encapsulation efficiency</td>
<td>UV spectrophotometry of samples treated with ethanol or methanol [25, 51, 53]</td>
<td>Dynamic light scattering [48]</td>
</tr>
<tr>
<td>Particle structure</td>
<td>X-ray diffraction [30, 47]</td>
<td>Differential scanning calorimetry [30, 47, 48]</td>
</tr>
<tr>
<td>Release profile</td>
<td>Dialysis/UV spectrophotometry [18, 31]</td>
<td>Franz diffusion cell/HPLC [25, 51]</td>
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</table>

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Vitamin E loading and encapsulation efficiency

The quantity of drug that is possible to encapsulate in these nanoparticulate systems, and hence the encapsulation efficiency, is strongly dependent on: (1) the nature of the molecule, which determines the compatibility with the lipids, and (2) the structure of the lipid matrix, which is related to its crystallinity [30, 57]. As
vitamin E is a lipophilic compound, its compatibility with the lipid matrix is generally good, thus the encapsulation efficiency (EE) is usually high, also allowing high drug loads (DL). The assessment of these parameters is quite important, and DL should be carefully quantified. This is because it defines the quantity of nanoparticles that need to be used depending on the purpose and also affects other crucial characteristics of NPs, like release profile [56]. There are many standard analytical techniques that can be employed, but spectroscopy and HPLC are the most popular methods [57]. Coincidently, these are the techniques used to assess DL and EE in lipid nanoparticles loaded with vitamin E by all the authors (See Table III). Generally, the nanoparticles are previously treated with methanol or ethanol, depending on their composition.

Almost all the studies report high encapsulation efficiencies (>70%), and some of them attain values close to 100% [17, 25, 30, 47]. This fact can be related to the lipophilic character of vitamin E, which favours its retention in the lipid phase during the formation of nanoparticles [30]. Only a few works refer to the influence of experimental conditions on encapsulation efficiency. For example, Kim et al. [52] affirmed that the encapsulation efficiency of vitamin E in NLCs rises with increasing liquid lipid proportion. Shylaja et al. found that higher EE was obtained by increasing the proportion of vitamin E. These results agree with the fact that the addition of liquid lipids to the solid lipids was just intended to increase the quantity of drug that can be accommodated in the lipid matrix.

Despite the importance of drug loading, as mentioned, only one investigation reports such results. Cortesi et al. (2017) obtained a nanosuspension of NLCs having 4.13 mg mL\(^{-1}\) of vitamin E [31]. The assessment of drug loading can help to complete the characterization of lipid particle suspensions. Thus, more attempts to calculate this parameter will be welcome.

Properties of the lipid matrix and particle structure

The particle structure is deeply influenced by the crystalline properties of the lipids, their affinity and compatibility with the encapsulated substance. The location of the drug in the particle structure is also affected by these parameters, and by the properties of the film-forming surfactant [30], the method used to produce the particles, and technological and composition variables. There are different models that have been proposed considering different situations. Figure 1 depicts details of these models, taken from an article by Souto et al. [58] published in 2007.

In addition, during storage, polymorphic transitions can occur on the crystalline structure of lipids leading to changes in the internal structure of the nanoparticles. This phenomenon is responsible for alterations in the release pattern or activity of the encapsulated compounds [30, 58, 59].

The most used lipids to obtain SLNs and NLCs crystallize into three main structures: hexagonal (\(a\)), orthorhombic perpendicular (\(b^0\)) and triclinic parallel (\(b\)) [58]. Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) can be used to study the crystalline properties within nanoparticles [54]. DSC allows the study of melting and crystallization behaviour of crystalline material that forms the nanoparticles, or as in the case of NLCs, drug and lipid interactions, and mixtures of solid lipids and liquid lipids [56]. On the other hand, the structure and domains of the liquid lipid can be analysed by nuclear magnetic resonance (NMR) [60].

