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Studies on nonionic surfactant bilayer vesicles of ciclopirox olamine

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Abstract

Context: Niosomal delivery can prove an alternative to improve the poor skin penetration and residence of the topical antifungal drugs that account for the long treatment regimes in cutaneous mycosis. *Objective*: To investigate niosomes as carriers for dermal delivery of ciclopirox olamine (CPO), a broad spectrum antifungal drug. *Materials and methods*: Niosomes were prepared by ethanol injection method using Span 60, cholesterol, diacetyl phosphate according to 3^2 factorial design and evaluated for physicochemical parameters, in vitro and ex vivo deposition in skin and stability study. *Results*: Unilamellar CPO niosomes of size 170–280 nm, entrapment efficiency 38–68%, and sufficient electrokinetic stability were obtained. Percent drug deposition in artificial membrane varied from 12.75 to 92.74. Deposition of CPO into rat skin from niosomal dispersion and its gel was significantly higher than that of plain CPO solution and its marketed product. Obtained niosomes possessed sufficient stability on storage. *Discussion*: Increasing amounts of Span 60 and cholesterol increase the vesicle size probably because of entrapment of CPO-ionized molecules in the aqueous compartment and interaction of its unionized counterpart with the bilayer constituents leading to increase in bilayer thickness. Consequently, the percent entrapment efficiency also increased. However, increasing Span 60 levels decreased the in vitro percent drug deposition. This might be attributed to the larger size of vesicles produced by high amounts of surfactant that showed poor deposition. The optimized batch possessed sufficient stability. *Conclusions*: The results of this investigation suggest that niosomes are promising tools for cutaneous retention of CPO.

Key words: *Antifungal; cholesterol; cutaneous deposition; ethanol injection; niosomes; Span 60; topical; unilamellar*

Introduction

Fungal infections or mycoses are one of the causes of the most prevalent cutaneous disorders in a host of human population, especially the immunocompromised ones. Superficial mycoses caused by the dermatophytes usually affect the dermis, subcutaneous tissues, muscle, and fascia[1]. There are a wide variety of antifungal drugs: systemic as well as topical to cure these diseases. Most cutaneous fungal infections are treated with topical antifungal agents unless the infection covers an extensive area or is resistant to initial therapy. But the high frequency of application of topical formulations and the side effects associated with the systemic drugs lead to poor patient compliance. Also, deep-seated infections require good penetration of the drug through the stratum corneum and high drug retention in the skin. A drug delivery is required that would enhance drug permeation through the stratum corneum and diffuse across the target biologic tissues, which have distinct architectures and compositions depending on their function[2]. To achieve this, one can follow the method of manipulating the topical delivery vehicles.

It is agreed that vesicular systems such as liposomes and niosomes can be suitable carriers to deliver the drugs by dermal or topical drug delivery for treatment of a variety of skin ailments and there are previous reports of vesicular delivery of antifungal agents to the skin using liposomal systems[3–5]. Among the vesicular systems, niosomes or nonionic surfactant vesicles are an attractive delivery system considered as an alternative

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to liposomes. Niosomes are similar to liposomes in terms of their architecture, physical properties, and methods of preparation but have advantages over the liposomes, such as entrapment of more substances, higher structural stability, and also precluding storage in special conditions[6,7]. They find a promising role in the topical delivery of a variety of agents such as anti-inflammatory drugs[8,9], noninvasive vaccines[10], anticancer[11,12] and anti-infective agents[13,14], and miscellaneous categories[15,16]. In cosmetic field too[17] niosomes are thought to improve the horny layer properties, both by reducing transepidermal water loss and by increasing smoothness via replenishing lost skin lipids[18].

This study was undertaken to investigate the potential of structured nonionic surfactant vesicles as topical delivery system capable of improving the cutaneous delivery of the antifungal drug, ciclopirox olamine (CPO). It was hypothesized that the vesicular entrapment of this antifungal drug would prolong its diffusion and increase its skin retention. CPO is a hydroxypyridone derivative having a wide spectrum of activity[19]. The minimal inhibitory concentration of CPO was found to be between 0.49 and 3.9 μg/mL for many human pathogenic fungi[20]. It is available in the form of cream, lotion, and nail lacquer[21].

