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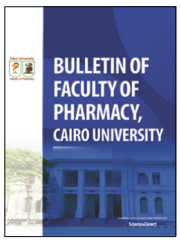

ORIGINAL ARTICLE

Diflucortolone valerate loaded solid lipid nanoparticles as a semisolid topical delivery system

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Abstract Solid lipid nanoparticles (SLNs) are promising delivery carriers that have been utilized for formulation and delivery of various drugs. For topical administration, they are usually incorporated into gel or cream to increase their residence time, which is time-consuming process and could affect their stability and characteristics. Preparation of solid lipid nanoparticles based semisolid formulations could have potential pharmaceutical applications. The aim of this study was to formulate the corticosteroidal drug, diflucortolone valerate (DFV) into topical semisolid SLN formulations using a rapid cheap one-step process. SLN formulations were developed using a high-shear homogenization combined with sonication, using different types of solid lipids (*e.g.*, Geleol®, Precirol® ATO5, Tristearin® and Compritol® 888ATO) and Poloxamer® 407 as a surfactant. Selection of the lipids and using high lipid concentration were the key elements to get semisolid formulation immediately after sonication without incorporating the nanoparticles into a gel or a cream base.
DFV SLN formulations possessed average particle size ranging from 203.71 ± 5.61 to 1421.00 ± 16.32 nm with a narrow size distribution and possessed shear thinning behavior. Incorporation of lipid based surfactants (Labrasol® or Labrafil®) was found to significantly increase DFV encapsulation efficiency (up to 45.79 ± 4.40%).
Semisolid DFV-loaded SLN with high drug encapsulation efficiency and acceptable rheological behavior for topical preparation could be prepared in a one-step process.

1. Introduction

Solid lipid nanoparticles (SLNs) are the first generation colloidal drug carrier systems developed at the beginning of the 1990s.[1] SLNs are similar to nanoemulsions, although liquid lipids used in emulsions are replaced by solid lipids, such as,

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glycerides or waxes.[2] In particular, SLNs are suitable for topical drug delivery, due to their ability to reduce skin irritation, protect the encapsulated active ingredients and allow for controlled release of the drugs.[3] In addition, they are well-suited for inflamed skin because they are composed of physiologically tolerated lipids.[4] Usually, lipid nanoparticle dispersions are incorporated into commonly used dermal carriers (*e.g.*, gels or creams) to obtain semisolid formulations. This multiple step production process is time-consuming, and incompatibilities between nanoparticles and gel or cream components may occur.[5,6] To overcome the previously mentioned challenges, we applied a one-step process to produce semisolid SLN formulations, using the high-shear homogenization and ultrasonication techniques.[5,6]

Topical corticosteroids are widely used for the treatment of skin disorders that require anti-inflammatory and immunosuppressive regimens.[7] They alleviate inflammation by inhibiting vasodilatation and increasing vascular permeability that occurs following inflammation, and they also decrease leukocyte emigration into inflamed sites.[8] Immunosuppressive corticosteroids reduce the response to delayed and immediate hypersensitivity reactions by inhibiting the toxic effect of antigen–antibody complexes that precipitate in vessel walls creating cutaneous allergic vasculities.[9]

Diflucortolone valerate (DFV) is a potent corticosteroid esterified with valeric acid.[10] It is insoluble in water, freely soluble in dichloromethane, 1,4-dioxane, slightly soluble in methanol, and sparingly soluble in ether. It is commercially available in the form of 0.1 and 0.3% cream, oily cream and ointment.[11] DFV is characterized by rapid onset of action and good tolerability in the treatment of cutaneous diseases[12] such as, eczema, psoriasis, and discoid lupus erythematosus.

Hence, development of lipid nanoparticles that can be loaded with the lipophilic drug, DFV, and applied topically as semisolid formulations could be promising in the treatment of several skin disorders. In addition, simplification of the preparation procedures will be extremely useful for scale-up of various pharmaceutical products which are based on these kinds of nanoparticles. Therefore, the aim of this work was the preparation of SLNs semisolid formulations with acceptable rheological properties, small particle size and low polydispersity index, in addition to high drug entrapment efficiency, using high-shear homogenization and ultrasonication techniques.

