Journal of Materials Science: Materials in Medicine (2020) 31:18
https://doi.org/10.1007/s10856-019-6351-6

DELIVERY SYSTEMS

Original Research

Skin permeation and thermodynamic features of curcumin-loaded liposomes

Virginia Campani[1] · Lorena Scotti[1] · Teresa Silvestri[1] · Marco Biondi[1,2] · Giuseppe De Rosa[1,2]

Received: 17 July 2019 / Accepted: 16 December 2019 / Published online: 21 January 2020

Abstract

This work describes the development of liposomes encapsulating curcumin (CURC) aiming to provide insights on the influence of CURC on the thermodynamic and skin permeation/penetration features of the vesicles. CURC-loaded liposomes were prepared by hydration of lipid film, in the 0.1–15% CURC:DPPC w/w ratio range. The obtained formulations were characterized for their size distribution, zeta potential and vesicle deformability, along with their thermodynamic properties and ex vivo skin penetration/permeation ability. Liposome size was 110–130 nm for all formulations, with fairly narrow size distribution (polydispersity index was ≤0.20) and a zeta potential mildly decreasing with CURC loading. DSC outcomes indicated that CURC interferes with the packing of DPPC acyl chains in liposome bilayer when CURC percentage was at least 10%, leading to a more fluid state than blank and low-payload vesicles. Consistently, the deformability index of liposomes with 15% CURC:DPPC was strongly increased compared to other formulations. This is congruent with ex vivo skin penetration/permeation results, which showed how more deformable liposomes showed an improved deposition in the epidermis, which acts as a reservoir for the active molecule. Altogether, results hint at a possible application of high payload liposomes for improved topical dermal accumulations of actives.

1 Introduction

Curcumin (CURC) is a lipophilic polyphenol and the main component of *Curcuma Long Linn*, which entices extensive pharmacological activities [1], such as antitumor, anti-inflammatory and anti-diabetic [2–4]. Although the beneficial effects of CURC have been demonstrated against cancer [5, 6], arthritis [7], immunodeficiencies [8] and cardiovascular diseases [9], its in vivo pharmacological potential is severely curtailed due to an extremely poor absorption profile [10]. Indeed, CURC is practically insoluble in water and its metabolism is extremely rapid. As a consequence, most of the orally ingested CURC is absorbed as inactive water-soluble glucoronate or sulfate metabolites, or is excreted unmodified by feces [11, 12] and its intestinal absorption is irrelevant [13].

Alternatively, transdermal route can be taken in consideration for CURC formulation. Skin delivery allows a high patient compliance and also the elusion of unwanted first-pass effects. In particular, CURC has a good skin compatibility and, when transdermally administered, has been tested for the treatment of a wide range of pathologies, such as psoriasis [14], many types of skin inflammation [15] and melanoma [16, 17], just to cite a few. Unfortunately, also the effectiveness of CURC transdermal delivery is limited by its poor skin permeation ability [18] and this often contributes to CURC rapid elimination from the epidermis. Consequently, it is important to produce new formulations for the dermal release of CURC in order to promote its penetration through the skin, as well as favoring a prolonged retention in the site of administration. In this panorama, it is crucial to overcome the barrier properties of skin which normally hinder the permeability of molecules [19, 20], so as to encourage the retention and penetration of the CURC and overcome possible treatment impairment [21].

In this regard, the development of vesicular nanocarriers for skin penetration of CURC is promising since it can

✉ Marco Biondi
mabiondi@unina.it

[1] Dipartimento di Farmacia, Università di Napoli Federico II, Via D. Montesano 49, Napoli, Italy

[2] Interdisciplinary Research Centre on Biomaterials—CRIB, Università di Napoli Federico II, P.le Tecchio, 80, Napoli, Italy

improve the topical release of active molecules [22]. In particular, liposomes have been employed with variable degrees of success to improve the topical efficacy of loaded molecules, by affecting their local skin penetration capacity [23, 24]. From a general point of view, liposome ability to promote the skin accumulation/permeation has been ascribed to the lipid composition, and also to the fluidity of the bilayer [24, 25]. Specifically, lipophilic compounds such as CURC are preferentially intercalated within the lipid bilayer [26], thereby favoring the interaction between the loaded molecule and the external surface of liposomes and affecting bilayer fluidity, depending on the concentration of the loaded molecule.

In this context, the aim of this study was to assess whether and how CURC loading within 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) liposomes affects the arrangement of liposome bilayer and, possibly, their penetration through skin. To this aim, DPPC liposomes encapsulating different amounts of CURC were prepared and characterized for their size, polidispersity index and zeta potential. Then, differential scanning calorimetry (DSC) analyses were performed to study the interaction between CURC and the phospholipid bilayer. Thermoanalytical experiments were further corroborated by ex vivo tests, conducted over excised pig skin aiming to determine the ability of the different liposomes formulations to promote CURC accumulation/permeation into/through the skin. To the best of our knowledge, in this work the effect of CURC concentration on membrane fluidity has been systematically studied for the first time. This is crucial to assess the relation between liposome deformability and skin penetration.