Span 60 possesses a gel–liquid transition temperature of 60°C and also gives maximum entrapment of the drug[22]. Hence it was chosen as the vesicle-forming nonionic surfactant. To stabilize the vesicular structure of cholesterol and charge-inducing agent, diacetyl phosphate (DCP) was included in the niosomal formulation. DCP provided a negative charge to the vesicles. The 3^2 factorial design approach was adopted to study the influence of varying amounts of Span 60 and cholesterol on the characteristics of the CPO-loaded niosomes, namely, vesicular size, entrapment efficiency (EE), amount of drug deposited in artificial membrane and excised rat skin, and stability of the niosomes.

Methods

Materials

CPO was a generous gift from Cipla Pvt. Ltd. (Mumbai, India). Span 60 and cholesterol were obtained from Research-Lab Fine Chem Industries Limited, Mumbai, India and Qualigens Ltd, Mumbai, India. DCP and terbium chloride were procured from Sigma Aldrich Company, Steinheim, Germany. Ethanol, disodium ethylenediaminetetraacetic acid (EDTA), boric acid, potassium chloride, and sodium hydroxide were of analytical grade. Distilled water was used throughout the experiment. Marketed CPO cream was procured from the local market.

Preparation of niosomes

The blank and drug-loaded niosomes were prepared by ethanol injection method[23,24]. Briefly, specific amount of Span 60 and cholesterol, CPO (10 mg), and DCP (8 mg) were dissolved in 1 mL of ethanol by warming to 60°C (Table 1). This was rapidly injected into the aqueous phase (at 60°C) under stirring at 500 rpm (Remi magnetic stirrer) using a Teflon-coated bead. The aqueous phase immediately turned milky because of niosome formation. The system was subjected to evaporation under vacuum at 60°C for 15 minutes to remove ethanol. It was further stirred magnetically at 500 rpm (Remi magnetic stirrer) at room temperature till the completion of 2 hours. Water was added to adjust the volume of final niosomal suspension to 10 mL. The dispersion was filtered through 2–20 μm filter (Ultipor GF Plus®, Pall Corporation, Pall India Pvt. Ltd., Mumbai, India) to obtain a uniform size distribution. Furthermore it was refrigerated for 2 hours for effective vesicle sealing.

Effect of variables

A prior knowledge and understanding of the process and the process variables under investigation led to preliminary experiments. Based on this preliminary data, the 3^2 factorial design was adopted to optimize the amount of Span 60 and cholesterol, identified as the independent variables affecting the vesicle size, the percent drug EE, and the percent in vitro drug deposition (dependent variables). The response surfaces of the obtained results were also plotted.

Fluorescence spectrophotometry

The concentration of CPO was estimated by fluorescence spectroscopy using the method reported by Walash et al.[25]. To exhibit fluorescence the CPO-containing samples were treated with terbium chloride solution and EDTA solution (final concentration of 2.5×10^{-5} and 2.3×10^{-5} mol/L for $TbCl_3$ and EDTA, respectively). The fluorescence intensity was recorded

Table 1. 3^2 factorial design with the batch codes and actual values of the levels of the variables.

Batch name	Amount of Span 60 (mg) X_1	Amount of cholesterol (mg) X_2
N1 (–1, –1)	30	25
N2 (–1, 0)	30	50
N3 (–1, +1)	30	75
N4 (0, –1)	60	25
N5 (0, 0)	60	50
N6 (0, +1)	60	75
N7 (+1, –1)	90	25
N8 (+1, 0)	90	50
N9 (+1, +1)	90	75

on a Varian Cary Eclipse fluorescence spectrophotometer equipped with a xenon lamp. The samples were excited at 295 nm; the excitation and emission slit widths both were set at 10 nm. The fluorescence intensity emitted at 490 nm was recorded. This method was calibrated, and it yielded the following equation of the calibration curve ($r^2 = 0.9975$):

$$y = 0.1267x + 6.44. \quad (1)$$

Vesicle characterization

Visualization by transmission electron microscopy

A drop of vesicle dispersion was applied to a carbon film-covered copper grid. Most of the dispersion was blotted from the grid with filter paper to form a thin-film specimen. The sample was then examined and photographed with a Zeiss EM 109 transmission electron microscope at an accelerating voltage of 80 kV and a magnification of 50,000×.