2. Materials and methods

2.1. Materials

Diflucortolone valerate (DFV) was purchased from Chemical Industries Development (CID) (El Ahram, Giza, Egypt) which was obtained from Bayer Schering Pharma, Germany. Geleol® (glyceryl monostearate 40–55%), Precirol® ATO5 (glyceryl distearate), Compritol® 888 ATO (glyceryl behenate), Capryol™ 90 (propylene glycol monocaprylate), Labrasol® (caprylocaproyl macrogol-8 glycerides EP) and Labrafil® (oleoyl macrogol-6 glycerides EP) were kindly donated by Gattefosse′ (St Priest, Cedex, France). Tristearin® (glyceryl tristearate), Poloxamer® 407 (pluronic F-127; a triblock copolymer of polyoxyethylene–polyoxypropylene) were purchased from Sigma Chemical Company (St. Louis, USA) and methanol used was of analytical reagent grade.

2.2. Preparation of diflucortolone valerate solid lipid nanoparticles

Blank and drug loaded solid lipid nanoparticles were prepared following the one step production method, as previously reported.[5,6] Briefly, solid lipid was melted at 10 °C above its melting point, then, DFV was dispersed in the melted lipid. The melted lipid phase was dispersed in the hot surfactant solution (Poloxamer® 407, 10% *w*/*w*) using high-shear homogenizer (Silent crusher homogenizer, Heidolph Instrument, Schwabach, Germany) at 26,000 rpm for 5 min at 70 °C, keeping hot condition during the process using a water bath. This o/w pre-emulsion was sonicated for 10 min using digital ultrasonicator (Model SH150-4L, MTI Corporation, California, USA) maintaining temperature 10 °C above the melting point of the lipid, and the cycle was repeated twice. The produced DFV dispersion was left to cool at room temperature.

2.3. Modification of diflucortolone valerate-loaded solid lipid nanoparticles using lipid-based surfactants

Modified SLN formulations were prepared using lipid-based surfactant aiming at increasing the solubility of the drug in the lipid phase, and hence increasing its EE%. The added percentage of lipid-based surfactant replaced an equal amount of the water content of each formula. Two lipid-based surfactants were investigated, namely, Labrasol® and Labrafil®. Each of them was tested at three concentration levels of 2.5, 5 and 10% *w*/*w*. DFV was dissolved in the lipid-based surfactant prior to the addition of the solid lipid then the mixture was heated to 10 °C above the lipid melting point. The drug lipid mixture was dispersed in an aqueous surfactant solution at the same temperature and then the high-shear homogenization and ultrasonication techniques were proceeded, as previously explained.

2.4. Characterization of DFV-loaded solid lipid nanoparticles

2.4.1. Particle size analysis

Mean particle size and polydispersity index (PDI), which is a measure of the distribution of nanoparticles population, were determined using Zetasizer Nano ZS (Malvern instruments, UK). Samples were prepared by diluting 0.2 g of the semisolid preparation with 10 ml distilled water, then, vortexed for 30 s and subsequently analyzed. Each sample was measured thrice.

2.4.2. Rheological studies

The rheological measurements were performed with a plate and plate rheometer (Anton Paar® GmbH, Ostfildern, Germany). Up and down portions of the flow curves were determined using parallel plate geometry (50 mm diameter), where, the gap between the two plates was 1 mm. About 0.5 g of the tested formulation was applied to the plate and left until the temperature of the plate reached 25 ± 1 °C. The measurements were made over the whole range of speeding setting from 0.5 to 350 rpm with 20 s between each two successive speeds. The rheological behavior of each formulation was evaluated by plotting the shear stress *versus* the obtained shear rate values. The flow behavior was studied according to Farrow's equation[13]:

$$\text{Log}\, D = N\ \text{Log}\, S - \text{Log}\, \eta$$

where, D is the shear rate (s^{-1}), S is the shear stress (Pa), N is Farrow's constant and η is the viscosity (Pa s).