2 Materials and methods

2.1 Materials

1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) was purchased from Lipoid GmbH (Germany), while curcumin (CURC) ((E,E)-1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) (purity > 90%) from Cayman Chemical Company (Michigan, USA) was used. The other reagents (ethanol, methanol, chloroform and acetonitrile) were from Carlo ErbaReagenti (Italy). Ascorbic acid and citric acid were from J-Baker(USA).

2.2 Liposome preparation

DPPC liposomes were prepared by hydration of lipid film, as previously described [27]. Briefly, CURC solutions in chloroform were prepared in the 0.06–9 mg/mL concentration range. Correspondingly, the percentage of CURC within the liposomes was 0.1–15% w/w with respect to the lipids. Liposome formulations were named as reported in Table 1. Then, DPPC was dissolved into a 2:1 (v/v) choloroform/methanol mixture at 20 mg/mL. For each batch, 300 µL of DPPC solution and 100 µL of CURC solution were placed inside a rotavapor flask. The organic solvents were removed by rotary evaporation under reduced pressure at 65 °C and 100 rpm (Laborota 4.010 digital, Heidolph, Schwabach, Germany). After solvent removal, 4 mL of distilled and filtered water were added into the flask. Glass beads were added to enhance the detachment of the lipid film. Thereafter, the flask was placed in a bath at 65 °C for 2 h, and then the formulations were extruded by a thermobarrel extruder system (Northern Lipids Inc., Vancouver, BC, Canada). Each liposome suspension was forced, under an inert nitrogen atmosphere, through a polycarbonate membrane (Nucleopore Track Membrane 25 mm, Whatman, Brentford, UK). Specifically, three extrusions were carried out on a 0.4 µm-membrane, three on a 0.2 µm-membrane and five on a 0.1 µm-membrane. Finally, to remove any non-encapsulated CURC, liposome suspensions were purified through a Sephadex G-25molecular exclusion chromatographic column, eluted in water (1 g in 10 mL of water). The purification step was carried out by centrifugation at 4 °C for 10 min at 1000 rpm. Finally, suspensions were stored at 4 °C. Three replicas for each formulation were prepared.

Table 1 Nomenclature of CURC-loaded liposomes

Formulation	CURC/DPPC (%w/w)
LC	–
LC-01	0.1
LC-1	1
LC-5	5
LC-10	10
LC-15	15

2.3 Liposome size

Photon correlation spectroscopy (PCS; N5; Beckman Coulter, Brea, CA, USA) was used to measure the mean size (nm) and polydispersity index (PI) of the produced liposomes. Prior to each analysis, 100 µL of liposome suspensions were added to 1 mL of water preliminarily filtered through 0.22 µm filters. Results have been expressed as the average of three different batches.

2.4 Liposome zeta potential

Surface charge of the vescicles was indicated by zeta potential (ZP, expressed in mV) measurements, performed by a Zetasizer Nano Z apparatus (Malvern Instruments,

Worcestershire, UK). For the analyses, liposome suspensions were diluted 1:10 v/v in 0.22 µm—filtered water, following the instructions of the manufacturer. The results were averaged over three different batches of the same formulation.

2.5 Determination of the lipid concentration into the liposomes

The concentration of lipids present in the liposome suspensions was determined using the Stewart assay [28]. Briefly, 10 µL of liposome suspension was diluted in an aqueous solution of $FeSCN_3$ (2 mL) and $CHCl_3$ (2 mL). The samples were briefly stirred and centrifuged at 1000 rpm at 4 °C for 5 min. The DPPC in the organic phase was quantified by an ultraviolet–visible spectrophotometric assay (UV VIS 1204; Shimadzu Corporation, Kyoto, Japan) at a 485 nm wavelength. The linearity of the response was assessed in the 0.1–0.01 mg/mL concentration range ($r^2 > 0.999$).

2.6 Curcumin encapsulation into the liposomes

The amount of CURC entrapped in liposomes was determined by High Performance Liquid Chromatography (HPLC), following a previously published procedure, with some modifications [29]. A computer-assisted Shimadzu HPLC system, consisting of an LC-10 AD pump and a Rheodyne injection valve 7725i, equipped with an SPV-10A ultraviolet–visible detector ($\lambda = 435$ nm); a SCL-10AVP system controller (Shimadzu) was used. A C18 chromatographic column was used (Luna 4.6 × 250 mm, 5 mm; Phenomenex, Torrance, CA, USA), at a flow rate of 1 mL/min, and run time was set at 8 min. A Class VP Client/Server software (v 7.2.1; Shimadzu Scientific Instruments, Columbia, MD, USA) was used for chromatogram acquisition. Analyses were carried out under isocratic conditions, using an acetonitrile organic phase (CH_3CN) and a (2:1) methanol/water mixture as a water phase. The concentration of the mobile phase was 40:60 v/v (CH_3CN: MeOH/H_20). The chromatographic peak with a retention time of about 4.8 min was attributed to CURC. HPLC was preliminarily calibrated in the 0.6–250 µg/mL concentration range ($r^2 = 0.998$). CURC amount entrapped within liposomes was calculated by dissolving 100 µL of each liposome suspension in 900 µL of methanol to allow CURC release in the organic solvent. Thereafter, the obtained solution was centrifuged at 13,000 rpm for 30 min (MIKRO 20; Hettich, Tuttlingen, Germany), and the supernatants analyzed by HPLC. During the analyses, liposomes were protected from the light to avoid the risk of CURC photodegradation. The encapsulation efficiency of the CURC was expressed as actually loaded percentage with respect to the theoretical loading. Results were averaged over at least three replicas.