Vesicle size measurement

The mean particle size of the niosomal dispersion was determined by laser diffraction technique using Malvern 2000SM (Malvern Instruments Ltd., Worcestershire, UK). Analysis was carried out at 30 ± 2°C temperature keeping the angle of detection at 90°. The mean vesicle size was expressed in terms of $d(0.9)$ nm.

Determination of entrapment efficiency

The unentrapped CPO was separated from the niosomes through minicolumn centrifugation. Niosomal dispersion (0.2 mL) was introduced into a Sephadex G-50 column and centrifuged at 2971 × *g* for 2 minutes at 4°C. The free drug remained bound to the column whereas vesicles were eluted out of the column. The vesicles were disrupted with absolute ethanol to release the entrapped drug. This solution was suitably diluted and the concentration determined by measuring the fluorescence intensity. The percent EE was calculated using Equation (2).

$$\%\ \text{EE} = \frac{\text{amount of drug entrapped in the niosomes}}{\text{total amount of the drug present}} \times 100. \quad (2)$$

Zeta potential measurement

The zeta potential of the niosomes was measured with the laser Doppler electrophoretic mobility measurements using Zetasizer 300 HSA (Malvern Instruments Ltd.) at a temperature of 25°C.

Fourier transform infrared spectroscopy

Appropriate amounts of CPO, Span 60, cholesterol, DCP, and lyophilized batch N8 niosomes were mixed separately with KBr. The IR spectra of the resultant mixture were recorded on a Jasco FT/IR—4100 (Jasco, Tokyo, Japan) equipped with Spectra manager version 2. Each measurement represented an average of 45 scans with a resolution of 1 cm^{-1}.

In vitro drug deposition studies

The in vitro deposition of CPO from the vesicles into the skin was studied using artificial cellophane membrane (Membra—Cel MD 34-14, cutoff 14 kDa). For this experiment a vertical Franz diffusion cell having a surface area of 2.54 cm^2 and a reservoir capacity of 32 mL was used. The artificial membrane was securely placed between the two halves of the diffusion cell. The receptor fluid consisted of a mixture of phosphate buffer (pH 7.4) and ethanol in the ratio 4:1, its temperature maintained at 37 ± 1°C, and stirred continuously using magnetic stirrer. The prepared CPO niosomal dispersions were added to the donor compartment. One milliliter of the sample was withdrawn from the receptor compartment at definite time intervals and replaced with equal volume of fresh receptor fluid. At the end of 24 hours, the diffusion assembly was dismantled and the artificial membrane was carefully removed from the cell. Drug present on the surface was removed by gentle scraping and washing the surface of the membrane 10 times with ethanol–water mixture. The percent drug deposition was calculated as follows:

$$\%\ \text{drug deposition} = 100 - \begin{bmatrix} \%\ \text{cumulative release at the end of 24 hours} \\ +\%\ \text{drug extracted by washing} \\ +\%\ \text{remaining in the donor compartment} \end{bmatrix}. \quad (3)$$

Preparation of niosomal gel

A niosomal gel of the optimized batch, N8, was prepared by incorporating the niosomal dispersion in a 2% (w/w) Carbopol® 940 P (Goodrich Co. Ltd., Cleveland, OH, USA) gel base. Initially required amount of Carbopol® 940 P was added to water and kept overnight for complete hydration of polymer chains. Triethanolamine was used to neutralize the pH of the gel to 6–7 and induce gelling. Niosomal dispersion N8 was added to the hydrated carbopol solution to obtain a final concentration of 0.78% (w/w) of CPO. The prepared gel was used for ex vivo drug skin deposition study.

