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Research paper

Lipid nanocapsules for dermal application: A comparative study of lipid-based versus polymer-based nanocarriers

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ABSTRACT

Lipid nanocapsules (LNC) are colloidal carriers providing controlled release profiles and improved bioavailability for many drug substances and diverse administration routes. However, they have not been explored before for transdermal application. Here, we study the behavior of LNC as a transdermal drug delivery system using ibuprofen as a model drug. A comparison to other lipid nanocarriers such as solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) and polymeric nanocarriers has been made. It was found that LNC could increase the flux rate of ibuprofen 21.9 ± 0.5 compared to 5.8 ± 0.4 μg/cm^2 h in case of drug solution. Similar flux rates were obtained for SLN and NLC with average values of 22.9 ± 0.5 and 22.5 ± 2.0 μg/cm^2 h, respectively. On the other side, comparison to polymeric nanoparticles showed that the polymer-based carriers of the same particle size had lower permeation-enhancing effect with a flux rate of 10.62 ± 1.84 μg/cm^2 h. Polymeric carriers had fourfold higher accumulation in the skin compared to that of the LNC and twice the accumulation of SLN and NLC. These results would suggest that the LNC can be considered as efficient as SLN and NLC for the transdermal drug delivery while polymeric nanoparticles are more suitable for localized drug delivery to the skin.

1. Introduction

Skin is a highly metabolic tissue that presents the largest surface area in the body and serves as the physical and biochemical protective layer for internal organs [1]. Being the largest organ in the body makes it a good candidate for systemic drug administration. On the other hand, its protective function makes it of very low permeability to external molecules including harmful toxins or intentionally applied drugs. The main barrier property of the skin is represented by the uppermost layer of the skin which is the stratum corneum (SC). It consists of dead keratin-filled cells called corneocytes sealed together with corneocytes desmosomes. The cell boundary, the cornified envelope, is a very densely cross-linked protein structure, which reduces absorption of drugs into the cells [2]. Corneocytes are surrounded by lipid matrix mainly composed of ceramides, cholesterol, and fatty acids through which permeation might take place through the tortuous pathway [3].

Transdermal drug delivery has been useful in developing new applications for existing drugs and for reducing first-pass drug degradation effects. Sometimes, it can also decrease the drug-associated side effects such as in case of nitroglycerin and fentanyl patches which exhibited fewer side effects than conventional oral dosage forms [4]. Different methods have been proposed to enhance the skin permeation of drugs using either chemical or physical penetration enhancers. One of the most controversial methods to increase drug transport across the skin is the use of nanocarriers [2].

Lipid nanocapsules (LNC) are a recently developed type of nanocarriers composed of a lipid core surrounded by a tensioactive shell [5]. Preparation is based on solvent-free method that utilizes the phase inversion principle upon thermal manipulation of an oil/water system. They have been investigated for different pharmaceutical applications using different routes of administration including oral [6–8] and parenteral routes [9–11]. The use of LNC has shown several advantages in that field including improved bioavailability, increased drug targeting, and achieving controlled drug release [12–14]. Other types of lipid nanocarriers like the solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have been intensively investigated for dermal application due to their higher stability and loading capacity compared to other carriers like liposomes [15,16]. The SLN are made up of lipids solid at room temperature stabilized by a surfactant shell while NLC are composed of a mixture of solid and liquid lipids. Lipid nanoparticles can increase the stability of the entrapped drugs

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while exhibiting lower biotoxicity as they are mostly prepared from biocompatible lipids [17]. However, LNC have not been explored yet for transdermal applications. Being colloidal, lipid-based particles would provide them with excellent tolerability making them advantageous for dermal applications.

Therefore, a comparative study between different lipid nanocarriers including LNC, SLN, and NLC was conducted for testing the effect of lipid carrier type on skin permeation. Polymeric nanoparticles were also tested to evaluate the difference in the behavior of polymer-based and lipid-based systems upon applying them to the skin. Ethyl cellulose and PLGA were used as two different polymeric carriers as they differ in the degree of hydrophilicity and biodegradability. In addition, some control solutions like drug solution in oils, phosphate buffer, and micellar surfactant solutions were tested to help the comprehension of the skin permeation experiments from different formulations. The in vitro skin permeation studies were carried out using porcine skin and Franz diffusion cells.