N is the slope of the plot of $\log D$ against $\log S$, which indicates the deviation from Newtonian flow. When N is less than one, it indicates dilatant flow (shear rate thickening). If N is greater than one, it indicates pseudoplastic or plastic flow (shear rate thinning). When the system showed thixotropic behavior, the hysteresis area (H.A.) between the upward and downward curves was measured adopting the trapezoidal rule. Farrow's constant was also calculated.

2.4.3. Determination of the entrapment efficiency

The entrapment efficiency (EE%) which corresponds to the encapsulation of the drug into the nanoparticles was determined by measuring the concentration of free DFV in the dispersion medium. The dispersion of 0.2 g of each DFV loaded sample in 5 ml methanol was vortexed for 30 s. Samples were then centrifuged for 5 min at 9000 rpm and −5 °C (Union 32R, Hanil Science Industrial, Korea) to extract the free drug from the semisolid samples. The supernatant was collected and filtered through Millipore® membrane filter (0.2 μm) then measured spectrophotometrically at λ_{max} 238 nm against blank that was prepared using the same ingredients and the same technique used in the preparation of the test formulations but without the drug. The entrapment efficiency was calculated as follows:

$$\text{EE}\ (\%\ w/w) = [(\text{Wa} - \text{Ws})/\text{Wa}] \cdot 100$$

where, Wa stands for the mass of DFV added to the formulation and Ws is the mass of DFV determined in the supernatant.

2.4.4. Scanning electron microscopy (SEM)

Prior to examination, samples were mounted on an aluminum stub using a double sided adhesive tape and were made electrically conductive by coating with a thin layer of gold (approximately 20 nm) under vacuum. The scanning electron microscope Jeol (Jxa-840A, Japan) was operated at an acceleration voltage of 1000 kV and a magnification of 2500×.

3. Results and discussion

3.1. Preparation of diflucortolone valerate-loaded solid lipid nanoparticles

Trials were carried out to prepare semisolid DFV loaded SLN formulations, using different solid lipids (Geleol®, Precirol® ATO5, Tristearin® and Compritol® 888 ATO). Table 1 represents different formulation, in which solid lipids were incorporated at two concentration levels of 10 and 20% w/w and Poloxamer 407 was used as a surfactant at different concentrations of 2.5, 5 and 10% w/w.

3.2. Characterization of DFV-loaded solid lipid nanoparticles

3.2.1. Particle size analysis

The results in Table 2 clearly show gradual decrease in particle size upon increasing Poloxamer® 407 concentration from 2.5 to 5 then to 10% w/w. This was in accordance with the fact that surfactant decreases the surface tension at the interface of the particles which cause portioning of the particles and hence formation of stabilized nanoparticles of smaller size and higher surface area.[14]

SLN formulations that contain 10% w/w Precirol®, Tristearin® and Compritol® were not examined, as they resulted in liquid dispersions and failed to show semisolid consistency. However, formulations containing 10% w/w Geleol® had semisolid appearance after cooling. This occurred due to the high concentration of monoglycerides in Geleol® composition that can form hydrogen bonds with water molecules, and thus causing swelling. The swelling property is likely to form the semisolid appearance of Geleol® based formulations, even in the presence low Geleol® concentration.[15]

Comparing the particle size of the SLNs prepared with 20% w/w solid lipids, Compritol®-based SLNs exhibited the largest particle size with all Poloxamer® 407 concentrations, followed by Geleol®, then Tristearin®, and finally Precirol® that exhibited the smallest particle size and PDI. A possible explanation for the large particle size of Compritol®-based SLNs may be due to its high melting point (65–77 °C) and the long hydrocarbon chain of behenic acid (C_{22}) which represents 85% of the acids esterifying glycerol in Compritol®. High melting point results in an increase in the viscosity and leads to an inefficient homogenization which causes an inefficient reduction of the particle sizes. Furthermore, the long hydrocarbon chains (HC) of behenic acid (C_{22}) in Compritol® resulted in bulkier molecules that are less susceptible to packaging into small size particulates.[16]

Table 1 Composition of solid lipid nanoparticles containing 0.1% w/w diflucortolone valerate.