There are few studies about the crystalline structure of SLNs/NLCs loaded with vitamin E, its behaviour over the time and impact on the nanoparticles’ characteristics. To the best of our knowledge, only two papers contain detailed information about this matter. Carvalho et al. found that SLNs without VE have a similar diffraction pattern to bulk lipid corresponding to the \(b^0\) polymorph of the solid lipid, while NPs containing VE have \(a\) and \(b\) polymorphic forms. These findings led them to think that the inclusion of this compound in the lipid matrix creates more imperfections in the crystalline lattice, favouring the retention of the drug inside the particle during shelf life. In addition, DSC analysis confirmed the presence of \(b^0\) polymorph by virtue of its melting point pattern, which decreased in absolute value, onset and endset, indicating the coexistence of \(a\) and \(b\) polymorphic forms. The accommodation of vitamin E in the solid lipid matrix reduced the crystalline character of the resulting structure [47]. Another study, made by Oehike...

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Figure 1 Models for the structure of solid lipid nanoparticles and nanostructured lipid carriers that can be obtained under different conditions determined by the nature of the components and their relative solubility/proportion.
et al. [30] reported that the inclusion of vitamin E in the particles did not interfere with the crystallization of the solid lipid. It was not possible for them to define which polymorphs were formed after particle solidification. Results obtained from DSC analysis revealed that melting enthalpy was proportional to the solid lipid content and did not change over time, indicating that the crystallinity remained constant during storage (15 weeks at 25°C). The inclusion of VE led to the broadening of the melting range, which is in agreement with the other results. These findings and the time-dependent changes of the radical scavenging activities of VE-SLNs made authors think that variations in the location of VE inside the particle occurred [30]. The different behaviour described here could be related to the nature of the systems, which differ in the solid lipid and the surfactant.

These studies could be useful to establish relations between the polymorphic forms present in the different SLNs/NLCs containing vitamin E and the physical stability of nanosuspensions.

Release profile of vitamin E

The in vitro release studies are important to compare the ability of different lipid nanoparticle preparations to retain the incorporated substance and release it from the lipid matrix in the desired way, according to the purpose of the system [56].

There are many factors that govern the release profile of an encapsulated substance: the particle size and size distribution; drug loading; internal structure of the particle; distribution of the encapsulated substance inside the particle; and compatibility between the components of the particles and the encapsulated molecules, and hence the interactions between them, among others [19, 61]. For example, tiny particles have a larger surface area, but larger particles have bulky cores accommodating more of the drug and further diffusion out. Therefore, when the drug is homogeneously dispersed in the lipid matrix, slower drug release can be achieved [55]. In relation to the drug content, it is strongly affected by the affinity of the drug and the rest of the excipients that form the particle and is also influenced by the production method. The last one is quite important to the final structure of the particle, which is also affected by the nature and concentration of the surfactant [61]. Considering this, an exhaustive investigation of the factors that significantly affect the release profile of each particular system can help to design the desired delivery system.

Release studies can be performed in several ways [62]. Specifically, for the lipid nanoparticles releasing vitamin E, these studies have been carried out in two ways:

1. by the dialysis method, incubating the particles in phosphate buffer saline (pH 7.4) at 32°C [18] or in ethanolic phosphate buffer saline (pH 7.4) at 23–25°C [31], with vitamin E assessment by HPLC, or
2. using a Franz diffusion cell for incubating the nanoparticles in methanolic phosphate buffer (pH 7.4) at 37°C [25] or in ethanolic phosphate buffer (pH 7.4) at 30 and 37°C [51], with vitamin E quantification by UV spectrophotometry.

The suspension of lipid nanoparticles loaded with vitamin E prepared by Abla and Banga [18] had quick release after incubation (30% in 2 h) followed by a controlled delivery period in which the VE released attained 75% in 24 h. The release profile exhibited by the suspension of SLN-VE obtained by Shylaja and Mathew [25] has a slow release step (20% in 2 h) followed by the controlled release of 75% in 8 h. These authors attributed the slow release stage to the difficulty of the diffusion of vitamin E through the lipid matrix [25]. Ying and Misran [51] reported that the NLC-VE formulated in a gel had the lowest release profile (30% in 24 h), followed by the formulation of free vitamin E in a gel (40% in 24 h), the suspension of the nanoparticles loaded with vitamin E (70% in 24 h) and a solution of free vitamin E (100% in 24 h).