Ex vivo skin deposition studies

The ex vivo skin deposition study was performed on excised Wistar rat skin according to the study protocol approved by the Institutional Animal Ethics Committee constituted under Committee for the Purpose of Control and Supervision on Experimental Animals, India. The abdominal skin of rat was shaved, carefully excised, and defatted to remove the subcutaneous fat. Further procedure was similar to that mentioned in the Section 'In vitro drug deposition studies'. The rat skin was placed on the Franz diffusion cell with the epidermal side facing the donor compartment and the dermal side in contact with the receptor solution.

The experiment was run for the N8 niosomal dispersion and Carbopol® 940 P gel-containing niosomes of batch N8. CPO dissolved in water—methanol mixture (4:1) acted as the control. To compare the results, a commercial cream, containing 1% (w/w) of CPO, was also tested. In all the experiments an amount of dispersion or gel or cream equivalent to 1 mg of CPO was applied to the skin in the donor compartment.

Stability study

For this study, the niosomal dispersion N8 was kept at 2–8°C and 25 ± 2°C/60% RH for a period of 3 months. The stability of the niosomes in terms of change in particle size and % EE was investigated.

Results

In this study, nonionic surfactant bilayered vesicles of CPO have been prepared to investigate their utility to localize CPO in the skin. Effect of the bilayer composition on the vesicle size, drug encapsulation, and drug cutaneous deposition was studied.

During the preliminary study, the concentrations of Span 60, cholesterol, and DCP, which would give a non-aggregating, nonsedimenting niosomal dispersion, were determined. The concentrations of Span 60 and cholesterol were predicted to be decisive in the preparation and stabilization of the niosomal system and 3^2 factorial design was employed to optimize their concentrations (Table 1). The concentrations of DCP and CPO were kept constant.

Transmission electron microscopy of the vesicles was performed to elucidate the morphology of the CPO niosomes. As shown in Figure 1, the niosomes obtained were spherical large unilamellar vesicles (UVs) with few ellipsoidal structures.

The values of zeta potential are shown in Table 2. In the absence of DCP, the niosomes had low negative zeta potential. The inclusion of DCP imparted sufficient stability to the niosomal dispersions as their zeta potential values approached –30 mV[26].

As per 3^2 factorial design, nine different batches were prepared. The responses of these batches are shown in Table 2. The data obtained were subjected to multiple regression analysis using 'PCP Disso V3' software (IIPC, PCP, Pune, India) and fitted in Equation (4):

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{11} X_1 X_1 + \beta_{22} X_2 X_2 + \beta_{12} X_1 X_2 . \quad (4)$$

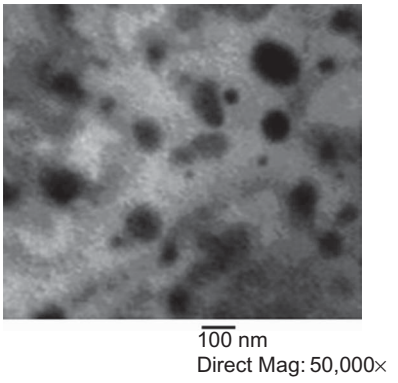

Figure 1. Photomicrograph of niosomal dispersion by transmission electron microscopy.

Table 2. Physicochemical characterization of the niosomes.