2.7 Liposome deformability

Extrusion method was employed to determine the deformability index of the produced liposome formulations. In brief, liposomes were forced through a 50 nm-membrane made of polycarbonate, under a 1 MPa pressure, by a thermobarrel extruder. The deformation index (DI) was used to express liposome deformability, according to the following equation [30, 31]:

$$D = J \cdot \frac{d_0}{p} \cdot \frac{d_0}{|d_1 - d_0|},$$

where J is the recovered liposome fraction after extrusion, d_0 and d_1 are the mean diameters of the vesicle before and after extrusion, and p is the pore size of the extruder membrane.

2.8 Differential scanning calorimetry

In order to evaluate the phase transition temperatures of CURC-loaded liposomes, thermoanalytical tests were carried out by a TA Q20 differential scanning calorimeter (DSC, TA Instruments, USA). Prior to DSC analyses, the samples were ultracentrifuged at 80,000 rpm and 4 °C for 40 min. Then, the pellet was re-suspended in 1 mL of distilled and filtered water. For each experiment, 20 µL of liposome suspension were placed in a hermetically sealed DSC pan, using an equal volume of distilled and filtered water as a reference. Mass conservation was assessed after each experiment to verify possible water evaporation during the experiments. Single scans were performed under an inert nitrogen atmosphere in the 10–80 °C temperature range at a 2 °C/min heating rate. Triplicate experiments were carried out on all formulations.

2.9 Ex vivo permeation experiments

The amount of CURC accumulated in, or penetrated through, the skin was determined by ex vivo permeation experiments on pig ear skin, kindly.pngted by Vendor Carni (Montefredane, Italy). Full thickness skin recovered from the dorsal side of freshly excised pig ears was cut in form of punches after the hair was cut, following a previously reported procedure [32]. In this study, the outer (stratum corneum) and inner (dermis) layers of the skin were used for permeation studies. Before permeation tests, phosphate buffer solution (PBS; 120 mM NaCl, 2.7 mM KCl, 10 mM phosphate salts; pH = 7.4) was produced and the skin was dried and cut in 3 cm-diameter circles. The samples were mounted in the cells of a Franz diffusion apparatus

(Microglass Heim, Italy), with the stratum corneum oriented upwards in the donor compartment. The receptor medium was composed of 8 mL of a 7:3 volume ratio PBS:ethanol mixture. Ascorbic acid and citric acid (0.1% w/v each) were used as preservatives [29, 33], while 1 ml of liposome suspensions (4 µg of encapsulated CURC/ml of liposomes) and of control solution of CURC (4 µg/ml in PBS pH 7.4) was added in the donor compartments. The diffusion area between the two compartments was 0.6 cm^2. The Franz cells were mounted on a H+P Labortechnik Variomag Telesystem (Munchen, Germany) and placed at 37 °C in a thermostatic bath (Haake DC30; Thermo Fisher Scientific, Waltham, MA, USA). A 600 rpm stirring rate was used throughout the experiments. At scheduled time points, 500 µL of the receptor medium were taken and replaced with the same volume of fresh medium, and the withdrawals filtered through 0.45 µm RC (regenerated cellulose) membranes and analyzed by HPLC for CURC quantification as described in Section 2.7. After 24 h, skin samples were gently washed with distilled water to remove the excess of formulation, and the dermis from separated from epidermis using a scalpel. CURC accumulation in epidermis or dermis was assessed by extraction with 1 mL of methanol followed by bath sonication (Branson 3510) at 37 °C for 20 times and 30 min. The supernatant was filtered using 0.45 µm membranes and finally analyzed by HPLC for CURC content. The amount of CURC accumulated in the two skin layers was expressed as percentage (%) of CURC calculated with respect to the amount of dermis or epidermis used for the experiment, similarly to previous publications [34, 35].

3 Results and discussion

Lately, CURC has been arousing an ever-increasing interest in the scientific community due to its elevated potential in the treatment of many pathologies, including skin diseases. Unfortunately, due to its unfavorable chemical and physical properties, the administration of CURC still represents a remarkable challenge. In this context, conventional liposomes are potentially useful release systems for incorporating lipophilic molecules such as CURC. In fact, CURC can be loaded within the phospholipid bilayer of liposomes and this can help promote the solubility and stability of the phytomolecule. In this work, the main focus was on the effect of CURC incorporation on the characteristics of the bilayer, and therefore on the defomability of the vesicles, without the use of edge activators or cosolvents.