Cortesi et al. [31] fitted the experimental data of the release profiles to semi-empirical equations describing Fickian dissiputive and diffusional release mechanisms. This analysis indicated that diffusion is probably the main mechanism involved in releasing vitamin E from these particles [31]. Similarly, Shylaja and Mathew [25] fitted their release profile data to models representing zero order, first order, Higuchi’s square root of time kinetics and Korsmeyer–Peppas semi-empirical equation. According to the results, the release of vitamin E encapsulated in these lipid nanoparticles follows a first-order kinetic [25].

It is not useful to compare results obtained by different authors because the nanoparticles have different properties, but it is important to remark that the encapsulation of vitamin E in SLNs or NLCs allows controlling the release of the active agent. It is important to study more thoroughly the mechanisms involved in the release of vitamin E from lipid nanoparticles.

Characterization and stability of vitamin E encapsulated in lipid nanoparticles

To assure the utility of lipid nanoparticles with vitamin E to develop commercial products, the activity of this compound should be preserved. Thus, the characterization of vitamin E after encapsulation, formulation and storage is necessary.

It is possible to use reversed-phase high-performance liquid chromatography with UV spectrophotometric detection to study the stability of the different forms of vitamin E. This technique was used by Dingler et al. [44] to prove that the stability of α-tocopherol acetate was better when it was encapsulated in solid lipid nanoparticles instead of being formulated in a soybean oil-in-water emulsion or dispersed in an aqueous surfactant solution. These authors diluted the vitamin E-loaded nanoparticles with methanol before analysis. Oehlke et al. [48] evaluated the antioxidant activity of vitamin E encapsulated in SLNs and found that this property remained unchanged after the encapsulation process. RP-HPLC was also employed by Abla and Banga [18] to test VE after exposing the nanosuspensions to a solar simulator. They demonstrated that VE encapsulated in NLCs remained unchanged, while VE free or included in mineral oil was almost completely degraded. These authors also evaluated the antioxidant activity of encapsulated VE by means of the ferric reducing antioxidant potential assay and found that VE retained all its activity [18]. Likewise, Chen et al. [17] investigated the stability of VE loaded in NLCs after exposure to a UV lamp. RP-HPLC analysis revealed that encapsulated VE retained 82–88% of the initial activity while non-encapsulated VE conserved 62% [17]. Another study was reported by Oehlke et al. [30], who observed that the initial recovery of VE was 77.4 ± 6.7%. They attributed this loss to the high temperature during particle preparation. After 15 weeks, the activity fell to 68.2 ± 6.5%. A final study conducted by the same authors demonstrated, by means of electron paramagnetic resonance spectroscopy, that the radical scavenging activity of encapsulated VE was completely retained during 15 weeks [30].

These studies show different ways to investigate the properties of vitamin E after encapsulation in lipid nanoparticles. They also
confirm that it is possible to prepare these delivery systems while preserving the activity of this compound.

**Formulation of lipid nanoparticles loaded with vitamin E**

After preparation, lipid nanoparticles should be included in a suitable pharmaceutical formulation, depending on the administration route. According to the main applications of vitamin E, topical formulations such as creams, lotions or gels can be used. The inclusion of these particles in a topical formulation not only makes them proper to administer, but also increases their physical stability. This is because the collisions between particles decrease by virtue of the dilution of particles in the formulation and the increase in the medium’s viscosity [44].

Production of creams containing lipid nanoparticles is a simple process. Generally, the aqueous phase is partially substituted by the aqueous SLN/NLC dispersion. Sometimes a little reduction in the oil phase content is necessary due to the lipid character of the particles to be added, which may lead to an increase in general viscosity of the formulation. During the addition of the nanosuspension and the homogenization process, efficient control of the temperature is required. This is to avoid the melting of the nanoparticles during the formulation process, thus preventing undesirable changes [58]. In the case of lotions, a part of the water can be replaced by the nanosuspension containing the lipid particles [22]. The formulation of lipid NPs in gels is relatively easy too. Commonly, the gel is produced with all excipients and a reduced quantity of water and then mixed with the SLN dispersion [45]. The nanosuspension that is incorporated into a gel or cream regularly has 5–10% of solid material [50].

