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Preparation and characterization of *n*-dodecyl-ferulate-loaded solid lipid nanoparticles (SLN®)

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Abstract

Solid lipid nanoparticles (SLN™) containing a novel potential sunscreen *n*-dodecyl-ferulate (ester of ferulic acid) were developed. The preparation and stability parameters of *n*-dodecyl-ferulate-loaded SLN have been investigated concerning particle size, surface electrical charge (zeta potential) and matrix crystallinity. The chemical stability of *n*-dodecyl-ferulate at high temperatures was also assessed by thermal gravimetry analysis. For the selection of the appropriated lipid matrix, chemically different lipids were melted with 4% (*m*/*m*) of active and lipid nanoparticles were prepared by the so-called high pressure homogenization technique. *n*-Dodecyl-ferulate-loaded SLN prepared with cetyl palmitate showed the lowest mean particle size and polydispersity index, as well as the highest physical stability during storage time of 21 days at 4, 20 and 40 °C. These colloidal dispersions containing the sunscreen also exhibited the common melting behaviour of aqueous SLN dispersions.

Keywords: *n*-Dodecyl-ferulate; Solid lipid nanoparticles; SLN; Sunscreens

1. Introduction

Ferulic acid ($C_{10}H_{10}O_4$) is a phenylpropenoid derived from the cinnamic acid 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid or 4-hydroxy-3-methoxycinnamic acid. It shows two isomers: *cis* (a yellow oily liquid) and *trans* (crystalline). Its nomenclature comes from the *Umbelliferae foetida Ferula* from which this active was isolated for the first time in 1866 Hlasiwetz and Barth (1866).

Ferulic acid is widely spread out in the vegetal kingdom as a transient product of the way of synthesis of the lignin or in the cellular wall of certain plants such as wheat and barley Nishizawa et al. (1998). It is known by its anti-oxidizing properties and is also used as a preservative in food products (Miller et al., 2000; Yang et al., 2001). Ferulic acid is also present in some Indian medicinal plants and it has been evaluated

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as a co-adjuvant anti-inflammatory, an anti-nociceptive and an analgesic (de Campos et al., 1998; Raichaski et al., 2004). Some of its esters have been tested as potential actives against lung, colon and skin tumours (Hudson et al., 2000; Murakami et al., 2002) and as antioxidants/radical scavengers (Kikuzaki et al., 2002; Anselmi et al., 2004a, 2004b). It can also be used as an UV-blocker in anti-aging products.

In this paper we present the detailed development process of *n*-dodecyl-ferulate-loaded solid lipid nanoparticles (SLN). Lipid based carrier systems, such as SLN, were developed to overcome some limitations of classical colloidal carriers (Müller and Lucks, 1996). When optimized, SLN exhibit high physical stability (Wissing, 2002), protection of incorporated labile actives against degradation (Jenning et al., 2000) and excellent in vivo tolerability (Müller et al., 2002). Because of their particulate character and adhesive properties, SLN are known to be highly suitable as carriers for UV-blockers in topical formulations (Saupe, 2004; Wissing and Müller, 2002). In fact, these carriers can also act as physical sunscreens on their own. In addiction, when incorporating molecular sunscreens into SLN, a synergistic effect on protective activity of particulate carrier and molecular sunscreen will be measured (Wissing and Müller, 2003). These properties make SLN highly alternative as a carrier for sunscreens because the total concentration of sunscreens can be decreased (and simultaneously decreased potential side effects) maintaining the sun protector factor (SPF). Ferulic acid is basically an interesting novel UV sunscreen, but a hot water soluble compound (oil insoluble) and therefore cannot be incorporated directly in the lipophilic SLN. Hence, a lipidic derivative was synthesized, the dodecyl conjugate. This C_{12} derivative has been chosen because of its highest radical scavenging activity compared to that of others ferulic acid derivatives with the same sunscreen activity. The advantage of this substance, in comparison to other molecular sunscreens, is related to its natural source for the UV light protection, minimizing possible interactions with the immune system and therefore the development of adverse side effects. This study investigates the preparation of SLN loaded with the dodecyl derivative including physical stability of the SLN dispersion as pre-requisite for sunscreen formulations based on creams or gels.