2. Materials and methods

2.1. Materials

Ibuprofen, Solutol HS15, Cremophor A25, and Cremophor A6 were kind samples from BASF (Ludwigshafen, Germany). Miglyol® 812 (medium chain triglyceride; MCT) was from Fagron GmbH (Barsbüttel, Germany). Soybean lecithin was purchased from Caelo, Germany. Ethyl cellulose (Ethocel standard 4 premium) was a kind gift from Colorcon, England. Poly(DL-lactide-co-glycolide) (Resomer RG 503H) was from Boehringer Ingelheim, Germany. Witepsol H15 was from Sasol GmbH, Witten, Germany. Polyvinyl alcohol 98–99% hydrolyzed, nile red, and cholic acid sodium salt hydrate were purchased from Sigma–Aldrich Chemie GmbH, Steinheim, Germany. All other chemicals were of analytical grade or equivalent purity.

2.2. Preparation of the nanoparticles

Lipid nanocapsules were prepared according to a solvent-free phase inversion method that allows the preparation of very small nanocapsules by thermal manipulation of oil/water system [5,7]. Briefly, an ibuprofen amount of 0.1 g and nile red (0.001 g) were dissolved in the internal oily triglyceride phase MCT (1 g) prior to all preparation steps by magnetic stirring for 5 min. The oil phase was then mixed with Solutol HS15 and distilled water in amounts of 0.9 g and 3 g, respectively. Sodium chloride (100 mg) and soybean lecithin (100 mg) were also added to give a total weight of 5 g. The mixture was heated under magnetic stirring up to 85 °C (until a distinct drop of conductivity occurs) to ensure that the phase inversion temperature was passed and a w/o emulsion was formed. Then, the emulsion was cooled to 55 °C. During the cooling, another complete phase inversion to an o/w emulsion occurs. This cycle was repeated twice before adding 5 ml of distilled water at 4 °C. The LNC suspension was then stirred for 10 min before further analysis. The effect of surfactant on ibuprofen skin permeation was studied by replacing Solutol by a mixture of Cremophor A25 and Cremophor A6 (in a ratio of 1:0, 0.75:0.25 and 0.5:0.5).

Solid lipid nanoparticles were prepared by melting 1 g of the solid lipid Witepsol with 0.1 g ibuprofen and nile red at 70 °C. The aqueous phase consisting of 9 ml water containing 0.1 g sodium cholate and 0.25 g Cremophor A25 was also heated to the same temperature and then added to the lipid melt followed by homogenization with ultraturrax at 10,000 rpm for 10 min. The hot emulsion was then sonicated for 20 min at 70 °C and left overnight before further investigations [18].

Nanostructured lipid carriers were prepared by mixing solid lipid 0.8 g with 0.2 g MCT with the drug and nile red at 70 °C. Nine milliliters of water containing 2% Cremophor A25 heated at 70 °C was mixed with the lipid phase by magnetic stirring followed by probe sonication for 5 min and then cooling at 4 °C overnight [19].

Polymeric nanoparticles were prepared by o/w emulsion solvent evaporation technique [6]. The polymer used either ethyl cellulose or PLGA, ibuprofen, and nile red as a florescent marker were dissolved in 3 ml dichloromethane or ethyl acetate. This organic solution was then poured into 10 ml of aqueous PVA solution (or Cremophor A25), and the coarse emulsion formed was further homogenized with an ultrasonic cell disruptor (Banoelin sonopuls, Berlin, Germany) for 4 min at 4 °C. Solvent evaporation was then performed in a Buchi Rotavapor RE 120 (Buchi, Flawil, Switzerland) with reducing the pressure stepwise down to 30 mbar with a diaphragm pump.

Lecithin MCT particles was prepared by mixing the MCT with lecithin and ibuprofen at 45 °C till complete dissolution of the solid components. The oil solution was then sonicated in water for 5 min. General composition of all formulations used in this study is given in Table 1.

2.3. Characterization of the nanoparticles

Different particles were characterized by measuring their particle size and size distribution in terms of the average volume diameters and polydispersity index by photon correlation spectroscopy using particle size analyser (Brookhoven Instruments Corporation, New York, USA) at fixed angle of 90° at 25 °C. The nanoparticles suspension was diluted with distilled water before analysis, and samples were analyzed in triplicate.

Entrapment efficiency of ibuprofen and nile red in nanoparticles suspensions was determined by dissolving samples from each for-

Table 1
Particle size analysis of the different ibuprofen-loaded LNCs and nanoparticles.