Formulation[a]	Lipid		Poloxamer® 407 concentration (% w/w)
	Type	Concentration (% w/w)	
SLN1	Geleol®	10	2.5
SLN2		10	5.0
SLN3		10	10.0
SLN4		20	2.5
SLN5		20	5.0
SLN6		20	10.0
SLN7	Precirol®	10	2.5
SLN8		10	5.0
SLN9		10	10.0
SLN10		20	2.5
SLN11		20	5.0
SLN12		20	10.0
SLN13	Tristearin®	10	2.5
SLN14		10	5.0
SLN15		10	10.0
SLN16		20	2.5
SLN17		20	5.0
SLN18		20	10.0
SLN19	Compritol®	10	2.5
SLN20		10	5.0
SLN21		10	10.0
SLN22		20	2.5
SLN23		20	5.0
SLN24		20	10.0

[a] Formulation weight was made up to 100% with distilled water.

Table 2 Mean particle size and polydispersity index-values of 0.1% *w/w* diflucortolone valerate loaded solid lipid nanoparticles.

Formulation	Mean particle size (nm)[a]	PDI[a]
SLN1	593.70 ± 36.12	0.600 ± 0.066
SLN2	485.15 ± 13.22	0.455 ± 0.042
SLN3	296.90 ± 20.12	0.438 ± 0.120
SLN4	445.40 ± 15.92	0.419 ± 0.095
SLN5	426.90 ± 10.43	0.507 ± 0.083
SLN6	398.50 ± 17.65	0.509 ± 0.099
SLN7	ND	ND
SLN8	ND	ND
SLN9	ND	ND
SLN10	531.70 ± 14.33	0.500 ± 0.100
SLN11	216.00 ± 30.26	0.203 ± 0.066
SLN12	203.71 ± 5.61	0.210 ± 0.070
SLN13	ND	ND
SLN14	ND	ND
SLN15	ND	ND
SLN16	ND	ND
SLN17	262.90 ± 29.40	0.365 ± 0.055
SLN18	271.15 ± 20.32	0.370 ± 0.062
SLN19	ND	ND
SLN20	ND	ND
SLN21	ND	ND
SLN22	1421.00 ± 16.32	0.316 ± 0.150
SLN23	1344.01 ± 25.50	0.770 ± 0.090
SLN24	1012.04 ± 28.95	1.000 ± 0.030

ND: not determined.
[a] Values represent (mean ± SD).

Geleol®-based SLNs showed particle size greater than those of Precirol® and Tristearin®. This may be due to the high content of monoglyceride in Geleol®, which resulted in a higher degree of interaction between the monoglyceride molecules with water, causing swelling and an increase in viscosity particle size. Similarly, Jensen et al. found that the size of the SLN increases as the monoglyceride content of the lipids increases.[15]

As mentioned previously, the hydrocarbon chain length of lipids has a great influence on the particle size. Tristearin® possesses a long hydrocarbon chain length of 57 carbon atoms (C_{57}) compared to the 39 carbon atoms (C_{39}) of Precirol®. As a result, Tristearin®-based SLNs exhibited larger particle size than that of Precirol®-based SLNs. The higher molecular weight of Tristearin® compared to Precirol® (891.48 and 625.02 g/mol, respectively) led to lower packaging efficiency of the lipid molecules in the SLNs and larger particle size. The higher the molecular weight of solid lipid, the greater the particle size of the formed nanoparticles.[17]

3.2.2. Rheological studies

The rheological behavior of the prepared SLN formulations was studied to determine the appropriate lipid type and concentration that can form semisolid matrices in a single-step process. The rheological data namely Farrow's constant (*N*) and the hysteresis area (H.A.) for the selected SLN formulations reveal that the semisolid SLN formulations exhibited Farrow's constant (*n*) values larger than one, which indicates shear thinning characteristics with variable thixotropy (data are not shown). The yield values for the investigated semisolid SLN formulations were greater than 20 Pa. Products with yield points below this value will flow readily by themselves. A lotion or cream with yield value above 20 Pa will flow more slowly.[18]

