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Skin permeation enhancement by sucrose esters: A pH-dependent phenomenon

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Abstract

The purpose of the present study was to evaluate the effect of sucrose esters (particularly, sucrose laureate and sucrose oleate in Transcutol®) on the percutaneous penetration of a charged molecule as a function of ionization. We have investigated the influence of these sucrose esters on the in vitro diffusion profiles of lidocaine hydrochloride, a weak ionizable base ($pK_a = 7.9$), at different pH values, using porcine ear skin as the barrier membrane. As expected, lidocaine flux in the absence of an enhancer, increased from pH 5 to 9 with a corrresponding increase in the level of the unionized base. However, when skin was pretreated with 2% laureate in Transcutol (2% L-TC), drug permeation was higher at pH 5.0 and 7.0 than at 9.0. A different trend was observed in experiments with 2% oleate in Transcutol (2% O-TC), where skin flux was maximal at a more basic pH, when the degree of ionization is low. The results suggest that sucrose laureate enhances the penetration of the ionized form of the drug (12-fold greater flux relative to control), whereas sucrose oleate is more effective in promoting permeation of the unionized species. The structural properties of the sucrose esters as well as the degree of ionization of the drug are important characteristics affecting the transdermal flux of lidocaine.
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Keywords: Lidocaine hydrochloride; Sucrose esters; Enhancer; Percutaneous absorption

1. Introduction

In the last few decades, a variety of chemicals with skin permeation enhancing properties have been investigated for use in topical and transdermal systems (Walters, 1989; Walters and Hadgraft, 1993; Hsieh, 1994; Ganem-Quintanar et al., 1998a). Although these compounds have been the subject of numerous studies (Suhonen et al., 1999), the relationship between enhancer structure and the effect induced in the membrane have yet to be fully understood.

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Among known permeation enhancers, non-ionic surfactants have clearly been shown to influence the percutaneous absorption rate of many drugs (Sarpotdar and Zatz, 1986; Walters et al., 1988; Bialik et al., 1993; Thevenin et al., 1996). These compounds commonly act by altering the ordered structure of the intercellular region of the stratum corneum (Suhonen et al., 1999; Andega et al., 2001; Moser et al., 2001; Williams and Barry, 2004). However, differences in functional groups, hydrocarbon chain length and degree and position of unsaturation, can all influence the efficacy of these enhancers. For example, it is generally accepted that saturated C_{18} fatty acid compounds (e.g., stearic acid) are ineffective as absorption enhancers. Nevertheless, numerous reports agree on the disrupting effect of oleic acid, a monounsaturated C_{18} fatty acid, particularly on the stratum corneum lipid domain (Green et al., 1988; Potts et al., 1991; Aungst, 1995; Naik et al., 1995).

Moreover, the enhancing efficacy of a surfactant is not only dependent on its structure, but also on the physicochemical properties of the drug, the nature of the vehicle and whether the enhancer is used alone or in combination. Numerous drugs are weak organic electrolytes, the ionization of which depends on the delivery medium pH. Consideration of this pH, as well as of the drug dissociation constant (pK_a), allow some degree of absorption to be predicted. Katayama et al. (2001), demonstrated that the penetration enhancement of acidic drugs by 1-menthol–ethanol systems varied depending on the pH. In this case, the pH-dependency of the skin permeation enhancement was affected by the lipophilicity and the pK_a of the permeant. In addition, the nature of the vehicle may also play an important role in the surfactant–skin interaction. Recent studies have shown that diethylene glycol monoethyl ether (Transcutol®), a powerful solubilizing agent, increased significantly the percutaneous penetration of several drugs, particularly if used in combination with suitable surfactants (Watkinson et al., 1991; Touitou et al., 1994; Ganem-Quintanar et al., 1997). The presence of a cosolvent promotes the absorption of the surfactant into the skin, favouring its interaction with the stratum corneum (SC) lipids. Furthermore, it has also been reported that the addition of a cosolvent may lead to a change in the solubility of a solute, altering its thermodynamic activity and consequently the skin/vehicle partition coefficient (Mura et al., 2000).

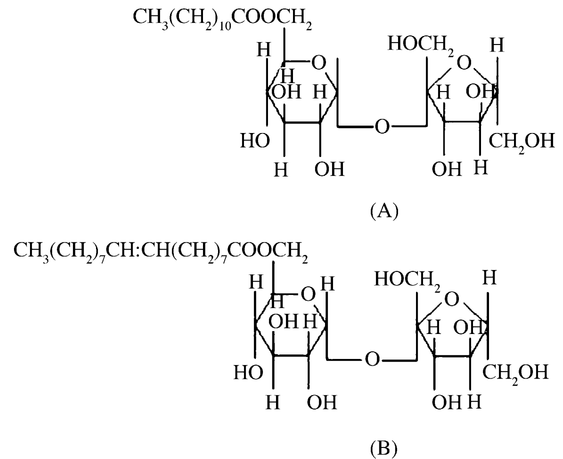

Fig. 1. Chemical structure of (A) sucrose laureate and (B) sucrose oleate.