2. Experimental

2.1. Materials

n-Dodecyl-ferulate was synthesized at the Department of Pharmaceutical Technology, Universita di Siena, Italy (Anselmi et al., 2004a). Concerning the lipids selected for production of SLN, Table 1 shows their chemical composition, melting point and the supplier. With regard to emulsifying agents, TegoCare®450 was a kind gift from Goldschmidt. Miranol® Ultra C32 and Tyloxapol® were purchased from Rhodia (Frankfurt, Germany) and Sigma–Aldrich (Deisenhofen, Germany), respectively.

2.2. Methods

2.2.1. Preparation of aqueous SLN dispersions

The hot high pressure homogenization (HPH) technique was applied for the preparation of aqueous SLN dispersions, according to Müller et al. (2000a). The lipid was melted at a temperature 5 °C above its melting point and *n*-dodecyl-ferulate was dissolved in this phase. Under mechanical stirring at 8000 rpm using an Ultra-Turrax T25 (IKA, Staufen, Germany) the melted lipid phase was dispersed in a hot aqueous surfactant solution of identical temperature for 1 min. The obtained pre-emulsion was homogenized at 500 bar using the APV Micron Lab 40 (APV Systems, Unna,

Table 1
Chemical composition and melting point of the selected lipids

Lipid	Composition	Melting point (°C)	Supplier (Germany)
Precifac® ATO5	Cetyl palmitate	43–49	Caelo GmbH
Dynasan®114	Trimyristate	55–58	Hüls AD
Dynasan®116	Tripalmitate	61–65	Hüls AD
Dynasan®118	Tristearate	70–73	Hüls AD
Softisan®154	Mono, di, triacylglycerols	55–60	Hüls AD

Germany). After three homogenization cycles the obtained o/w nanoemulsion was cooled, the lipid recrystallized forming aqueous SLN dispersions.

2.2.2. Particle size analysis

Laser diffractometry (LD) was performed using a Coulter LS 230 (Beckmann Coulter Counter, Krefeld, Germany) and the obtained data were evaluated using the volume distribution (d50%, d90% and d99%), which means that if the diameter 99% (d99%) was registered as 1 μm, 99% of particles possess a diameter of 1 μm or lower. Note that larger particles are over weighted in a volume distribution. PCS measurements were performed in order to determine the mean particle size (z-average, Z-ave) and the polydispersity index (PI). PCS measurements were performed using a Malvern Zetasizer IV (Malvern Instruments, UK). The Z-ave and PI values of the aqueous SLN dispersions were obtained by the average of 10 measurements at an angle of 90° in 10 mm diameter cells. The system was thermostated at 25 °C.

2.2.3. Zeta potential analysis

The surface electrical charge of SLN was determined by the assessment of zeta potential of the lipid nanoparticles using the Helmholtz–Smoluchowsky equation, i.e. based on the particle electrophoretic mobility. Again, the Malvern Zetasizer IV (Malvern Instruments, UK) was used. SLN were suspended in distilled water previously adjusted to a conductivity of 50 μS/cm with a solution of 0.9% (*m*/*v*) NaCl (pH 5.5–6.0). The measurements were performed in triplicate at 25 °C using the large bore capillary cell (4 mm) with a field strength of 20 V/cm.

2.2.4. Differential scanning calorimetry (DSC)

DSC measurements were performed on a Mettler DSC 821e apparatus (Mettler Toledo, Gieβen, Germany). A sufficient amount of active was accurately weighted in 40 μl aluminium pans. DSC scan was recorded from 25 to 200 °C at a heating rate of 5 K/min, using an empty pan as reference.

2.2.5. Thermal gravimetry analysis (TGA)

TGA measurements were performed using a Mettler TG-DTA analyser (Mettler Toledo, Gieβen, Germany). The loss of weight was recorded weighting approx. 15 mg of active, which was heated in an aluminium oxide crucible from 20 to 200 °C at 10 K/min.