Dingler et al. [44] included lipid nanoparticles containing VE in a conventional cream. The nanosuspension was diluted 1:10 in a previously formulated cream. The resulting formulation was then evaluated in terms of stability, occlusivity properties and penetration into the skin layers [44]. A hydrogel made of xanthan gum was gelling agent and glycerol as hydrating excipient was used by Wissing and Müller [45] to formulate SLNs containing VE. The stability of the formulation was evaluated as well as its UV-blocking ability and occlusivity properties [45]. Niculae et al. [32] formulated NLCs with VE in a previously prepared cream. They lyophilized the nanoparticles before addition to the cream. The photoprotective properties and protection factor of these creams were then studied [32]. Ying and Misran [51] incorporated nanoparticles in a thermosensitive gel made of carboxymethylcellulose and iota-carrageenan. Rheological studies of formulations revealed that the inclusion of lipid nanoparticles with vitamin E in the gel increases the rigidity of the system. The encapsulation of VE in NLCs together with the inclusion of particles in a gel formulation resulted in the slowest release profile of the active agent [51].

When SLNs/NLCs containing VE are going to be included in a pharmaceutical dosage form, it is necessary to prove that the formulation really stabilizes the nanoparticles, because the excipients can negatively interact with them, affecting their stability. For example, lipid nanoparticles can interact with the oil droplets of the cream, depending on the compatibility [44, 45]. In this case, lipid nanoparticles can dissolve in the oil phase of the emulsion, releasing the encapsulated substance. Consequently, preformulation studies should be performed to help find the best dosage form for each system.

**Stability of lipid nanoparticles containing vitamin E**

The stability of lipid nanoparticles should be analysed in the suspension and after the formulation in a suitable pharmaceutical formulation. Because in suspension the surfaces of particles develop charge, zeta potential is very useful to allow predictions about the storage stability of a colloidal dispersion [36]. However, there are some other aspects to be studied over the time: mean particle diameter, size distribution, lipid polymorphism, drug content, etc.

Most of the published works about the encapsulation of vitamin E in lipid nanoparticles focus attention on studying the stability of nanosuspensions in the way they are at the end of the preparation process. Such studies give an idea about the influence of some components or experimental parameters in stabilizing the structures in suspension, but evaluation of the stability of lipid nanoparticles when they are already formulated is crucial. This is because they can interact with the lipophilic components of the formulations, as already mentioned. Such interactions can favour changes in the structure of particles, which can also affect the quantity of encapsulated substance that remains inside the lipid matrix, and their activity. The release profiles can also be modified. In addition, partial dissolution of the nanoparticles may occur if the compatibility of the lipids forming them and the lipophilic components of the formulation is very high. The content of lipid nanoparticles in a cream can be analysed by DSC [44, 45].

Table IV summarizes the stability studies reported for lipid nanoparticles containing vitamin E. It is not useful to make comparisons because the systems are very different in relation to the composition and the preparation conditions. However, results of the stability experiments indicate it is possible to obtain stable lipid nanoparticles. Size and PDI are the parameters evaluated most to ascertain the stability of lipid particles containing vitamin E, but more investigations aimed to determine how much vitamin E remains inside the particles during storage can contribute to further this topic. New stability studies of lipid nanoparticles loaded with VE included in suitable pharmaceutical dosage forms will be welcome too.