3.1 Preparation and characterization of liposomes

The mean diameter, size distribution, zeta potential, lipid amount and CURC encapsulation efficiency were assessed for the produced liposome formulations, and the results are summarized in Table 2. Mean diameter of blank and CURC-loaded liposome formulations ranged between 104 and 133 nm, with fairly narrow size distributions, as indicated by the PI values ranging between 0.10 and 0.20. Moreover, CURC loading did not influence the size of liposomes. Interestingly, high CURC loading slight influenced the technological features of the liposomes, in that the mean size and polydispersity index were found to be (slightly) reduced compared to the blank, control DPPC formulation. This has been reasonably ascribed to the incorporation of lipophilic CURC within liposome bilayer, thereby promoting CURC intercalation within the lipophilic phospholipid tails and, consequently, the size reduction. Zeta potential values of blank liposomes showed near-zero/weakly negative values, as shown in the Table 2. On the contrary, when CURC amount exceeded 2% w/w with respect to DPPC, zeta potential values were more negative, and steadily around −15 mV or mildly less, therefore indicating that the concentration of the active molecule is high enough to partially locate on liposome surface, therefore contributing to surface charge [36, 37].

CURC encapsulated into liposomes was assessed by HPLC. In all the chromatograms, the peak with the retention time of CURC was observed around 5 min. In all cases, CURC encapsulation efficiency was roughly constant, around 30%, with loading. This indicates that higher CURC concentrations lead to higher amounts of the active molecule retained within the liposomes.

Table 2 Mean size, polydispersity index (PI), zeta potential (ZP), encapsulation efficiency (EE%), and lipid amount ad deformation index (DI) of blank and CURC-loaded liposomes (0.1–15%)

Formulation	Meandiameter (nm) ± SD	PI ± SD	ZP (mV) ± SD	Encapsulationefficiency, EE% ± SD	DI	Lipids (Recovery %)
LIPO	117 ± 3	0.11 ± 0.02	−6.6 ± 1.9	–	–	60.9 ± 3.9
LC-01	133 ± 28	0.12 ± 0.04	4.3 ± 1.7	31.1 ± 16.9	25	56.5 ± 5.0
LC-1	104 ± 18	0.20 ± 0.01	−15.7 ± 7.0	32.4 ± 17.5	27.2	56.2 ± 4.4
LC-5	111 ± 1	0.20 ± 0.01	−16.3 ± 3.1	38.7 ± 15.9	23.8	59.9 ± 6.1
LC-10	108 ± 2	0.10 ± 0.01	−16.7 ± 5.7	43.0 ± 5.6	16.9	49.5 ± 14.2
LC-15	109 ± 1	0.10 ± 0.02	−16.6 ± 4.6	34.5 ± 6.3	77.2	59.2 ± 4.3

3.2 Deformability

As shown in Table 2, the detected DI values for all liposome formulations at CURC loading <10% were low, roughly ranging between 7 and 17. Thus, the passage of liposome formulation through the 50 nm membrane used for the test led to a significant decrease of the vesicle mean diameter (data not shown). Interestingly, in the case of LC15 formulation, DI values were 2.8–4.6 fold higher than all the other formulations, thereby indicating that high CURC loading strongly influenced liposome flexibility/deformability.

3.3 Differential scanning calorimetry

The main transition temperature (Tc) of phospholipids can be used to investigate the interactions occurring between the acyl chains of phosphatidylcholines and the encapsulated substances. In detail, phospholipid membrane melting is accompanied by the transition of the lipid lamellar phase from gel state to liquid crystal state [38]. In this work, the effect of CURC loading on the arrangement of lipid bilayers was studied by DSC experiments. DPPC is a convenient phospholipid in the context, since it shows a sharp endothermic peak corresponding to the thermotropic transition, around 42 °C, as reported in Fig. 1. In general, DPPC displays a pre-transition temperature very close to the physiological temperature when in the dried state [39]. In this work, thermoanalytical experiments have been carried out on liposomes suspended in water to assess the thermal transitions of liposomes in the hydrated state. In the investigated temperature range, the pre-transition was not detected in suspension, even in blank liposomes, and no other transitions are visible. As shown in Fig. 1, the Tc of CURC-free liposomes was 41.8 ± 0.03 °C. Increasing amounts of CURC elicited the appearance of increasingly broader peaks and the reduction of peak heights, along with a slight reduction in Tc values, to 39–40 °C in the case of LC-10 and LC-15 formulations. Detailed information on Tc and ΔH values are summarized in Figs 2 and 3. These outcomes indicate that, at higher loadings, CURC induces a reduced packing of lipid bilayers and a possible enhanced hydration, with the subsequent reduction of the melting temperature of acyl chains. Figure 1 also shows that the endothermic peaks of transition were increasingly broader with increasing CURC concentration, which further indicates the hampered packing of acyl chains within DPPC bilayer, compared to blank liposomes. Therefore, the effect of CURC on the thermotropic properties of DPPC bilayers is an overall reduction of Tc, and this phenomenon is at its maximum at 10% CURC loading. These outcomes clearly indicate that the lipophilic molecule is mostly incorporated within the lipid compartment of liposome bilayers, thereby altering their organization at the molecular level.