3. Results and discussion

3.1. Chemical stability of active at high temperatures

In order to obtain information about the melting point of *n*-dodecyl-ferulate, DSC assay was performed for the analysis of pure active. The obtained DSC scan is presented in Fig. 1. The melting point corresponds to the maximum of the heating curve.

As shown in Fig. 1, *n*-dodecyl-ferulate melted within the range between 46 and 56 °C, showing a melting peak at 48.09 °C with a heating enthalpy of 147.29 J/g.

Concerning thermal gravimetry analysis (TGA), Fig. 2 depicts the obtained result. At a temperature above the melting point of *n*-dodecyl-ferulate (>46 °C), the active melts and reduces slightly its weight during the further heating process. However, the thermal gravimetry graph shows only a mass loss of 4% under the temperature range of 25–200 °C. SLN production

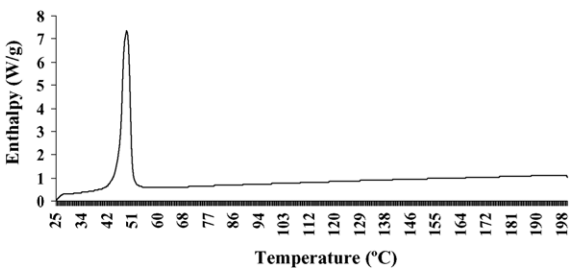

Fig. 1. DSC analysis of *n*-dodecyl-ferulate.

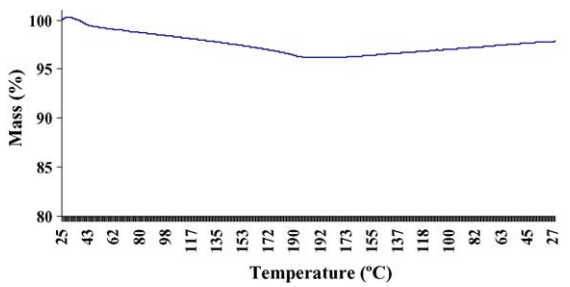

Fig. 2. TGA analysis of *n*-dodecyl-ferulate.

Table 2
DSC results of pure lipids and of physical mixtures of *n*-dodecyl-ferulate with five different lipids

Formulation	Melting point (°C)	Onset (°C)	Enthalpy (J/g)
Dynasan®114	56.42	54.93	171.87
Dynasan®114 + NDF	57.18	55.34	171.42
Dynasan®116	64.21	61.01	175.34
Dynasan®116 + NDF	64.11	62.40	165.19
Dynasan®118	71.56	69.54	192.51
Dynasan®118 + NDF	69.10	67.42	148.27
Softisan®154	56.89	54.32	159.80
Softisan®154 + NDF	57.15	55.06	130.73
Precifac®ATO5	52.57	50.60	209.35
Precifact®ATO5 + NDF	50.59	47.55	176.42

is typically performed 5 °C above the melting point of the lipid, which means that for the lipids used in this study production temperature was in the range of approx. 50–70 °C. The loss in weight in TGA analyses up to 70 °C was less than 1%. According to this result the decomposition of *n*-dodecyl-ferulate during production could be excluded. From this first study regarding incorporation ability, dodecyl derivative shows a sufficient stability.

3.2. Solubility studies of n-dodecyl-ferulate in different lipids

Due to the small amount of active available for the present study, only a small number of different lipids was used for the lipid screening for *n*-dodecyl-ferulate. Thus, Dynasan®114, Dynasan®116, Dynasan®118, Precifac®ATO5 and Softisan®154 were selected for the solubility test of this active. The solubility of *n*-dodecyl-ferulate in five different lipids was evaluated by mixing the active in different concentrations (1 and 5%, *m*/*m*) with the lipid and melting the mixture at 90 °C. The solubility was determined visually after 1 h at 90 °C, and after solidification of the lipid at room temperature (20 °C). It has been observed, that both at high and low temperatures, this active was well soluble in all selected lipids. No crystals were detectable in solidified melts.