**In vitro studies to explore the potential effectiveness and toxicity of lipid nanoparticles with vitamin E**

Novel formulations based on drug delivery systems are generally expensive to develop and to introduce in the pharmaceutical industry. Consequently, their development should be justified by the advantages of such systems over the conventional formulations. Many in vitro tests are commonly carried out with this purpose. Tests to evaluate the occlusivity, UV-blocking capacity, photoprotection or skin permeation have frequently used to prove the potential advantages of topical formulations containing lipid nanoparticles with vitamin E. On the other hand, the safety of these novel formulations should be explored. Therefore, it is frequent to find cytotoxicity or skin irritation studies as preliminary investigations with this objective. Table V shows the main results obtained in different in vitro studies carried out to investigate the potential effectiveness or toxicity of SLNs or NLCs containing VE.

These studies show that the encapsulation of VE in SLNs/NLCs can increase UV absorption, occlusion capacity, photoprotective effect and skin permeation of vitamin E, with low cytotoxicity and without skin irritation.
Table IV  Stability studies carried out with lipid nanoparticles (SLNs and NLCs) loaded with vitamin E

<table>
<thead>
<tr>
<th>Type of NP</th>
<th>Formulation</th>
<th>T (°C)</th>
<th>Studied characteristics</th>
<th>Main conclusions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLN</td>
<td>Suspension</td>
<td>4, 40</td>
<td>Size (PCS)</td>
<td>Stable during 3 months at 4°C. Only a slight increase in diameter occurred under this condition</td>
<td>Dingler et al. [44]</td>
</tr>
<tr>
<td>SLN</td>
<td>Suspension</td>
<td>4-8</td>
<td>Size, PDI (PCS)</td>
<td>Particle size and PDI did not changed in 1 year</td>
<td>Wissing and Müller [45]</td>
</tr>
<tr>
<td>SLN</td>
<td>Gel</td>
<td>4-8</td>
<td>Size (PCS)</td>
<td>It was considered stable because after 560 days, size increased only from 121.2 ± 3.6 to 180.7 ± 4.9 nm and PDI rose from 0.172 to 0.221</td>
<td>Ma et al. [50]</td>
</tr>
<tr>
<td>NLC</td>
<td>Suspension</td>
<td>4</td>
<td>Size, PDI (PCS)</td>
<td>Stable during 6 months. The quantity of particles remained constant</td>
<td></td>
</tr>
<tr>
<td>NLC</td>
<td>Concentrated suspension</td>
<td>25</td>
<td>Size, PDI (PCS)</td>
<td>Stable during 30 days</td>
<td></td>
</tr>
<tr>
<td>SLN</td>
<td>Suspension</td>
<td>6, 21, 40</td>
<td>Size, PDI (PCS), zeta potential (LDV), recovery of VE (RP-HPLC)</td>
<td>Stable during 21 days at 6°C because all the evaluated parameters remained constant. During storage at 21 and 40°C, VE recovery decreased</td>
<td>Carvalho et al. [47]</td>
</tr>
<tr>
<td>SLN</td>
<td>Suspension</td>
<td>4, 25, 40°C/75% HR</td>
<td>Physical appearance, VE loading (UV-Vis)</td>
<td>Stable during 60 days because no changes were found in the evaluated parameters.</td>
<td>Shylaja and Mathew [25]</td>
</tr>
<tr>
<td>NLC</td>
<td>Suspension</td>
<td>NI</td>
<td>Physical appearance</td>
<td>Stable for 3 weeks.</td>
<td>Abla and Banga [18]</td>
</tr>
<tr>
<td>NLC</td>
<td>Suspension</td>
<td>RT</td>
<td>Physical appearance, size (PCS)</td>
<td>Stable for 6 months. The mean diameter only increased slightly.</td>
<td>Cortesi et al. [31]</td>
</tr>
<tr>
<td>NLC</td>
<td>Suspension</td>
<td>4</td>
<td>Size, PDI (PCS)</td>
<td>Stable for 4 weeks because the size and PDI remained almost unchanged.</td>
<td>Ying and Misran [51]</td>
</tr>
</tbody>
</table>

NI, not informed; RT, room temperature.