A further insight in CURC/DPPC interaction can be grasped by observing the trend of the heats involved in the

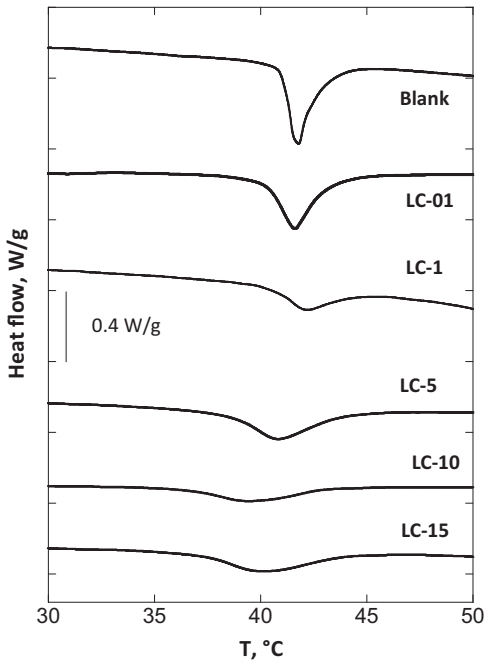

Fig. 1 DSC traces of CURC-loaded DPPC liposomes (0.1–15% w/w). Heat flow values were normalized with respect to the actual mass of liposomes. Exotherm points upward

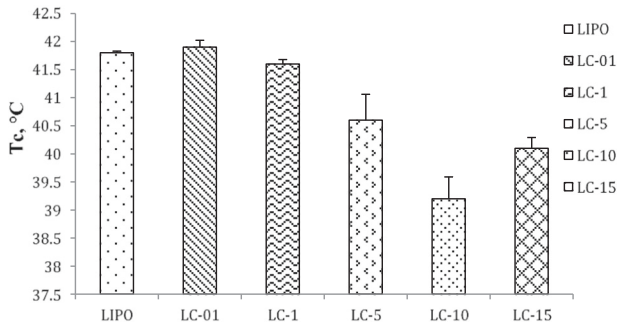

Fig. 2 Main transition temperature of CURC-loaded liposomes

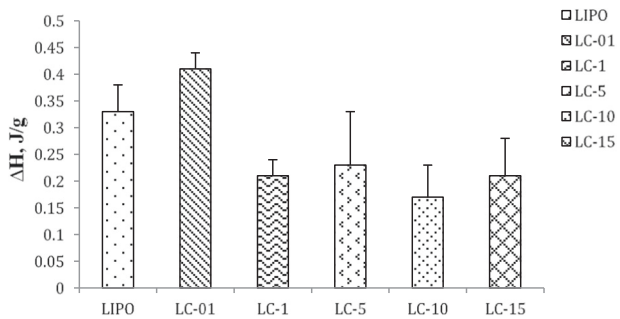

Fig. 3 Heats of transition of CURC-loaded liposomes. The values were normalized with respect to the actual mass of liposomes

transition. There is a slow decline of the heat of transition when CURC loading exceeded 0.5% w/w. It should be noted that, differently, there is no apparent decrease of Tc up to a CURC loading one order of magnitude higher (5% w/w). This suggests that, even at low CURC loading, the active molecule tends to self-aggregate into clusters that perceivably interfere with the arrangement of acyl chains buthas no ability to produce the shift in Tc values, which requires higher CURC amounts.

3.4 Ex vivo skin permeation and penetration

To evaluate the influence of CURC concentration within liposomes on the dermal and transdermal delivery ability of liposomes, ex vivo penetration and permeation studies were performed in non-occlusive conditions using a Franz diffusion cells apparatus and ear pig skin.

Bare CURC or suspensions of CURC-loaded liposomes were placed in the donor compartment and the permeated CURC percentage in the receptor compartment was quantified in time by HPLC. Figure 4 shows the permeation profiles through porcine skin of CURC and CURC-loaded liposomes. After 24 h contact, the permeation percentage of the active molecule, as such or from LC-01 formulation, is low (barely > 5%). In the case of other formulations, the permeation percentage is lower, but it must be taken into account that, due the higher CURC:DPPC mass ratio, higher overall amounts of the active molecule did actually cross the skin in the experimental time frame used in this work.