Formula	Core material	Surfactant used	Particle diameter (nm)	Polydispersity index
LNC1	MCT	Solutol HS15	50.9 ± 0.6	0.06 ± 0.02
LNC2	MCT	Solutol HS15	289.3 ± 6.4	0.09 ± 0.03
LNC3	MCT	Cremophor A25	51.5 ± 0.5	0.17 ± 0.01
LNC4	MCT	Cremophor A25:A6 (75:25)	49.9 ± 0.6	0.23 ± 0.02
LNC5	MCT	Cremophor A25:A6 (50:50)	53.1 ± 0.6	0.15 ± 0.02
SLN1	Witepsol	Cremophor A25 + Na cholate	87.8 ± 5.6	0.22 ± 0.05
SLN2	Witepsol	Cremophor A25 + Na cholate	305.2 ± 7.2	0.23 ± 0.06
NLC1	Witepsol + MCT	Cremophor A25	90.3 ± 7.8	0.21 ± 0.03
NLC2	Witepsol + MCT	Cremophor A25	331.7 ± 8.2	0.17 ± 0.04
FP1	EC	PVA	54.3 ± 0.6	0.05 ± 0.02
FP2	EC	PVA	529.0 ± 30.3	0.03 ± 0.01
FP3	EC	Cremophor A25	59.5 ± 9.6	0.25 ± 0.05
FP4	EC	Cremophor A25	527.9 ± 7.2	0.05 ± 0.01
FP5	PLGA	PVA	48.0 ± 5.6	0.05 ± 0.02
FP6	PLGA	PVA	484.3 ± 22.1	0.03 ± 0.02
Lec_MCT particles	MCT	Lecithin	218.9 ± 15.3	0.05 ± 0.02

mulation in ethanol and measuring its ibuprofen and nile red content. Ibuprofen was measured using HPLC/UV while nile red was analyzed by spectofluorometry using 544-nm excitation filter and emission at 595 nm (Wallac 1420 Victor2 Multilabel counter, PerkinElmer).

Reversed-phase HPLC analysis of ibuprofen was performed on a Kontron instrument (Serlabo Technologies, France) equipped with a reversed phase column (Lichrospher RP 18, particle size 5 μm, 250 × 4.6 mm internal diameter, Merck, Darmstadt, Germany). A filtered and degassed mixture of methanol, water, and acetic acid in the ratio of 600:377:23 was employed as the mobile phase with a flow rate of 0.8 ml/min, and detection of ibuprofen was made by measuring its UV absorption at 264 nm. Each injection was containing 20 μl of solution, and drug retention time was 18 min at 25 °C.

2.4. Skin permeation experiments

2.4.1. Preparation of pig ear skin

Fresh pig ears were obtained from local slaughter house directly after animals sacrifice and before steam brewing. Full-thickness skin of the back of pig ears was carefully removed from the underlying subcutaneous lipids and cartilages using a scalpel, washed, and used for skin permeation experiments.

2.4.2. In vitro skin permeation studies

The excised skin was cut into appropriate pieces and soaked in phosphate buffer, pH 7.4, for one hour before use. Skin permeation experiments were carried out using Franz diffusion cells and infinite dose conditions. Skin was then mounted in open two chamber Franz-type diffusion cells filled with phosphate buffer, pH 7.4, with the stratum corneum side up (diffusion area was 3.14 cm^2; recipient volume 11 ml). The diffusion cells were placed in thermostatically controlled water bath resulting in a temperature of 32 °C at the skin surface. The receptor compartment was constantly stirred with a Teflon-coated magnetic bar. Test formulations (300 μl which contained 3 mg ibuprofen) were then applied to the stratum corneum surface, and the whole cells were covered with aluminum foil to minimize evaporation and to protect the fluorescent marker nile red. Samples of 1 ml were withdrawn from the receptor medium at predetermined time intervals and replaced by fresh thermostated buffer. Samples were tested for their ibuprofen content using HPLC analysis. All experiments were carried out at least six times, and average results were obtained.

2.4.3. In vitro skin retention studies

At the end of the skin permeation experiment, skin samples were removed, cleaned with cotton soaked in phosphate buffer for three times to remove any formulations remaining and homogenized in absolute ethanol and kept shaking for 24 h to extract all the retained ibuprofen or nile red. Samples were then centrifuged to remove any skin debris, and supernatant was separated for analysis of its ibuprofen and nile red content. Extraction of untreated skin samples was made as a control to compensate for any fluorescent signal from skin tissue components. Validation of the extraction efficiency and the recovery of both nile red and ibuprofen were performed by extracting skin incubated with test formulations overnight without washing where 100% of both compounds could be efficiently extracted.