In vivo studies of lipid nanoparticles containing vitamin E

It is common to find in the scientific literature the studies carried out with animals having different purposes. However, to the best of our knowledge, such experiments do not appear in the specific works about solid lipid nanoparticles containing vitamin E. This could be related to the fact that vitamin E is a well-known and comprehensively studied active agent. Another reason could be that today many in vitro tests are available for the evaluation of potential effectiveness or toxicity of vitamin E or any drug for topical administration. These tests provide enough information without the use of animals.

Studies involving human volunteers are scarce too. In fact, we only found one report [44]. In this study, solid lipid nanoparticles incorporating vitamin E were administered on areas of 4 cm² of the forearms of healthy volunteers. The applied dose (0.25 mg cm⁻²) remained at the administration site for 30 min before the stripping process. Vitamin E was then extracted from the strips using methanol and further analysed by HPLC. The analyses revealed that more vitamin E was accumulated in the stratum corneum when the formulation containing SLNs was used. The authors interpreted this finding in two ways: the occlusive effect promotes penetration of vitamin E and active ingredients incorporated in this kind of delivery system can be released after application to the skin [44].

Commercial products based on lipid nanoparticles loaded with vitamin E

Because of the benefits that lipid NPs can offer for topical administration of active agents, the existence in the market of several products based on this delivery system with VE is expected. However, we were only able to identify two of these products (Table VI) [63], perhaps because usually the information about the delivery systems included in formulations is not detailed enough in the product description.

Regulatory issues

With recent advances in nanotechnology, the emergence of related pharmaceutical products requires the development of regulations that guarantee their safety [54]. A prerequisite for introducing a product in the pharmaceutical market is the use of excipients accepted by regulatory authorities, because companies do not want to assume the costs of toxicity and safety studies of new excipients. This is a problem for most of the new drug delivery systems. However, in the case of lipid nanoparticles, the scenario is more favourable. This is because most of the excipients used to prepare lipid nanoparticles slated for topical administration are already approved by regulatory agencies because they have been used in topical formulations for many years [35]. However, these particles are quite small, which gives them special characteristics. Consequently, nanoparticles must be considered a new class of materials for regulation purposes [58]. Particles having diameters smaller than 100 nm can normally be taken up by all cells of the body through endocytosis. Thus, they have a priori a higher toxicity potential and can be considered harmful in a general way [19]. But lipid nanoparticles, and specifically those prepared with vitamin E, can escape from this classification because generally they are fabricated with approved excipients and also it is more common to prepare nanoparticles with size greater than 100 nm [19]. However, more published data about the toxicological problems associated with lipid nanoparticles could provide the groundwork for proper
Table V In vitro studies to evaluate potential effectiveness or toxicity of lipid nanoparticles (SLNs and NLCs) containing vitamin E