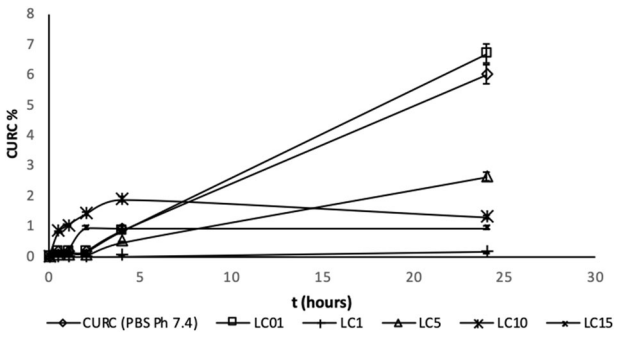

Fig. 4 Permeation profiles of LC formulations up to 24 h

Figure 5 displays the percentage of CURC accumulated in 24 h of skin incubation in the presence of free CURC or with the different liposome formulations within epidermis and dermis, respectively. Massive CURC accumulation was detected in the epidermis, while 2–7% of the active molecule was found in the dermis. This suggests that epidermis plays a reservoir role, which is increasingly important with CURC loading in liposomes. In particular, CURC accumulation in epidermis due to LC-15 liposome was lower than in the case of LC-10 formulation. On the contrary, the use of high CURC concentrations led to an increase of its accumulation within the deeper skin layers. This can be correlated to the results of deformability and DSC experiments, which showed that, in the case of formulations with higher CURC loading, the heat and the temperature of transition are lower. This points at the role of CURC at concentrations higher than 10% w/w in liposomes, in increasing liposome deformability and fluidity, thereby allowing the prepared vesicles to promote the crossing of CURC through the external skin layer, while showing little effect beyond the dermis. It is worth noting, that in the case of DPPC liposome, the penetration or crossing into the skin is not expected [40]. Thus, the enhanced accumulation into the epidermis and dermis can be ascribed to the interaction of the DPPC with similar lipids of the skin [41], with a consequent alteration of the lamellar structure of the stratum corneum and increased fluidity and permeability [42, 43]. This, in turn, can enhance CURC diffusion into the viable

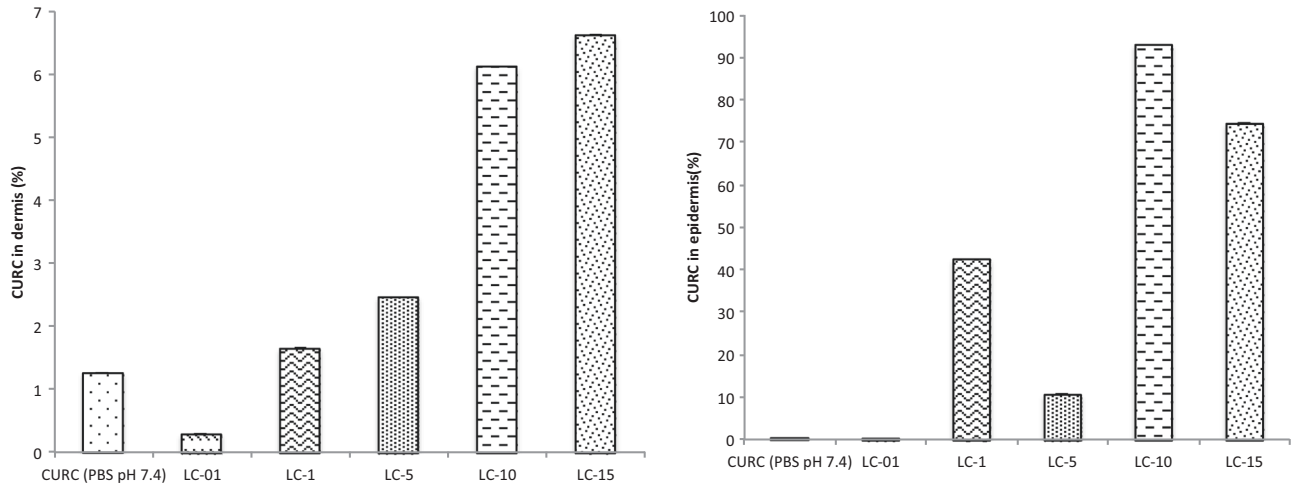

Fig. 5 Percentage of CURC retained in the dermis (left) epidermis (right) after 24 h

layers of the skin. This process can be facilitated by the increased fluidity of the bilayer found with some formulations. To sum up, the use of high CURC loading significantly affected the ability of liposomes to promote CURC migration toward the dermis. Considering that permeation rate at 24 h was generally negligible, high-loading DPPC liposomes can be envisaged as promising vectors in the view of topical administration of CURC. More in general, these data provide a new insight in the role of the encapsulated molecule, beside the lipid, in changing physical properties of liposomes and, in turn, their interaction with tissues. This is particularly important in the case of skin delivery for which the interaction of liposomes with the skin influences their ability to promote the penetration, and following permeation, of the encapsulated molecule. Thus, starting from previous studies on the use of liposomes for CURC delivery into the skin [44–46], this study proposes to correlate DSC data with ex vivo delivery of the encapsulated molecule. For a further correlation, future studies should aim understanding the mechanism by which liposomes are able to promote the penetration/permeation of CURC into the skin.