The combined shear thinning behavior and thixotropy are desirable characteristics for topical formulations, as they facilitate processing during manufacture and the flow from the container, and improve spreading on the skin. In addition, the applied film can gain viscosity instantaneously and thus resist running.[19]

3.2.3. Determination of entrapment efficiency

None of the prepared SLNs showed measurable entrapment of DFV probably due to the low solubility of DFV in a wide array of solid lipids, in spite of its lipophilicity. Moreover, when the dispersion is performed above the lipid melting point, an exchange of drug substance between lipid and aqueous phase may occur during processing.[15] Upon increasing the temperature, the hydrophilic chains of the copolymer of the surfactant (Poloxamer® 407) were desolvated due to the breakage of the hydrogen bonds that were established between water and these chains. This phenomenon favors the hydrophobic interactions among the polyoxyethylene domains and leads to gel formation which is micellar in nature and has solubilizing properties.[20]

Formulations prepared with 20% *w/w* Precirol® and 5 and 10% *w/w* Poloxamer® 407 (SLN11 and SLN12, respectively), as well as, those prepared with 20% *w/w* Tristearin® and 5 and 10% *w/w* Poloxamer® 407, (SLN17 and SLN18, respectively), showed the smallest size values of the formed particles (216.0 ± 30.26, 203.7 ± 5.60, 262.9 ± 29.4 and 271.15 ± 20.32 nm, respectively), and PDI values (0.203 ± 0.066, 0.210 ± 0.070, 0.365 ± 0.055 and 0.370 ± 0.062, respectively).

SLN11 had a low viscosity and small hysteresis loop, and thus indicating a low thixotropic behavior that may prevent sticking on the skin for sufficient time after application.[21] SLN17 showed poor physical stability as a semisolid consistency was found immediately after preparation that became harder with flake-like appearance after a few hours. This may be due to the low concentration of Poloxamer® 407 (5% *w/w*) that was insufficient to emulsify all the Tristearin®, leading to interactions between the glyceryl tristearate and water. Tristearin® (triglycerides) can be broken apart with water (hydrolysis) and produce stearic acid of the high melting point (70 °C).[22] Therefore, SLN12 and SLN18 were selected for further modifications aiming at enhancing their entrapment efficiency.

3.2.4. Modification of 0.1% w/w diflucortolone valerate-loaded solid lipid nanoparticles using lipid based surfactants

Modified SLN formulations were formulated using caprylocaproyl polyoxylglycerides (Labrasol®) and oleoyl polyoxylglycerides (Labrafil® M1994CS) at concentrations of 2.5, 5 and 10% *w/w* (Table 3).

3.3. Characterization of modified 0.1% w/w diflucortolone valerate loaded solid lipid nanoparticles

3.3.1. Particle size analysis

Table 4 represents the mean particle size and PDI values of modified DFV-loaded Precirol® and Tristearin® SLN formulations. The mean particle size of SLNs ranged from

Table 3 Composition of modified solid lipid nanoparticles containing 0.1% *w/w* diflucortolone valerate.

Formulation[a]	Lipid		Poloxamer® 407 concentration (% *w/w*/formula)	Lipid based surfactant	
	Type	Concentration (% *w/w*/formula)		Type	Concentration (% *w/w*/formula)
SLN12A	Precirol®	20	10	Labrasol®	2.5
SLN12B		20	10		5.0
SLN12C		20	10		10.0
SLN12D		20	10	Labrafil®	2.5
SLN12E		20	10		5.0
SLN12F		20	10		10.0
SLN18A	Tristearin®	20	10	Labrasol®	2.5
SLN18B		20	10		5.0
SLN18C		20	10		10.0
SLN18D		20	10	Labrafil®	2.5
SLN18E		20	10		5.0
SLN18F		20	10		10.0

[a] Formulation weight was made up to 100% with distilled water.

188.7 ± 17.82 to 457.3 ± 21.33 nm and PDI ranged from 0.251 ± 0.12 to 0.405 ± 0.07. Results reveal that gradual increase in Labrasol® concentration in Precirol® containing SLNs, resulted in a significant increase in particle size ($p < 0.05$). This may be due to the hydrophilic properties of Labrasol® of HLB value of 14, which allowed partitioning in the aqueous phase and failed to reduce the size of particles.