All the selected lipids for the screening of the most suitable SLN formulation were analysed by DSC (Table 2) in order to assess: (i) a possible melting point depression of the lipid, (ii) the crystalline character (polymorphic transitions) of the lipid matrix, as a function of its loading capacity, and to evaluate (iii) the crystalline character of incorporated active substance.

All selected lipids appeared to be suitable for preparation of *n*-dodecyl-ferulate-loaded aqueous SLN dispersions. Therefore, and due to the small amount of active available, only Precifac®ATO5, Dynasan®118 and Softisan®154 were chosen for development of lipid nanoparticles.

3.3. Production and characterization of n-dodecyl-ferulate-loaded SLN

Following the production of active-free SLN formulations, 4% (*m*/*m*) of *n*-dodecyl-ferulate-loaded SLN (corresponding to the aqueous dispersion) were prepared. Table 3 shows the composition of developed active-free (a-formulations) and active-loaded

Table 3
Composition of developed active-free and active-loaded formulations

Formulation code	Lipid 20% (*m*/*m*)	*n*-Dodecyl-ferulate % (*m*/*m*)	Surfactant % (*m*/*m*)	Water ad % (*m*/*m*)
SLN-1a	20% Precifac®ATO5	0	1.8% TegoCare®450	100
SLN-1b	16% Precifac®ATO5	4	1.8% TegoCare®450	100
SLN-2a	20% Dynasan®118	0	1.8% Miranol Ultra C32	100
SLN-2b	16% Dynasan®118	4	1.8% Miranol Ultra C32	100
SLN-3a	20% Softisan®154	0	5% Tyloxapol	100
SLN-3b	16% Softisan®154	4	5% Tyloxapol	100

Table 4
PCS diameters (Z-ave), PI and LD diameters of developed active-free (a) and active-loaded (b) formulations obtained on day 0 and after 1 day of storage at three different temperatures