4 Conclusions

In the present investigation, DPPC liposomes loaded with CURC in a wide concentration range (0.1–15% w/w of the active molecule with respect to the phospholipid) were produced and characterized for their technological and thermodynamic features. A particular focus was devoted to shed light on the relation between these latter properties and liposome deformability, which in turn indicates the ability of the vesicles to enhance the permeation of the encapsulated active. DSC, deformation index and permeation results consistently indicate that CURC can significantly interfere with the packing of DPPC acyl chains only at the highest payload used in this work. More interestingly, LC15 formulation, which displayed the lowest Tc, showed an enhanced penetration ability within the epidermis, but with a limited crossing capacity. Overall results indicate that high-payload CURC-loaded DPPC vesicles are interesting candidates to take advantage of CURC anti-inflammatory efficacy for topical (trans)dermal delivery.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as "Curecumin": from kitchen to clinic. Biochem Pharmacol. 2008;75:787–809.
2. Caon T, Mazzarino L, Simoes CM, Senna EL, Silva MA. Lipid- and polymer-based nanostructures for cutaneous delivery of curcumin. AAPS PharmSciTech. 2017;18:920–5.
3. Ramsewak RS, DeWitt DL, Nair MG. Cytotoxicity, antioxidant and anti-inflammatory activities of curcumins I-III from Curcuma longa. Phytomedicine. 2000;7:303–8.
4. Ammon HP, Wahl MA. Pharmacology of Curcuma longa. Planta Med. 1991;57:1–7.
5. Asher GN, Spelman K. Clinical utility of curcumin extract. Altern Ther Health Med. 2013;19:20–2.
6. Bhattacharyya S, Mandal D, Saha B, Sen GS, Das T, Sa G. Curcumin prevents tumor-induced T cell apoptosis through Stat-5a-mediated Bcl-2 induction. J Biol Chem. 2007;282:15954–64.
7. Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. Phytother Res. 2012;26:1719–25.
8. Jagetia GC, Aggarwal BB. "Spicing up" of the immune system by curcumin. J Clin Immunol. 2007;27:19–35.
9. DiSilvestro RA, Joseph E, Zhao S, Bomser J. Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. Nutr J. 2012;11:79.
10. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharm. 2007;4:807–18.
11. Schiborr C, Kocher A, Behnam D, Jandasek J, Toelstede S, Frank J. The oral bioavailability of curcumin from micronized powder and liquid micelles is significantly increased in healthy humans and differs between sexes. Mol Nutr Food Res. 2014;58:516–27.
12. Nelson KM, Dahlin JL, Bisson J, Graham J, Pauli GF, Walters MA. The essential medicinal chemistry of curcumin. J Med Chem. 2017;60:1620–37.
13. Wahlstrom B, Blennow G. A study on the fate of curcumin in the rat. Acta Pharmacol Toxicol. 1978;43:86–92.
14. Sun L, Liu Z, Lin Z, Cun D, Tong HH, Yan R et al. Comparison of normal versus imiquimod-induced psoriatic skin in mice for penetration of drugs and nanoparticles. Int J Nanomed. 2018;13:5625–35.
15. Asada K, Ohara T, Muroyama K, Yamamoto Y, Murosaki S. Effects of hot water extract of Curcuma longa on human epidermal keratinocytes in vitro and skin conditions in healthy participants: a randomized, double-blind, placebo-controlled trial. J Cosmet Dermatol. 2019;18:1866–74.
16. Peram MR, Jalalpure S, Kumbar V, Patil S, Joshi S, Bhat K et al. Factorial design based curcumin ethosomal nanocarriers for the skin cancer delivery: in vitro evaluation. J Liposome Res. 2019;29:291–311.
17. Nabavi SM, Russo GL, Tedesco I, Daglia M, Orhan IE, Nabavi SF et al. Curcumin and Melanoma: from chemistry to medicine. Nutr Cancer. 2018;70:164–75.
18. Raja MA, Zeenat S, Arif M, Liu C. Self-assembled nanoparticles based on amphiphilic chitosan derivative and arginine for oral curcumin delivery. Int J Nanomed. 2016;11:4397–412.
19. Patel NA, Patel NJ, Patel RP. Formulation and evaluation of curcumin gel for topical application. Pharm Dev Technol. 2009;14:80–9.
20. Gupta NK, Dixit VK. Development and evaluation of vesicular system for curcumin delivery. Arch Dermatol Res. 2011;303:89–101.
21. Lauterbach A, Muller-Goymann CC. Applications and limitations of lipid nanoparticles in dermal and transdermal drug delivery via the follicular route. Eur J Pharm Biopharm. 2015;97:152–63.