Batch name	Blank vesicle $d(0.9)$ (nm) ± SD*	Loaded vesicle $d(0.9)$ (nm) ± SD*	% EE ± SD*	Zeta potential (mV) ± SD*	% drug deposition in artificial membrane ± SD*
N1	182.33 ± 0.47	178.66 ± 2.5	42.17 ± 1.2	−19.3 ± 1.2	89.90 ± 3.5
N2	174.66 ± 0.94	169.66 ± 3.5	38.64 ± 6.5	−23.5 ± 2.3	92.74 ± 4.4
N3	181.00 ± 0.81	212.00 ± 8.3	52.83 ± 2.8	−20.0 ± 2.9	60.08 ± 2.8
N4	178.66 ± 0.94	215.66 ± 5.0	54.33 ± 1.8	−13.3 ± 3.7	28.36 ± 3.9
N5	168.33 ± 0.94	180.66 ± 8.1	45.90 ± 3.3	−19.7 ± 0.8	69.78 ± 1.8
N6	174.66 ± 0.47	273.33 ± 43.1	60.85 ± 6.8	−15.5 ± 2.0	61.41 ± 3.2
N7	208.33 ± 0.47	218.00 ± 2.0	59.82 ± 5.5	−15.3 ± 1.4	18.85 ± 3.4
N8	164.66 ± 0.94	200.66 ± 6.1	67.89 ± 3.0	−24.9 ± 0.8	62.92 ± 4.1
N9	166.00 ± 0.81	280.00 ± 6.5	77.06 ± 5.2	−16.4 ± 3.3	12.75 ± 4.3

Note: *Results are expressed as meant ± standard deviation ($n = 3$).

Table 3. Summary of regression analysis of results of measured responses.

	Coefficients							
Parameters	β_0	β_1	β_2	β_{11}	β_{22}	β_{12}	r^2	P
Loaded vesicle size	183.66	22.94	25.61	–	46.05	–	0.9143	<0.05
Percent EE	55.49	11.85	5.736	–	–	–	0.8473	<0.05
Percent drug deposition in artificial membrane	55.19	–24.7	–	–	–	–	0.5389	<0.05

The results of multiple regression analysis of the obtained data are summarized in Table 3. The insignificant variables are not mentioned in the table. The adequacy of fitted model was checked by analysis of variance (ANOVA). To study the main and interaction effects of the independent variables, response surface plots were constructed using 'PCP Disso V3' software (IIPC, PCP).

The mean vesicle size was in the range of 170–280 nm, and it was strongly affected by the selected variables. The multiple regression analysis of the mean particle size of the factorial batches revealed a good fit (r^2 = 0.9143). The positive coefficients of the terms for both the independent variables and the interaction X_2X_2 indicated a favorable effect on the mean vesicle size with cholesterol influencing more than Span 60. The X_2X_2, that is, cholesterol–cholesterol interaction effect pointed out a curvilinear relationship with the mean vesicle size (Figure 3).

The %EE ranged from 38% to 68%. A fair correlation (r^2 = 0.8473) was observed between the %EE and the independent variables. However, the independent variables exhibited a positive influence on the %EE, wherein Span 60 predominantly affected than cholesterol.

The percent in vitro drug deposition was in the range of 12–92% where the concentration of Span 60 displayed a negative effect as seen in Figure 4. As compared to the vesicle size and % EE, the percent in vitro drug deposition was influenced to a lesser extent by the variables of the study.

From the findings presented in Table 2, batch N8 niosomal dispersion having acceptable % EE, good drug deposition, and maximum electrokinetic stability was selected for further ex vivo skin deposition and stability study. The results of the study depicted in Figure 2 reveal that the percent drug deposition into rat skin was significantly higher for niosomal dispersion (60.62 ± 1.8%) and niosomal gel (63.18 ± 2.5%) as compared to the plain CPO solution (37.13 ± 3.9%) and the marketed preparation (38.4 ± 3.4%).

The stability study suggested that the prepared niosomes were stable at room temperature (25 ± 2°C) for 6 weeks and at 2–8°C for 10 weeks as there was no significant change in the mean vesicle size and percent EE of the niosomes on storage at the respective conditions (Table 4).

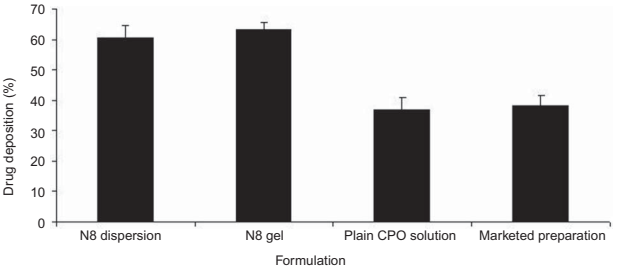

Figure 2. Ex vivo drug deposition study in rat skin at the end of 24 hours.