The size of Tristearin® SLN formulations modified with Labrasol® at concentrations of 2.5, 5 and 10% *w/w* (SLN18A, SLN18B and SLN18C, respectively) were not measured due to the hard solid consistency that was formed upon cooling. This may be due to the transformation of α or β′ polymorphic form of Tristearin® to the β form upon cooling. The α and β′ polymorphic forms of triacylglycerols are more desirable than the β form because they have better appearance, texture and fluidity. The β form may give rise to rough or sandy texture. Unfortunately, α or β′ forms are thermodynamically unstable and are prone to transform to the more stable but undesirable β form.[23] These results were further investigated by examining SLN18C using a scanning electron microscope. Fig. 1 shows the rough and porous surface of SLN18C, which may be due to the formation of the β form of Tristearin® after cooling, with the undesirable rough texture. Tristearin® SLNs modified with Labrafil® did not show this rough texture probably due to the lipophilic properties of Labrafil® with HLB value of 4, which increases its miscibility in Tristearin®, and thus leading to stabilization of the polymorphic form of Tristearin® in the desired α or β′ forms.

The mean particle size was not significantly ($p > 0.05$) affected by the gradual increase of Labrafil® concentration in Precirol® SLN formulations. However, Tristearin® SLN formulations modified with Labrafil® showed a significant decrease in particle size upon increasing Labrafil® concentration from 2.5 to 5 and to 10% *w/w* ($p < 0.05$). The decrease in size of nanoparticles upon increasing surfactant concentrations may be due to the effective reduction in the interfacial tension between the aqueous and the lipid phase, and thus forming emulsion droplets of smaller size.[24]

Precirol® SLN formulations modified with 2.5 and 5% *w/w* Labrasol® did not show significant differences ($p > 0.05$) in particle size, in comparison to those containing Labrafil®. However, particle size of Precirol® SLN formulations modified with 10% *w/w* Labrafil® exhibited smaller particle size ($p < 0.05$) than those modified with 10% *w/w* Labrasol®, probably due to the hydrophilicity of Labrasol®, as explained previously.

Table 4 Mean particle size and polydispersity index of modified 0.1% *w/w* diflucortolone valerate loaded solid lipid nanoparticles.

Formulation	Mean particle size (nm)[a]	PDI[a]	Entrapment efficiency (%)[a]
SLN12A	201.8 ± 14.50	0.251 ± 0.12	14.13 ± 1.90
SLN12B	240.6 ± 11.32	0.308 ± 0.05	21.80 ± 2.90
SLN12C	447.7 ± 15.11	0.374 ± 0.11	31.13 ± 2.40
SLN12D	188.7 ± 17.82	0.298 ± 0.06	21.71 ± 3.58
SLN12E	195.1 ± 20.05	0.338 ± 0.15	25.22 ± 0.29
SLN12F	211.7 ± 13.44	0.252 ± 0.13	32.58 ± 3.50
SLN18A	ND	ND	ND
SLN18B	ND	ND	ND
SLN18C	ND	ND	ND
SLN18D	457.3 ± 21.33	0.405 ± 0.07	31.87 ± 5.80
SLN18E	323.2 ± 25.42	0.395 ± 0.08	31.64 ± 7.38
SLN18F	245.2 ± 18.31	0.280 ± 0.12	45.79 ± 4.40

ND: not determined.
[a] Values represent (mean ± SD).

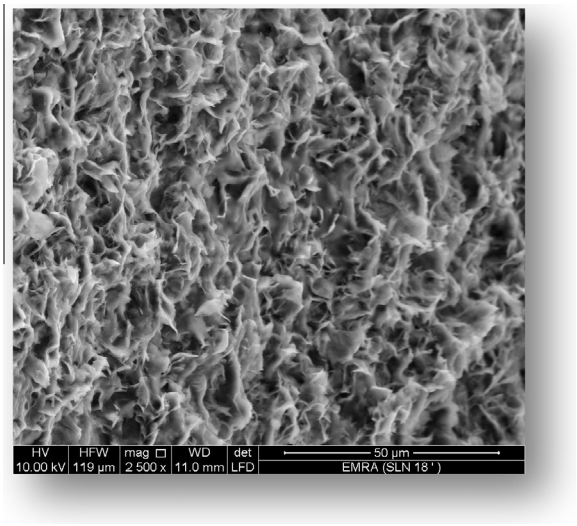

Figure 1 Scanning electron microscope micrograph showing the surface of SLN18C.