Among non-ionic surfactants, sucrose fatty acid esters (SE) have been shown to temporarily alter membrane barrier properties. Previous studies (Ganem-Quintanar et al., 1998b) have shown that pretreatment with sucrose laureate enhances lidocaine permeation through porcine buccal mucosa. Although these compounds show many advantages as penetration enhancers (e.g., biodegradability and lack of toxicity), very few studies examining their mode of action have been reported. Ayala-Bravo et al. (2003), in an in vivo human study using infrared spectroscopy, demonstrated that sucrose oleate and sucrose laureate (Fig. 1) act on the SC lipids by fluidizing and extracting intercellular lipids. Furthermore, the authors found that SE were effective when combined with Transcutol, and importantly, that they lost their effectiveness above the critical micellar concentration. The present work investigates the effect of sucrose esters (laureate and oleate) in combination with Transcutol, on the permeation of lidocaine (a weak base) as a function of vehicle pH.

2. Materials and methods

Lidocaine hydrochloride was purchased from J.T. Baker (Phillipsburg, USA). Sucrose laureate (Ryoto Sugar Ester® L-1695) and sucrose oleate (Ryoto Sugar Ester® O-1570) were generously donated by Mitsubishi-Kasei Food Corporation (Tokio, Japan); butanol and glacial acetic acid were obtained from Merck

(Naucalpan de Juárez, México). Transcutol® was provided by Gattefosé (Saint-Priest, France). Aqueous solutions were prepared using deionized water supplied by a Milli-Q water purification system (Millipore Corp., Bedford, M.A.). Silica gel 60 thin layer plates, 10 cm × 20 cm were obtained from Merck (Darmstadt, Germany). All other chemicals were of at least analytical grade.

2.1. Solubility studies

An excess of lidocaine was added to a known volume of phosphate buffer solution at different pH values (5.0, 7.0 and 9.0). The mixtures were agitated in a water bath using teflon-coated magnetic bars at 37 ± 0.5 °C for 24 h. The suspensions were centrifuged at 2500 rpm for 15 min, and the L-HCl content was determined by spectrophotometry at 265 nm.

2.2. Distribution coefficient determination

Octanol/buffer distribution coefficients were obtained using phosphate buffer at pH 5.0, 7.0 and 9.0. Both organic and aqueous phases were mutually saturated for 1 h before use. Lidocaine and an equivalent amount of sucrose laureate or sucrose oleate were dissolved and stirred continuously for 24 h at 25 ± 0.5 °C. After phase separation, the lidocaine content was analysed in the organic phase by high performance thin-layer chromatography (HPTLC) following the procedures described in Section 2.4. The amount in the aqueous phase was determined by difference with respect to the initial amount of lidocaine. Experiments were performed in triplicate.

2.3. Skin permeation experiments

In vitro permeation studies with porcine ear skin were performed using Franz-type glass diffusion cells. Porcine tissue was chosen as a model for human skin, based on the similarity in permeability and morphology of their epithelia (Priborsky and Muhlbachova, 1990; Dick and Scott, 1992; Andega et al., 2001; Schmook et al., 2001). The skin was excised (353 μm thickness) with an electro-dermatome (Zimmer, Indiana USA), wrapped in aluminum film and stored in the freezer at −20 °C before use (no more than 1 week). Pieces of porcine skin were thawed in isotonic solution and placed as a barrier between the donor and receptor compartments of a diffusion cell. The area available for diffusion was 0.8 cm^2. The receptor phase (1.5 ml of phosphate buffer pH 7.0) was constantly stirred with a teflon-coated magnetic bar and maintained at 37 °C throughout the experiment. The donor side of the tissue was hydrated for 30 min with the receptor medium and then dried with a gauze-pad, before filling. Thereafter, 300 μl of a saturated solution of lidocaine in phosphate buffer at different pH values (5.0, 7.0 or 9.0) was applied to the surface of the skin. In the case of the enhancers, the skin was pretreated with 100 μl of 2% L-TC or 2% O-TC. These were maintained in contact with the membrane for 1 h and subsequently removed with a cotton swab. The donor compartment was filled with 300 μl of a saturated solution of lidocaine in phosphate buffer at either pH 5.0, 7.0 or 9.0. During the experiments (8 h), the receptor phase was replaced hourly with fresh buffer solution. At the end of the experiments, lidocaine was extracted by soaking the tissues in 5 ml of ethanol for 48 h at 37 °C. The extraction suspensions were centrifuged and the supernatant was membrane-filtered (0.45 μm, polypropylene micro-centrifuge tube filters, Whatman, Maidstone, England). Lidocaine content was analyzed using high performance thin-layer chromatography. Experiments were generally performed in sextuplicate.