2.4.4. Confocal laser scanning microscopy (CLSM)

After completion of the skin permeation experiments for 8 h, skin was removed from the Franz cell, cleaned with phosphate buffer, and placed on microscope slides without further processing. Skin treated with LNC1, SLN1, NLC1, FP5, and MCT drug solution was used as examples of skin interaction with LNC, SLN, NLC, polymeric nanoparticles, and oily solutions, respectively. For tracking the nanoparticles penetration into different skin layers, skin samples were examined directly using the inverted confocal laser scanning microscope Nikon *Eclipse* Ti (Nikon Corporation Inc., Tokyo, Japan). Examination was carried out using the objectives of Plan-Apochromat 10×/0.45 DIC, Plan-Apo VC 20×/0.75 DIC N2. The system was equipped with HeNe laser (excitation wavelength at 543 nm) for the observation of nile red fluorescence. The fluorescence signals were collected using bandpass filter of 595 nm. The samples were examined either for 2D surface view or optically sectioned into the *z* axis to get a 3D reconstruction of the skin. Interference by red auto-fluorescence from skin samples was avoided by carrying out control experiment using untreated skin from the same animal.

2.5. Statistical analysis

All results were expressed as mean values ± SD. ANOVA on ranks was used to investigate differences statistically, and Student–Newman–Keuls test was then used for the pairwise multiple comparison between different groups. Differences were considered significant at $p < 0.05$.

3. Results

3.1. Particles characterization

Different types of lipid nanocarriers including LNC, SLN, and NLC were prepared using different surfactants and different sizes to test the influence of lipid carrier type, particle size and surfactant type on the in vitro skin permeation of ibuprofen. The same was done for the polymeric nanoparticles based on two different polymers namely ethyl cellulose (EC) and poly DL-lactide-co-glycolide (PLGA). Results of the particle size analysis of the different nanocarriers used in this study are shown in Table 1.

3.2. Skin permeation experiments

Flux rates of ibuprofen resulting from skin permeation experiments with different formulations are shown in Fig. 1. The lowest flux was obtained from the ibuprofen solution in phosphate buffer, pH 7.4, followed by the micellar solution in cremophor. The flux rate of ibuprofen from all other tested formulations was significantly higher than the flux rate from the buffer solution except for the PLGA 500 nm NPs.

The comparison of the flux from LNC1 and LNC2 which had a distinctly larger diameter showed higher permeation for the smaller size of LNC ($p < 0.05$). LNC prepared using different surfactants either solutol or cremophor in the size range of 50 nm showed comparable permeation profiles. Similar values were obtained for both SLN and NLC, showing the same tendency for higher permeation when the particle size decreases. Flux rates from all lipid nanocarriers were higher than those from all types of polymeric nanoparticles. For ethyl cellulose nanoparticles prepared using PVA as a surfactant, there was an increase in the drug permeation with increasing the particle size. This was not obtained for the ones prepared with cremophor A25 or for the PLGA nanoparticles where there was no difference between the two tested sizes of 50 and 500 nm. MCT and paraffin oil solutions had nearly the same flux rates, which were as high as the different LNC while Lec-MCT particles had slightly lower permeation-enhancing effect.

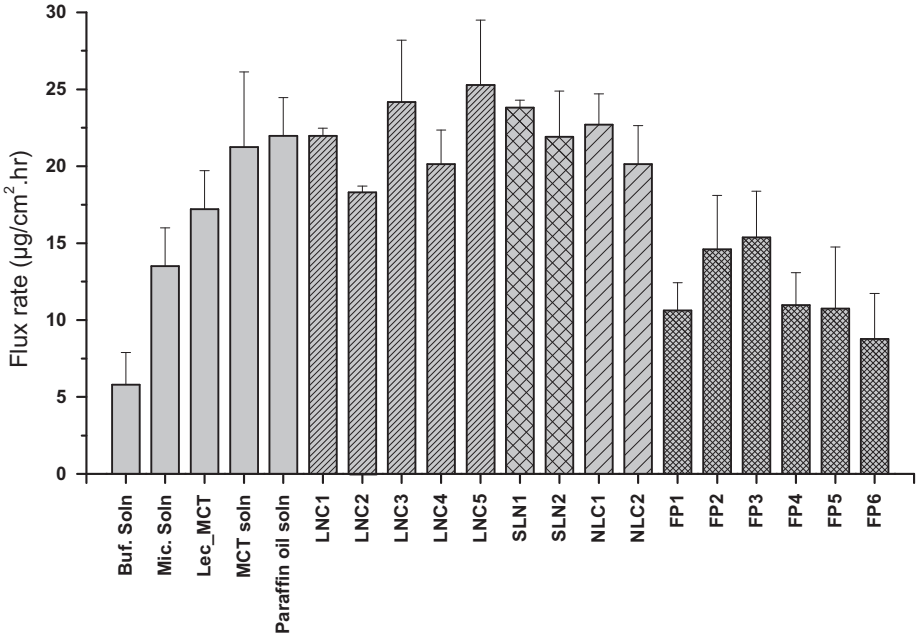

Fig. 1. Flux rates of ibuprofen from different formulations across porcine skin using Franz cells and phosphate buffer, pH 7.4, as a receptor medium, (n = 6). Flux rates of all lipid-based nanoparticles were significantly higher than polymeric particles ($p < 0.05$).