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Formulation</th>
<th>Principle of the study</th>
<th>Main conclusions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV-blocking effect</td>
<td>SLN-VE suspension</td>
<td>Measures the colour developed by a sensitive dye after UV exposure.</td>
<td>SLN-VE in suspension had higher UV absorption compared to SLNs in suspension, VE in emulsion and placebo emulsion</td>
<td>Wissing and Müller [45]</td>
</tr>
<tr>
<td></td>
<td>SLN-VE suspension</td>
<td>Compares the UV absorption between 200 and 450 nm.</td>
<td>Co-encapsulation of VE with 3,4,5-trimethoxybenzoylchitin in SLNs enhanced the UV absorption of the formulation</td>
<td>Song and Liu [46]</td>
</tr>
<tr>
<td>Occlusivity</td>
<td>SLN-VE suspension, cream</td>
<td>Quantifies the loss of water through a filter covered with the formulation.</td>
<td>SLN-VE, in suspension or in a cream, had higher occlusion factor than the cream alone (40 at 6 h vs. 20 at 24 h)</td>
<td>Dingler et al. [44]</td>
</tr>
<tr>
<td></td>
<td>SLN-VE suspension, gel</td>
<td></td>
<td>The presence of SLN-VE in suspension or gel increased the occlusion factor twice in relation to the placebo formulations</td>
<td>Wissing and Müller [45]</td>
</tr>
<tr>
<td>Photoprotection</td>
<td>NLC-VE suspension</td>
<td>Compares cell activity of UVB irradiated HaCaT keratinocytes, pre-treated or not with different dilutions of NLC-VE.</td>
<td>Cells incubated with NLC-VE (1:600) had comparable activity to the non-irradiated cells, suggesting a photoprotective capacity of this formulation. Cell uptake of VE was necessary to achieve the photoprotective effect</td>
<td>Ma et al. [50]</td>
</tr>
<tr>
<td></td>
<td>NLC-VE cream</td>
<td>Compares the UV absorption spectra and SPF of NLCs free or containing VE alone or combined with a sun filter</td>
<td>The presence of γ-tocopherol in the lipid matrix led to a slight decrease in the erythemal UVA protection factors and SPFs of creams containing VE and the UVA filter in NLCs when compared to those with UVA filter encapsulated alone</td>
<td>Niculae et al. [32]</td>
</tr>
<tr>
<td>Radical scavenging activity (RSA)</td>
<td>SLN-VE suspension</td>
<td>Determines RSA by the reduction in Fremy’s salt using EPR spectroscopy</td>
<td>The radical scavenging activity of vitamin E was conserved after the encapsulation process and completely retained during 15 weeks</td>
<td>Oehlke et al. [30]</td>
</tr>
<tr>
<td>Permeation</td>
<td>NLC-VE suspension</td>
<td>Compares permeation of VE in NLCs or others in a Franz cell with human cadaver skin as membrane</td>
<td>The amount of vitamin E delivered into the epidermis was significantly higher when it was encapsulated in NLCs as compared to the non-encapsulated NLCs and mineral oil</td>
<td>Abla and Banga [18]</td>
</tr>
<tr>
<td>Cytotoxicity</td>
<td>NLC-VE suspension</td>
<td>Compares the activity of HaCaT keratinocytes incubated in culture medium alone or with NLC-VE</td>
<td>Concentrated suspensions of NLC-VE (1:50–1:200) affected the cell activity while the more diluted ones had similar behaviour as the control. NLC-VE (1:600) was non-cytotoxic</td>
<td>Ma et al. [50]</td>
</tr>
<tr>
<td></td>
<td>SLN-VE suspension</td>
<td>Studies the effect of co-loading VE with doxorubicin on cancer cells</td>
<td>SLN-VE with doxorubicin had significantly increased cytotoxicity over the SLNs containing only doxorubicin</td>
<td>Oliveira et al. [28]</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>NLC-VE suspension</td>
<td>Evaluates the skin irritation by determining the cell viability by a three-dimensional tissue culture model called EpiDerm™</td>
<td>Cells treated with NLC-VE had 92.7% of the viability shown by the untreated cells, while the ones treated with 5% SDS had only 5.7%. Tissue treated with NPs remained intact, while the stratum corneum of cells treated with SDS was disrupted</td>
<td>Abla and Banga [18]</td>
</tr>
</tbody>
</table>

NE, nanoemulsions; SPF, sun protection factor; EPR, electron paramagnetic resonance.

Table VI Commercial topical formulations containing NLCs with vitamin E (adapted from Puglia and Bonina [63])

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Principal ingredients</th>
<th>Year of introduction</th>
<th>Producer/distributor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olivenol Anti Falten Pflegekonzentrat</td>
<td>Olea europaea oil, panthenol, acacia senegal, tocopheryl acetate</td>
<td>2008</td>
<td>Dr. Theiss</td>
</tr>
<tr>
<td>Olivenol Augenpflegebalsam</td>
<td>Olea Europaea oil, prunus amygdalus dulcis oil, hydrolysed milk protein, tocopheryl acetate, rhodiola rosea root extract, caffeine</td>
<td>2008</td>
<td>Dr. Theiss</td>
</tr>
</tbody>
</table>
conjugated dienes. These systems are an attractive drug delivery system due to their potential advantages they offer. Accordingly, lipid nanoparticles are an attractive drug delivery system to develop advantageous pharmaceutical and cosmetic products with vitamin E.

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