Table 4. Stability study.

Parameter	Initial (0 day)	25 ± 2°C/60% RH (6 weeks)	2–8°C (10 weeks)
d(0.9) nm ± SD[a]	200.66 ± 6.1	204.22 ± 3.8	202.24 ± 2.6
Percent EE ± SD[a]	67.89 ± 3.0	63.52 ± 2.9	66.86 ± 1.8

[a]Results of stability study of batch N8 expressed as mean ± standard deviation of three samples.

Discussion

Nonionic surfactant vesicles or niosomes are an attractive approach to deliver drugs topically. This investigation aimed at utilizing niosomes as carriers for maximizing the accumulation of the broad-spectrum antifungal, CPO in skin. Niosomes were prepared by ethanol injection method, and it yielded unilamellar spherical vesicles of sufficient stability.

Fourier transform infrared spectroscopy (FTIR) study performed to study the characteristic groups revealed slight shift in principal peaks of CPO in the niosomal formulation. As seen in Figure 6, the major stretching band in the region of 3000–3500 cm^{-1} of CPO corresponded to hydrogen bonding of associated water molecules and/or intramolecular hydrogen bonding between hydroxyl and carbonyl oxygen of CPO[19]. The narrowing of this band in the niosomal formulation spectrum indicated an absence of such intramolecular hydrogen bonding and liberation of the –N–OH group of CPO, which is essential for the antifungal activity[27]. The spectrum of CPO also showed stretching bands within the carbonyl

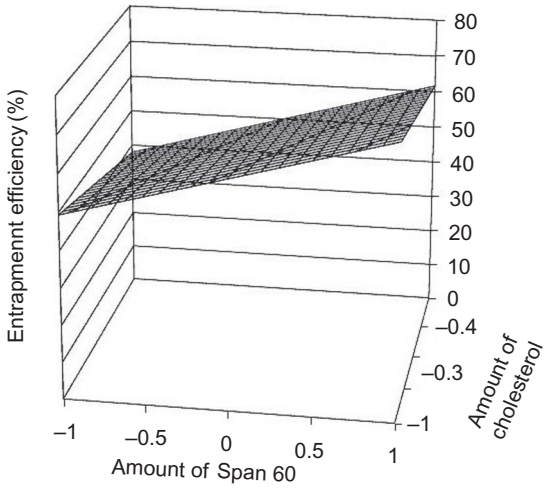

Figure 3. Effect of variables on the percent entrapment efficiency.

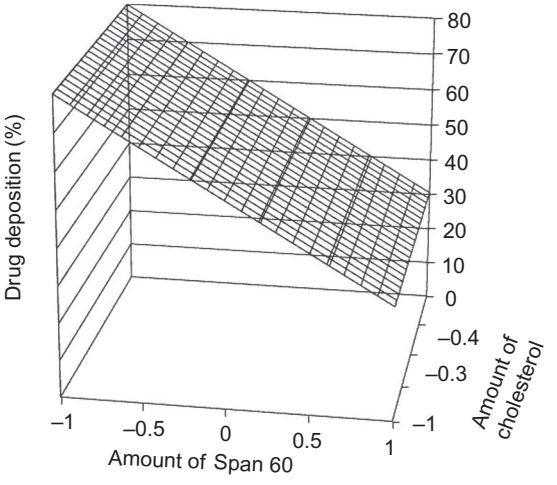

Figure 4. Effect of variables on in vitro drug deposition.

region (1635 cm^{-1}), which was slightly shifted to the higher side (1647 cm^{-1}) in the niosomal formulation. This might be attributed to the interaction of carbonyl group with the hydroxyl groups of Span 60 or cholesterol.