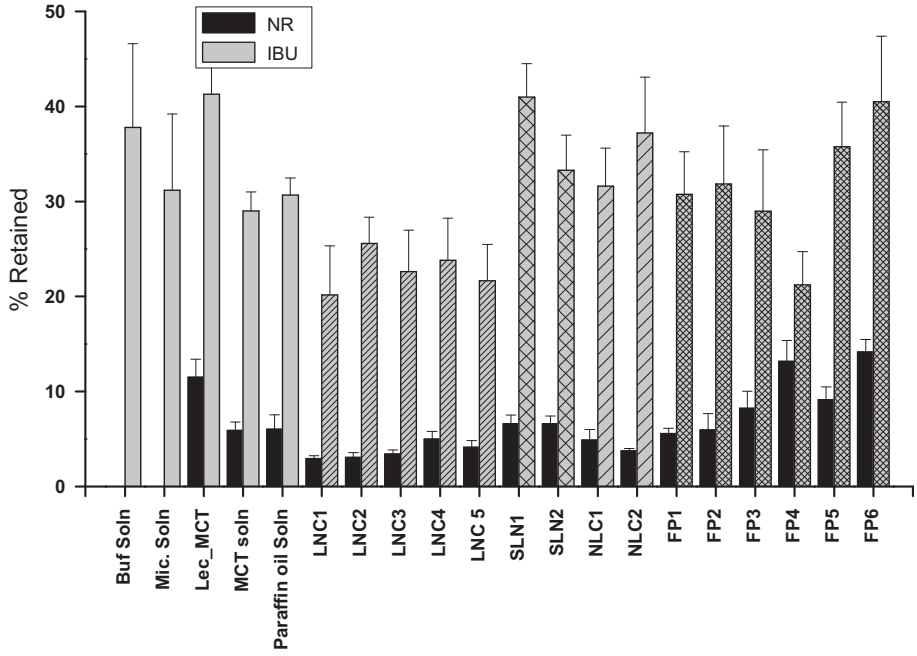

Fig. 2. Skin retention of nile red and ibuprofen after application of different formulations.

3.3. Skin retention experiments

The retention studies have been carried out by measuring the amount of nile red in the skin ethanolic extract as an indication to the amount of nanoparticles retained in the skin. The concentration of ibuprofen was also measured in the skin extract to indicate the tendency of the used system to have a localized effect on the skin tissue. Skin retention values of both nile red and ibuprofen after application of different formulations for 8 h are shown in Fig. 2. For all LNCs, the amounts of nile red and ibuprofen retained on the skin were lower than those obtained from SLN and NLC. For polymeric nanoparticles, higher retention values were obtained compared with LNC, which also increased with larger particles. The highest retention was observed for the PLGA nanoparticles of the size 500 nm. Paraffin and MCT solutions gave comparable results, and both were similar to the results of LNCs.

Skin retention experiments were also carried out using LNC1 and FP5 as examples for lipid- and polymer-based carriers over the period of 8 h. Results of the skin retention of both nile red and ibuprofen are shown in Fig. 3. The amount of nile red retained