22. Muzzalupo R, Tavano L, Cassano R, Trombino S, Ferrarelli T, Picci N. A new approach for the evaluation of niosomes as effective transdermal drug delivery systems. Eur J Pharm Biopharm. 2011;79:28–35.
23. Sinico C, Fadda AM. Vesicular carriers for dermal drug delivery. Expert Opin Drug Deliv. 2009;6:813–25.
24. Benson HA. Transdermal drug delivery: penetration enhancement techniques. Curr Drug Deliv. 2005;2:23–33.
25. Subongkot T, Ngawhirunpat T. Effect of liposomal fluidity on skin permeation of sodium fluorescein entrapped in liposomes. Int J Nanomed. 2015;10:4581–92.
26. Simao AMS, Bolean M, Cury TAC, Stabeli RG, Itri R, Ciancaglini P. Liposomal systems as carriers for bioactive compounds. Biophys Rev. 2015;7:391–7.
27. Campani V, Marchese D, Pitaro MT, Pitaro M, Grieco P, De RG. Development of a liposome-based formulation for vitamin K1 nebulization on the skin. Int J Nanomed. 2014;9:1823–32.
28. Stewart JC. Colorimetric determination of phospholipids with ammonium ferrothiocyanate. Anal Biochem. 1980;104:10–4.
29. Serri C, Argiro M, Piras L, Mita DG, Saija A, Mita L et al. Nanoprecipitated curcumin loaded particles: effect of carrier size and drug complexation with (2-hydroxypropyl)-beta-cyclodextrin on their biological performances. Int J Pharm. 2017;520:21–8.
30. Manca ML, Zaru M, Manconi M, Lai F, Valenti D, Sinico C et al. Glycerosomes: a new tool for effective dermal and transdermal drug delivery. Int J Pharm. 2013;455:66–74.
31. Mura S, Manconi M, Sinico C, Valenti D, Fadda AM. Penetration enhancer-containing vesicles (PEVs) as carriers for cutaneous delivery of minoxidil. Int J Pharm. 2009;380:72–9.
32. Gillet A, Lecomte F, Hubert P, Ducat E, Evrard B, Piel G. Skin penetration behaviour of liposomes as a function of their composition. Eur J Pharm Biopharm. 2011;79:43–53.
33. Mayol L, Serri C, Menale C, Crispi S, Piccolo MT, Mita L et al. Curcumin loaded PLGA-poloxamer blend nanoparticles induce cell cycle arrest in mesothelioma cells. Eur J Pharm Biopharm. 2015;93:37–45.
34. Campani V, Biondi M, Mayol L, Cilurzo F, Franze S, Pitaro M et al. Nanocarriers to enhance the accumulation of vitamin K1 into the skin. Pharm Res. 2016;33:893–908.
35. Campani V, Biondi M, Mayol L, Cilurzo F, Pitaro M, De RG. Development of nanoemulsions for topical delivery of vitamin K1. Int J Pharm. 2016;511:170–7.
36. Manca ML, Castangia I, Zaru M, Nacher A, Valenti D, Fernandez-Busquets X et al. Development of curcumin loaded sodium hyaluronate immobilized vesicles (hyalurosomes) and their potential on skin inflammation and wound restoring. Biomaterials. 2015;71:100–9.
37. Castangia I, Nacher A, Caddeo C, Valenti D, Fadda AM, Diez-Sales O et al. Fabrication of quercetin and curcumin bionanovesicles for the prevention and rapid regeneration of full-thickness skin defects on mice. Acta Biomater. 2014;10:1292–1300.
38. Barcelo F, Prades J, Encinar JA, Funari SS, Vogler O, Gonzalez-Ros JM et al. Interaction of the C-terminal region of the Ggamma protein with model membranes. Biophys J. 2007;93:2530–41.
39. Wu RG, Dai JD, Wu FG, Zhang XH, Li WH, Wang YR. Competitive molecular interaction among paeonol-loaded liposomes: differential scanning calorimetry and synchrotron X-ray diffraction studies. Int J Pharm. 2012;438:91–7.
40. Elsayed MM, Abdallah OY, Naggar VF, Khalafallah NM. Lipid vesicles for skin delivery of drugs: reviewing three decades of research. Int J Pharm. 2007;332:1–16.
41. Pierre MB, Dos Santos Miranda Costa I. Liposomal systems as drug delivery vehicles for dermal and transdermal applications. Arch Dermatol Res. 2011;303:607–21.
42. Ogiso T, Niinaka N, Iwaki M. Mechanism for enhancement effect of lipid disperse system on percutaneous absorption. J Pharm Sci. 1996;85:57–64.
43. Yokomizo Y, Sagitani H. The effects of phospholipids on the percutaneous penetration of indomethacin through the dorsal skin of guinea pig in vitro. 2. The effects of the hydrophobic group in phospholipids and a comparison with general enhancers. J Control Release. 1996;42:37–46.
44. Vollono L, Falconi M, Gaziano R, Iacovelli F, Dika E, Terracciano C, Bianchi L, Campione E. Potential of curcumin in skin disorders. Nutrients. 2019;11: E2169.
45. Heenatigala Palliyage G, Singh S, Ashby CR Jr, Tiwari AK, Chauhan H. Pharmaceutical topical delivery of poorly soluble polyphenols: potential role in prevention and treatment of melanoma. AAPS PharmSciTech. 2019;20:250.
46. Hussain Z, Thu HE, Ng SF, Khan S, Katas H. Nanoencapsulation, an efficient and promising approach to maximize wound healing efficacy of curcumin: a review of new trends and state-of-the-art. Colloids Surf B Biointerfaces. 2017;150:223–41.