The effect of the identified variables in 3^2 factorial design on the characteristics and performance of the niosome was studied. The findings of the study are presented as the influence of the bilayer composition on the various parameters studied.

Effect of Span 60

CPO is an ion pair of weak acid ciclopirox [6-cyclohexyl-1-hydroxy-4-methylpyridin-2-(1H)-one] with aminoethanol possessing log *P* and the pK_a values of 2.3 and 7.2, respectively. At the pH of the system used for niosome preparation CPO existed in the ionized as well as in the unionized form. As seen in Table 3, increase in the Span 60 concentration increased the vesicle size and the EE. The positive influence of the nonionic surfactant on the mean vesicle size and percent EE can be explained by its possible effects on these ionized and unionized forms. The soluble ionized form is localized in the aqueous core of the niosomes leading to an increase in the vesicle size. The larger size of the drug-loaded vesicles compared with that of the blank niosomes provides evidence to the entrapment of the drug. The increase in the surfactant amount causes an increase in the volume of the enclosed water leading to an increase in the vesicle size and consequently the percent EE[28].

The hydrophobic unionized molecules have an affinity toward the bilayer microenvironment. The structure of CPO bears several groups capable of forming bonds with –OH groups of the bilayer composition, and as revealed in the FTIR study, CPO can associate with polar –OH group of Span 60 present at the aqueous–bilayer interface and at the same time driving the large hydrophobic cyclohexyl ring into the interior of the hydrophobic bilayer milieu. As a consequence, the bilayer thickness is increased resulting in increase in the vesicle size. The percent EE also shows a rise as the surfactant loading increases the number of sites for the possible interaction between the drug and the surfactant, supported by the FTIR study. Similar interaction was reported during the preparation of salidroside liposomes in which the interaction between the polar groups of salidroside and the lipid favored encapsulation of the drug[24].

The results of drug deposition study revealed that niosomes are promising carriers for cutaneous accumulation of CPO. Surfactants in formulations serve as penetration enhancer by raising the fluidity and reducing the barrier property of stratum corneum[29]. It was also postulated that niosomes fuse at the interface of the stratum corneum and that high local concentration in the vesicle bilayers generates a high thermodynamic activity of the drug in the upper part of the stratum corneum[30]. Fusion of the vesicles on the surface of the skin has been demonstrated using electron microscopy[31]. In this investigation too, the nonionic surfactant has a bearing on the skin deposition of the drug. The in vitro release profile of all the batches (data not shown) showed an initial rapid release followed by a constant release phase. The regression analysis of the drug deposition in skin predicted a negative coefficient for Span 60 (Table 3), suggesting a negative influence on the drug accumulation. Higher concentration of Span 60 did not favor drug cutaneous deposition. This can be attributed to the effect of the nonionic surfactant on the size of the vesicles whereby the percent drug deposition decreased with an increase in the size of the vesicles. Similar results were reported in the study on the effect of size of liposomes on dermal drug delivery[32]. It was

concluded that small vesicles of sizes <70 and <120 nm for lipophilic and hydrophilic substances, respectively, showed maximum accumulation in the deeper layers of the skin. Vesicles of larger sizes did not show appreciable drug deposition. The effect of size and lamellarity of niosomes on tretinoin skin accumulation has also been studied[15]. It was reported that UVs were always better carriers than multilamellar vesicles for the delivery of tretinoin locally to skin. Upon contact with skin the smaller UVs are less stable than larger multilamellar vesicles and disintegrate faster to obtain a close contact and material exchange between their constituents and skin lipids, leading to diffusion of free molecules as well as small membranal fragments into the stratum corneum[15].

Effect of cholesterol

Cholesterol, independently, exhibits the same effect as Span 60 on the particle size and the percent EE. It has been reported that the inclusion of cholesterol generally reduces the vesicle size due to reduction in the curvature of the vesicles due to interactive forces between Span 60 and cholesterol[33]. However, in this work, inclusion of cholesterol produced contrasting effect on vesicular size. Similar influence of cholesterol was observed during the preparation of salidroside liposomes[24]. The increase in vesicular size of CPO niosomes might be attributed to the increase in bilayer thickness because of the probable association of the 3-OH group of cholesterol with CPO. The increase in the EE caused by increasing cholesterol levels can also be ascribed to the aforementioned association.