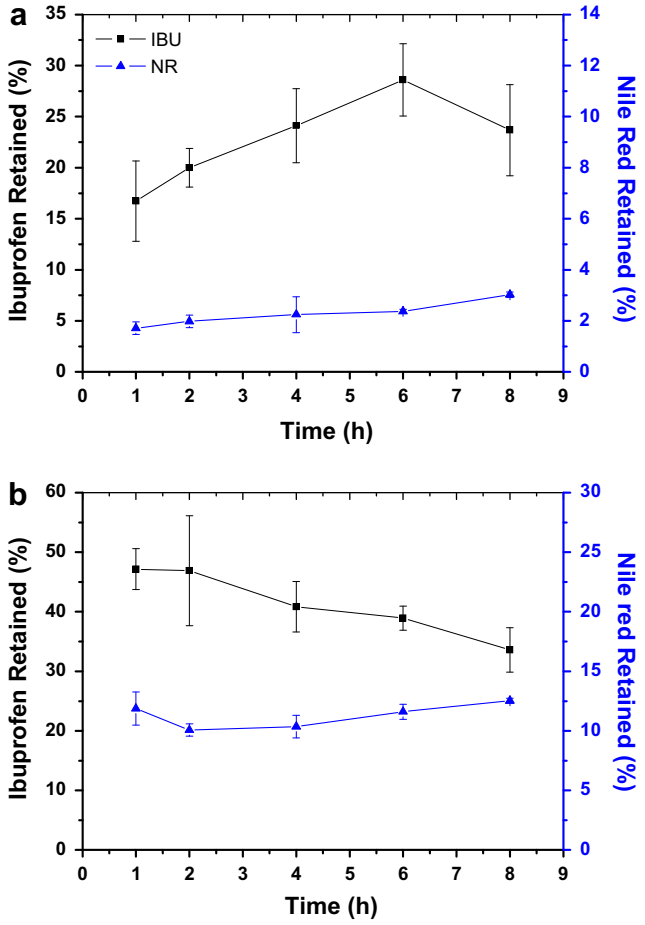

Fig. 3. Time profile of the skin retention of nile red and ibuprofen after treatment with: (a) LNC and (b) FP5. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in the skin, although higher amounts were retained from the polymer NPs, was constant for both types all over the whole treatment period. In case of LNC1, the amount of ibuprofen was found to increase gradually reaching a maximum after 6 h and then started to decline again. For the polymer NPs, ibuprofen was retained the most in the first hour of treatment and then decreased with time.

3.4. Confocal laser scanning microscope

Application of the LNC1, SLN1, NLC1, or FP5 to the skin showed accumulation of the nanocarriers on the whole skin surface including the hair follicular space but without any further penetration into deeper skin layers (Fig. 4a–d). These formulations were selected as examples for each particle type, and all were having the same particle size around 50 nm. In case of using MCT, the nile red fluorescence was only observed on the surface and no signal was detected from the hair follicles or deeper skin layers (Fig. 4e).

4. Discussion

In the present work, the aim is to test LNC for skin application and to put in the comparative context of other nanocarriers. For the lipid particles, SLN and NLC were used, and for the polymeric particles, we tested two polymers: ethyl cellulose and PLGA. Ibuprofen was selected in order to see the influence of the carrier system on the flux. For that purpose, experiments were carried out using Franz cells and porcine skin as it is a frequently used model