Formulation code	Z-ave (nm)	Polydispersity index	LD (μm)		
			d50%	d90%	d99%
SLN-1a (day 0)	231.8 ± 5.8	0.096 ± 0.032	0.239 ± 0.024	0.396 ± 0.003	0.497 ± 0.005
SLN-1a (day 1)					
4 °C	234.0 ± 6.6	0.086 ± 0.057	0.222 ± 0.032	0.387 ± 0.008	0.492 ± 0.002
20 °C	235.9 ± 4.5	0.115 ± 0.053	0.254 ± 0.011	0.407 ± 0.003	0.517 ± 0.003
40 °C	232.5 ± 3.4	0.114 ± 0.027	0.216 ± 0.029	0.387 ± 0.005	0.492 ± 0.004
SLN-1a (day 21)					
4 °C	229.1 ± 3.8	0.147 ± 0.074	0.122 ± 0.039	0.392 ± 0.007	0.496 ± 0.004
20 °C	223.0 ± 6.3	0.104 ± 0.051	0.240 ± 0.004	0.398 ± 0.006	0.505 ± 0.013
40 °C	223.2 ± 5.4	0.119 ± 0.070	0.175 ± 0.027	0.371 ± 0.009	0.487 ± 0.005
SLN-1b (day 0)	241.0 ± 4.2	0.144 ± 0.041	0.203 ± 0.029	0.371 ± 0.009	0.449 ± 0.005
SLN-1b (day 1)					
4 °C	233.2 ± 5.8	0.155 ± 0.058	0.214 ± 0.028	0.400 ± 0.005	0.512 ± 0.004
20 °C	234.4 ± 6.6	0.133 ± 0.069	0.188 ± 0.040	0.386 ± 0.012	0.497 ± 0.004
40 °C	245.5 ± 5.5	0.115 ± 0.062	0.233 ± 0.019	0.395 ± 0.002	0.498 ± 0.006
SLN-1b (day 21)					
4 °C	248.3 ± 5.1	0.254 ± 0.185	0.323 ± 0.010	0.473 ± 0.027	0.978 ± 0.196
20 °C	219.6 ± 5.8	0.126 ± 0.047	0.127 ± 0.008	0.349 ± 0.019	0.480 ± 0.002
40 °C	226.8 ± 4.2	0.164 ± 0.054	0.277 ± 0.066	0.803 ± 0.154	0.899 ± 0.260
SLN-2a (day 0)	210.9 ± 3.2	0.153 ± 0.082	0.145 ± 0.003	0.301 ± 0.003	0.422 ± 0.006
SLN-2a (day 1)					
4 °C	207.7 ± 5.3	0.113 ± 0.063	0.146 ± 0.005	0.314 ± 0.021	0.459 ± 0.009
20 °C	211.3 ± 4.9	0.162 ± 0.079	0.156 ± 0.006	0.332 ± 0.012	0.468 ± 0.008
40 °C	238.2 ± 6.5	0.204 ± 0.053	11.573 ± 9.704	32.070 ± 4.769	52.690 ± 8.277
SLN-2a (day 21)					
4 °C	208.5 ± 3.1	0.151 ± 0.054	0.169 ± 0.052	6.064 ± 10.033	10.195 ± 16.978
20 °C	219.5 ± 4.6	0.130 ± 0.066	10.033 ± 8.575	37.103 ± 4.879	69.723 ± 11.395
40 °C	232.4 ± 4.8	0.206 ± 0.035	3.799 ± 6.099	19.335 ± 16.485	34.686 ± 29.693
SLN-2b (day 0)	210.2 ± 58.1	0.491 ± 0.097	60.003 ± 6.112	209.211 ± 13.924	493.805 ± 23.882
SLN-2b (day 1)					
4 °C	>1000	>1000	87.080 ± 4.619	274.000 ± 23.352	502.400 ± 18.866
20 °C	209.7 ± 52.3	0.512 ± 0.131	62.047 ± 5.453	213.733 ± 17.062	485.700 ± 59.312
40 °C	224.4 ± 48.6	0.431 ± 0.189	15.877 ± 0.490	34.560 ± 1.330	235.067 ± 8.130
SLN-2b (day 21)					
4 °C	>1000	>1000	>1000	>1000	>1000
20 °C	>1000	>1000	>1000	>1000	>1000
40 °C	>1000	>1000	>1000	>1000	>1000
SLN-3a (day 0)	215.7 ± 5.6	0.293 ± 0.067	0.100 ± 0.000	0.223 ± 0.004	0.483 ± 0.000
SLN-3a (day 1)					
4 °C	188.0 ± 5.2	0.248 ± 0.059	0.103 ± 0.001	0.193 ± 0.001	0.456 ± 0.007
20 °C	220.4 ± 4.9	0.287 ± 0.081	0.106 ± 0.000	0.224 ± 0.005	0.481 ± 0.001
40 °C	189.8 ± 5.9	0.246 ± 0.081	0.103 ± 0.001	0.194 ± 0.000	0.314 ± 0.002
SLN-3a (day 21)					
4 °C	224.1 ± 11.9	0.489 ± 0.059	16.943 ± 1.614	34.173 ± 4.275	99.283 ± 18.997

Table 4 (*Continued*)

Formulation code	Z-ave (nm)	Polydispersity index	LD (μm)		
			d50%	d90%	d99%
20 °C	210.0 ± 5.7	0.301 ± 0.034	0.114 ± 0.009	0.266 ± 0.014	0.748 ± 0.453
40 °C	210.7 ± 29.8	0.225 ± 0.052	0.112 ± 0.001	0.235 ± 0.012	0.467 ± 0.002
SLN-3b (day 0)	500.9 ± 37.6	0.690 ± 0.063	11.934 ± 0.553	36.576 ± 2.173	111.004 ± 14.874
SLN-3b (day 1)					
4 °C	>1000	>1000	11.852 ± 0.601	60.453 ± 5.572	136.033 ± 14.896
20 °C	538.3 ± 41.7	0.695 ± 0.054	12.013 ± 0.705	36.323 ± 3.534	110.263 ± 14.865
40 °C	167.1 ± 18.4	0.399 ± 0.089	10.793 ± 0.857	39.253 ± 2.030	126.367 ± 4.565
SLN-3b (day 21)					
4 °C	>1000	>1000	>1000	>1000	>1000
20 °C	>1000	>1000	>1000	>1000	>1000
40 °C	>1000	>1000	>1000	>1000	>1000

(b-formulations) aqueous SLN dispersions containing 20% (*m*/*m*) of lipid phase.