The response surface plot of effect of variables on particle size (Figure 5) displayed a curvilinear effect of the interaction variable X_2X_2. The effect of this interaction appeared to be very complex. Possibly, at low and medium concentrations, cholesterol–cholesterol interaction caused the vesicle to reconstruct in a desirable conformation of the bilayer favoring reduction in the vesicle size. At still higher concentrations, cholesterol crystallites or aggregates might have formed in the bilayer with a consequent rise in vesicle diameter.

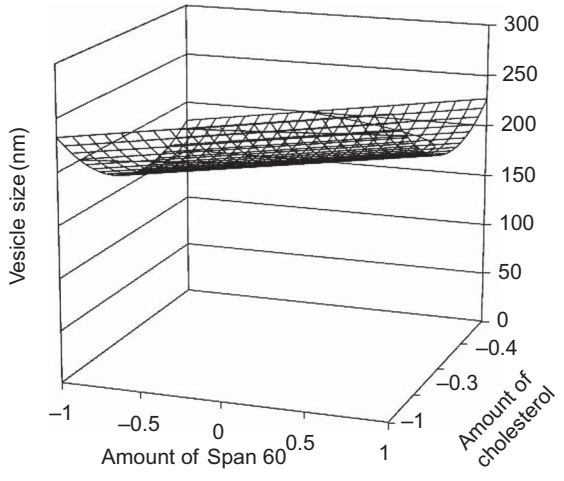

Figure 5. Effect of variables on the vesicle size.

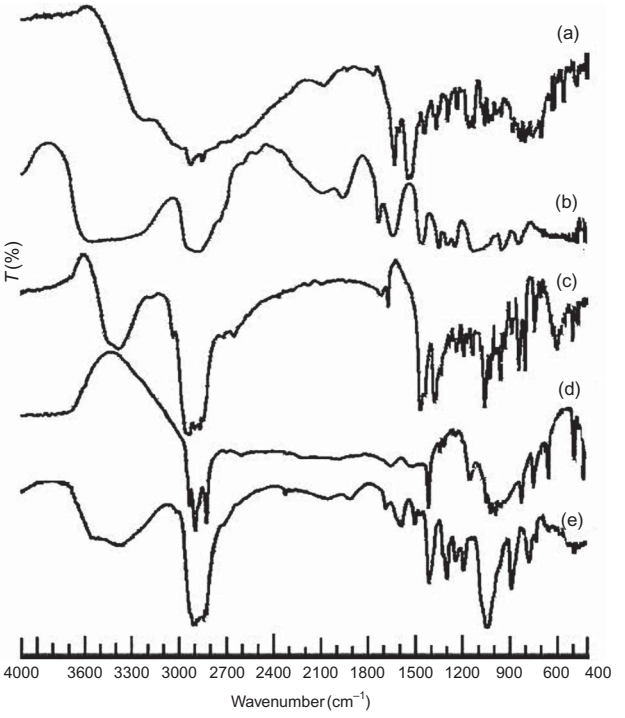

Figure 6. FTIR study of (a) Ciclopirox olamine, (b) Span 60, (c) Cholesterol, (d) diacetyl phosphate (e) Batch N8 niosomal dispersion.

Conclusions

This study revealed that the bilayer composition of the CPO niosomes, more precisely, the intermolecular interaction between the drug and the components of the bilayer governed the physicochemical properties and drug retention into the skin. Span 60 and cholesterol caused a proportionate rise in the vesicle size and encapsulation efficiency; however, a decline in the skin drug deposition was observed with an increase in Span 60 concentration. The niosomal delivery of CPO is expected to reduce the frequency of the application of the dosage form during the treatment regime. Thus, this study has proven niosomes as useful tool for the cutaneous delivery of CPO.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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