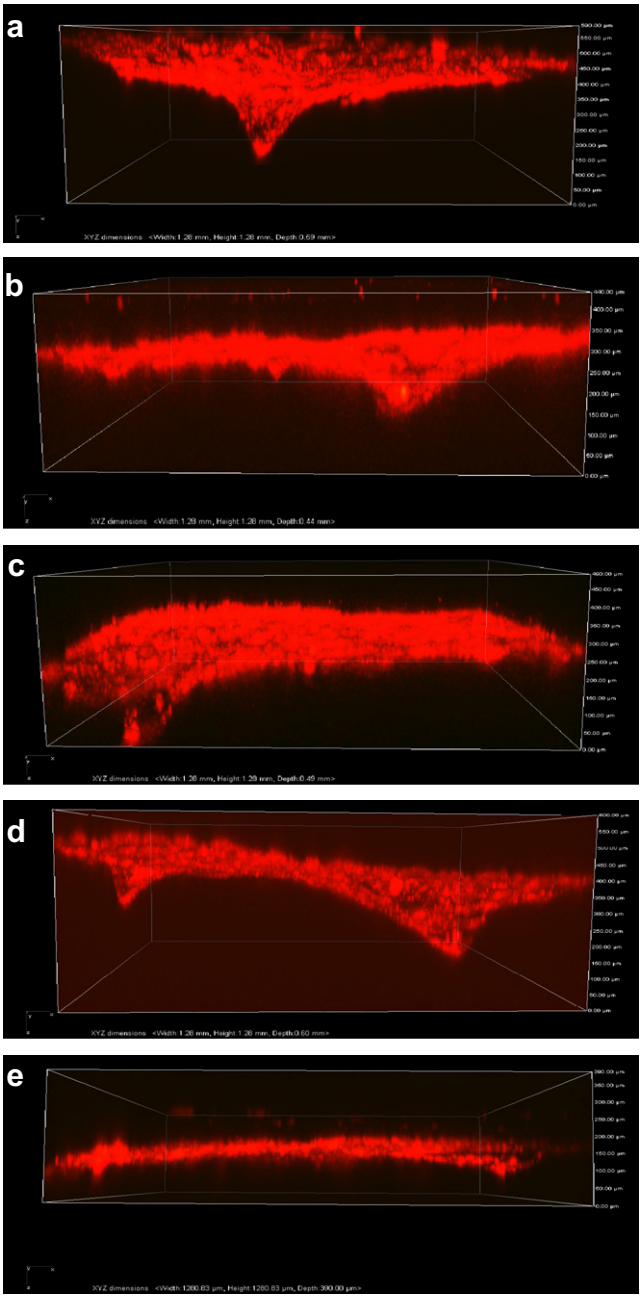

Fig. 4. Confocal laser scanning microscopy of skin treated with: (a) LNC1, (b) SLN2, (c) NLC2, (d) FP5, and (e) MCT. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

for human skin showing a similar penetration for topically applied substances [20–23].

The lowest flux rate of ibuprofen was obtained from the buffer solution (pH 7.4). This was expected since the drug is nearly completely ionized at this pH which decreases the permeation resulting in a flux rate of 5.8 ± 0.4 μg/cm^2 h [24].

The preparation of micellar solution of ibuprofen using cremophor has increased the flux rate of ibuprofen to be 13.5 ± 2.5 μg/cm^2 h. Penetration of nonionic surfactants in the intercellular regions of SC leads to increased fluidity, solubility, and extraction of lipid components combined with disruption of the corneocytes with subsequent increased permeation [25,26].

A higher flux rate of ibuprofen from both MCT solution and paraffin oil solution was obtained which was also similar to the values

obtained from the different LNC. This can be explained by the ability of the oil solution to make the drug instantly accessible to the skin that facilitated its permeation across the SC [27]. The hydrating effect of these oils also has a great role in increasing skin hydration resulting in SC swelling and opening with subsequent higher drug permeation [28].

The incorporation of ibuprofen in Lec_MCT particles could also increase its permeation through the skin compared with drug solution. This can be explained by the combined effect of oily occlusive components and phospholipids. The lecithin may join the SC lipid bilayer in the intercellular regions between corneocytes leading to an overall increase in the membrane permeability to the applied drug [29,30].

Increased permeation rates were obtained from the different tested LNC compared with drug solution. It is clear from the CLSM images that the intact LNC could not penetrate the skin deeper than the SC. This indicates that the increased drug permeation is not due to intact LNC penetrating the skin. Also the surfactant type seems to have no effect on the drug permeation since the difference between flux rates from different LNC of the same size prepared with different surfactants was not significant. Proposed explanation to the increased drug permeation from LNC compared to drug solutions, and polymeric NPs would depend on the interpretation of lipid carriers–skin interactions. Most probably, the LNC are disintegrating on the skin surface and their individual components can penetrate the stratum corneum with subsequent fluidization and modification of SC lipids as previously described for the different control solutions.

Ibuprofen permeation was significantly lower for the LNC of larger size although using the same surfactant type in preparation. This may be because of the lower surfactant concentration used in preparing the larger LNC and to the effect of particle size on the skin interaction with LNC.

In the case of SLN and NLC, flux rates of ibuprofen were comparable with those from LNC. This indicates that all the lipid-based nanoparticles had comparable permeation enhancing effect with only some minor differences. Also higher permeation was observed from the smaller particles in both types. However, the permeation-enhancing mechanisms are probably different between the solid and liquid lipid nanocarriers. Due to the solid nature of these carriers at skin temperatures, water evaporation after their application to the skin is supposed to result in a transition of their lipid matrix into more ordered structure supersaturated with the drug leading to drug expulsion. This supersaturation would enhance the drug permeation to a great extent [31]. Moreover, this ordered lipid structure forms a film over the skin surface leading to higher occlusion and hydrating effect which opens the compact structure of the horny layer and enhance drug permeation consequently.

About the drug permeation from polymeric nanoparticles, it was found that there was increased drug permeation upon increasing the particle size. This could be explained by the larger contact area between the individual large particles compared to the smaller ones, which enhanced the movement of the drug to the skin [32]. Therefore, lower flux and higher skin retention of ibuprofen were obtained for the smaller sizes of EC NPs. In case of the more hydrophobic polymer PLGA, the partitioning of the drug from the NPs was decreased compared to the less hydrophobic EC resulting in lower flux rate from PLGA particles. In contrary to lipid particles, the low flux rates obtained from the different polymer-based particles indicated higher tendency of polymerics to exert a localized effect on the skin rather than a permeation-enhancing effect.