Particle size analysis of developed formulations was monitored during 21 days of storage at three different temperatures (4, 20 and 40 °C, long term stability). Table 4 shows the PCS diameters (Z-ave), PI and LD diameters of developed active-free and active-loaded formulations obtained on day 0, on day 1 and after 21 days of storage at three different temperatures.

The incorporation of *n*-dodecyl-ferulate into Dynasan®118 and Softisan®154 based lipid nanoparticles revealed an increase in particle size measured by PCS and LD (SLN-2b and SLN-3b), in comparison to active-free formulations (SLN-2a and SLN-3a). These SLN-2b and 3b formed particles in micrometer range during storage. In contrast, the presence of active into wax-based nanoparticles (SLN-1b) did not influence the mean particle size, showing a colloidal particle distribution at three different temperatures of storage.

DSC analysis was performed for all developed active-free and active-loaded formulations after 3 days of storage at three different temperatures. The recorded DSC parameters are presented in Table 5.

Table 5
DSC results of developed active-free (a) and active-loaded (b) formulations obtained after 3 days of storage at three different temperatures

Formulation code	Temperature of storage (°C)	Melting point (°C)	Onset (°C)	Integral (mJ)	Enthalpy (J/g)
SLN-1a	4	49.59	45.37	968.69	34.79
	20	49.33	45.39	754.31	31.87
	40	49.36	45.35	849.97	34.48
SLN-1b	4	48.91	43.99	649.74	41.30
	20	48.31	43.85	564.14	22.29
	40	48.27	44.32	582.89	20.22
SLN-2a	4	54.38	49.64	674.84	23.79
	20	69.58	55.99	707.76	24.88
	40	69.19	64.02	994.01	34.32
SLN-2b	4	68.57	63.56	566.58	35.83
	20	67.37	61.85	492.48	38.25
	40	65.05	61.76	924.90	38.48
SLN-3a	4	55.12	49.74	1139.8	31.52
	20	55.88	50.35	963.90	32.23
	40	57.31	53.13	886.35	33.70
SLN-3b	4	54.09	52.41	772.60	34.34
	20	55.80	53.03	673.94	34.82
	40	57.80	49.40	925.98	33.23

For all developed aqueous SLN dispersions the melting peaks were detected in the melting range of the bulk lipid. Active-loaded SLN based on Precifac® ATO5 (SLN-1b) showed a lower degree of crystallinity (i.e. lower melting enthalpy), in comparison to the other developed formulations. This result might indicate the presence of a metastable polymorphic matrix (β′-modification), which is responsible for a higher loading capacity, in comparison to the more stable one (β-modification).

According to the obtained results after particle size and DSC analysis of developed aqueous SLN dispersions, SLN prepared with Precifac® ATO5, i.e. cetyl palmitate, was selected for the production and long-term stability studies (i.e. 21 days) of *n*-dodecyl-ferulate-loaded SLN. In general, SLN with less ordered structure provide higher loading capacities for actives. Actives are incorporated, e.g. in the imperfections at the less crystalline lipid matrix, a strategy exploited in the second generation of lipid nanoparticles, the nanostructured lipid carriers (NLC) (Müller et al., 2000b).

3.4. Long-term stability studies

In order to evaluate the physical stability of *n*-dodecyl-ferulate-loaded SLN, both particle size and zeta potential measurements were performed over a period of 21 days. Figs. 3 and 4 show, respectively, the PCS and LD results of SLN-1b formulation during storage time at room temperature (20 °C).