3.3.2. Determination of entrapment efficiency

The mean EE% of the modified SLN formulations ranged from 14.13 ± 1.9 to 45.79 ± 4.40% (Table 4). It is worth noting that incorporation of 2.5% of the surfactants increased the EE% of the drug in a range of 14–31% compared to 0% EE for the non-modified formulations.

The EE% of DFV in Precirol® SLN formulations showed a gradual significant increase ($p < 0.05$) upon increasing Labrasol® concentration from 2.5 to 5 and to 10% *w*/*w*, (SLN12A, SLN12B and SLN12C, respectively). Tristearin® SLN formulations modified with Labrasol® at concentrations of 2.5, 5 and 10% *w*/*w* (SLN18A, SLN18B and SLN18C, respectively) were not examined for their EE% because of their hard consistency.

There was no significant increase ($p > 0.05$) in the EE% of DFV in either Precirol® or Tristearin® SLN formulations upon increasing Labrafil® concentration from 2.5 to 5% *w*/*w* (SLN12D and SLN12E, SLN18D and SLN18E, respectively). However, upon increasing Labrafil® concentration to 10% *w*/*w*, the EE% increased significantly ($p < 0.05$), in both Precirol® and Tristearin® SLN formulations. This significant increase in the EE% may be attributed to the enhancement of solubility of DFV in the lipid phase, which resulted in a higher EE%.

The EE% of the drug in Tristearin® SLNs modified with 2.5% *w*/*w* Labrafil® (SLN18D) did not differ significantly ($p > 0.05$) from those containing Precirol® (SLN12D) at the same concentration of Labrafil®. However, Tristearin® SLN formulations modified with 5 and 10% *w*/*w* Labrafil® (SLN18E and SLN18F, respectively) showed a significantly higher ($p < 0.05$) EE% compared to those containing Precirol® (SLN12E and SLN12F). This might be due to the fact that an increase in the alkyl chain length (C_{57} for Tristearin® *versus* C_{39} for Precirol®) increases the lipophilicity of the molecule. Hence, the lipophilic surfactant (Labrafil®) exhibited higher miscibility in Tristearin® than in Precirol®, and, thus, increasing the entrapment of the drug in the lipid phase.

The effect of Labrasol® and Labrafil® on the EE% of DFV in SLN formulations in presence of Precirol® as solid lipid was compared which revealed that the EE% of the drug in SLN formulations modified with 2.5% *w*/*w* Labrafil® (SLN12D) was significantly ($p < 0.05$) higher than that containing 2.5% *w*/*w* Labrasol® (SLN12A). This might be due to the ability of Labrafil® with HLB value of 4, even at low concentration, to solubilize the drug in the lipid phase more efficiently, being more lipophilic than Labrasol® of HLB value of 14. However, no significant difference in the EE% ($p > 0.05$) was recognized at the higher concentrations of Labrasol® and Labrafil® (5 and 10% *w*/*w*).

4. Conclusion

Semisolid formulations that have particle size in the nano-range and adequate drug encapsulation efficiency, as well as, viscoelastic properties, were prepared and characterized. It was found that the use of lipid-based surfactants (Labrasol® or Labrafil®) enhances the solubility of the lipophilic drug, and thus, increase its entrapment efficiency in the SLNs. Although the prior art reported that 30–50% lipid content is needed in the one-step method to get the semisolid SLN formulations, this study revealed that 10–20% *w*/*w* solid lipid was enough to produce SLNs semisolid formulations. The proper selection of type of lipids and surfactants, and their incorporated concentrations, is critical in the formation of SLN-based semisolid formulations that have the desirable properties for potential topical applications.

Declaration of interest

The authors reported no declaration of interest.

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