In an attempt to confirm this result, another experiment was carried out using LNC1 and FP5 as examples for lipid and polymer particles respectively. Retention of the nile red and ibuprofen after skin treatment with both LNC and polymeric nanoparticles was followed over a period of 8 h. It was found that the amount of nile red in the skin extract is constant over the whole period in both cases. This means that the particles are accumulating in the stratum corneum layer with no further penetration into the deeper skin layers, which was also clear in CLSM images. So the amount of nile red extracted corresponds to the amount of particles enough to saturate the stratum corneum layer. However, higher values were obtained for the polymeric nanoparticles compared to LNC, which indicated a higher tendency of polymeric nanoparticles to retention on the skin surface. It was observed that the amount of ibuprofen accumulating in the skin after LNC1 application was increasing with time until the time of 6 h. This means that there was continuous supply of the drug to the skin from the LNC. The LNC are disintegrating with time and diffusing through the skin giving rise to increasing drug concentration in the skin extract. After 6 h, the drug concentration in skin extract decreased again probably indicating the beginning of drug depletion from the LNC. On the other hand, using FP5, the ibuprofen was at its highest concentration in the skin at the first hour, which starts to decrease by time continuously. This confirms that the polymeric nanoparticles are retained on the skin surface, and after 1 h, the whole stratum corneum is covered with a constant amount of nanoparticles from which the drug starts to partition and permeate across deeper skin layers to the receptor medium.

To evaluate LNC and other carriers as topical or transdermal drug carriers, it is interesting to compare the amount of drug accumulated in the skin (s) versus the drug permeated through the skin (m) from each formulation as an indication of the ability to locally accumulate the drug into the skin. When the steady state flux is established, the concentration gradient across the skin is considered nearly linear, and the amount of the drug retained in the skin will depend on the partition coefficient K. On the other side, the amount of drug permeating through the skin is proportional to the permeability coefficient P.

$$\text{Where } P = K * D/h \tag{1}$$

As D is the effective diffusion coefficient and h is the thickness of the skin [33].

In this case, comparing the accumulated drug to the permeating drug (s/m) will yield a relation as follows:

$$(s/m) \approx K/(K * D/h) = h/D$$

This means that the local accumulation of the drug from different formulations is inversely proportional to the diffusivity of the drug trough the skin, which is changing as a result from the interaction of each carrier system with the skin. It was observed that the drug accumulation values for the different tested LNC were very low. These results suggest that the main effect of these lipid nanocarriers is to help the transdermal permeation of the drug and enhancing its systemic availability by increasing its diffusion through the skin. Comparable values were obtained for the drug solution in MCT or in paraffin oil that embraces the effect of the lipid nature of the formulation on its permeation enhancing action. Higher values of accumulated drug were obtained for all the polymeric nanoparticles indicating their ability to increase the local drug concentration into the skin. The highest values of local accumulation were obtained for the PLGA nanoparticles and the small sizes of EC nanoparticles, which suggest that the accumulation of drugs in the skin can be enhanced by the proper selection of the polymer, surfactant, and particles size of the used nanocarrier.

The above findings can be considered valuable for obtaining an optimized therapeutic regimen by selecting the appropriate nanocarriers for skin applications. Transdermal delivery involves the permeation of drug across the skin layers reaching the systemic circulation and giving a systemic therapeutic effect. For such a purpose, the liquid lipid nanocapsules seem to be suitable carrier as seen from the high permeation enhancing effect, accompanied by

low accumulation in the skin. This allows maximum delivery of drugs to the systemic circulation with minimum loss and undesired local side effects. In case of dermal drug delivery, the aim is to deliver the drug in high concentrations to the skin with minimum systemic absorption. This is required when the skin itself is the target organ in cases such as skin inflammation and infections. Polymeric nanoparticles would be a proper selection in such cases as they have high accumulation tendency on skin with minimum permeation-enhancing effect.

5. Conclusion

Lipid nanocapsules have been investigated as a transdermal drug delivery system. They proved to have a higher permeation-enhancing effect compared to polymeric nanoparticles, on the other hand; they had similar permeation to SLN and NLC but with the advantage of lower intradermal drug accumulation as well as higher loading efficiency combined with less stability problems compared to SLN. LNC surface properties had no effect on their transdermal drug delivery, while the smaller particle size seemed to be more effective than the larger one. Polymeric nanoparticles tend to behave better as localized drug delivery system since they gave higher drug accumulation into the skin with lower flux rates compared to lipid nanoparticles. Polymer hydrophobicity and particle size of the polymeric nanoparticles had an influence on their skin interaction pattern. Therefore, proper selection of the particle type, size, and degree of hydrophobicity can be used to control the drug delivery from nanoparticles to the skin.

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