Considering the particle sizes measured during 21 days of storage at room temperature, it can be stated that *n*-dodecyl-ferulate-loaded SLN are physically stable, showing no particle growth under these shelf storage conditions. As presented in Fig. 3, the mean particle size remained between 220 and 240 nm and the PI slightly fluctuated between 0.1 and 0.2. With regard to LD analysis, all particles showed diameters lower than 500 nm after 21 days of storage at 20 °C.

Concerning the electrochemical stability of aqueous SLN dispersions, zeta potential of both active-free and active-loaded formulations was also evaluated during storage time. Fig. 5 compares the obtained results on day 3 and 14 of storage at three different temperatures.

The presence of *n*-dodecyl-ferulate slightly decreased the absolute value of zeta potential. For both active-free and active-loaded formulations the storage time slightly increased the zeta potential values. Once the absolute value of zeta potential is higher than 30 mV for both formulations it can be concluded that they are electrochemically stable at three different temperatures.

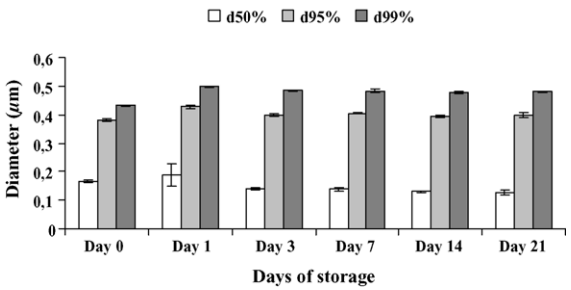

Fig. 4. LD diameters (μm) of SLN-1b formulation measured after 1, 3, 14 and 21 days of storage at room temperature (20 °C).

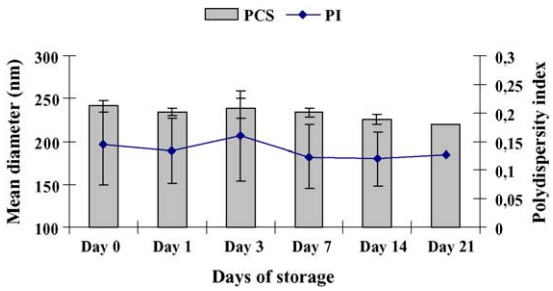

Fig. 3. Mean diameter (nm) and PI of SLN-1b formulation measured after 1, 3, 14 and 21 days of storage at room temperature (20 °C).

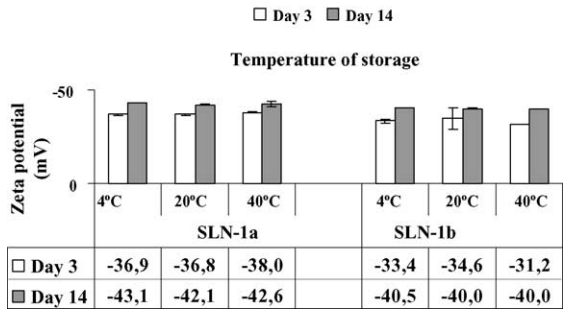

Fig. 5. Zeta potential of SLN-1b formulation measured after 3 and 14 days of storage at room temperature (20 °C).

4. Conclusions and further developments

In conclusion, this study shows that is possible to prepare physicochemically stable *n*-dodecyl-ferulate-loaded SLN. The obtained results indicate that SLN prepared with Precifac® ATO5 might be suitable as active delivery system intended for topical delivery of this sunscreen. The physical stability of aqueous *n*-dodecyl-ferulate-loaded SLN dispersion was proven for at least 3 weeks. Previous data have shown that incorporation of SLN in viscous gels or o/w creams leads to enhancement of physical stability, i.e. SLN unstable in aqueous dispersion are sufficiently stabilized. From this, it can assume that the 3 weeks physically stable aqueous dispersion SLN-1b will lead to long term stable sunscreen gels/creams. Next steps are formulation of gels/creams and tests of their sun protection efficiency.

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