The steady-state flux (J) of lidocaine was calculated from the slope of the linear portion of plots of cumulative amount in the receptor solution versus time. J is mathematically expressed as follows:

$$J = \frac{dQ/dt}{A} \quad (1)$$

where dQ/dt is the cumulative amount permeated per unit time and A is the diffusion surface area (0.8 cm^2). The apparent permeability coefficients (P_{app}) were calculated according to the following equation:

$$P_{app} = \frac{dQ/dt}{C_s A} \quad (2)$$

where C_s is the concentration of lidocaine in the buffer solutions.

Enhancement ratios were calculated according to the following expression:

$$ER = \frac{J_{(enh)}}{J_{(ctrl)}} \quad (3)$$

where $J_{(enh)}$ is the enhanced steady state flux and $J_{(ctrl)}$ is the flux of drug without the presence of enhancer.

2.4. HPTLC assay

The samples (aqueous receptors and lidocaine extracted from the tissue) were spotted on HPTLC plates (silica gel 60, 10 cm × 20 cm without concentration zone) using an Automatic TLC Sampler III (CAMAG, Muttenz, Switzerland). Plates were previously sprayed with tributilamine. Separations were carried out in developing chambers (CAMAG), presaturated with the developing solvent system consisting of butanol/glacial acetic acid/acetone (7:3:5). The solvent front was allowed to migrate to 4.5 cm above the origin. After drying the plates at 25 °C, they were scanned with a CAMAG TLC Scanner III at 265 nm, in the Refl–Abs mode. Calibrations curves were calculated on the basis of peak area measurements.

2.5. Data analysis

The data were expressed as mean ± S.D. The results were analyzed statistically using Student's t-test or analysis of variance (ANOVA). Significance was determined at $P < 0.05$. Duncan's separation of means procedure was used to determine those average values that differed significantly from the set of averages when a significant F-value was found.

2.6. Scanning electron microscopy of the skin

Porcine ear skin was introduced into a water bath at 60 °C for 1 min and the epidermal tissue was removed by hand. Epidermal sheets were then soaked in phosphate buffer (pH 7.0), 2% L-TC, 2% O-TC or Transcutol for 1 h. Skin samples of approximately 3 mm diameter were dried at room temperature for 2 days. The preparations were coated with gold particles (20 nm) by a Sputter Coater JFC-1100 (JEOL, Japan) and observed under a Scanning Electron Microscope JSM-25SII (JEOL, Japan), operating at 15 KV. The magnification adopted here was 1500×.

3. Results and discussion

The fraction of unionized lidocaine at pH 5.0, 7.0 and 9.0 was estimated in order to determine the influence of the degree of drug ionization on skin permeation enhancement. Mathematically, the fraction of unionized species for basic drugs is expressed as follows:

Table 1
Experimental octanol/buffer distribution coefficients for lidocaine through porcine ear skin at different pH values

pH	Experimental distribution coefficients ± S.D.	Unionized fraction (f_{un})
5.0	0.09 ± 1.6E−03	0.00
7.0	1.15 ± 6.6E−03	0.11
9.0	1.17 ± 4.3E−03	0.93

$$f_{(un)} = \frac{1}{1 + 10^{pK_a - pH}} \quad (4)$$

As expected, without enhancer, the highest steady state flux was determined at pH 9.0 when more than 90% of the drug is unionized (Tables 1 and 2). These results agree with those found in earlier investigations (Siddiqui et al., 1985; Kushla and Zatz, 1991; Valenta et al., 2000). This is consistent with the determined experimental distribution coefficients of lidocaine, which increase from pH 5.0 to 9.0 in accordance with the pH-partition theory (Table 1).

The cumulative lidocaine transport across untreated porcine ear skin as a function of pH is shown in Fig. 2. In the absence of enhancer, the highest amount of drug was transported at pH 9.0 when lidocaine is predominantly unionized, without a significant difference between data at pH 7.0 and 9.0 ($t = 2.14 < t_{0.05/2.5} = 2.45$). Nevertheless, although the total amount permeated at pH 7.0 (2.91 ± 0.14 mg) and 9.0 (3.27 ± 0.32 mg)

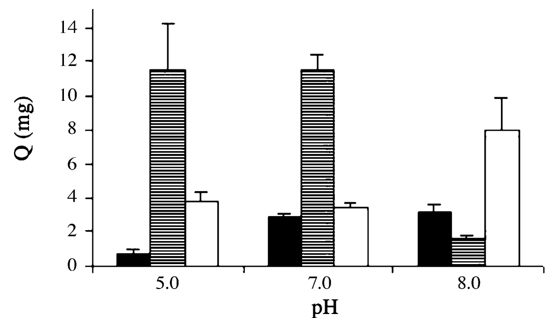

Fig. 2. Cumulative amount permeated (Q) of lidocaine per unit area of stratum corneum.(■) Control; (▤) 2% L-TC; (□) 2% O-TC. Each value represents the mean ± S.D. of six experiments.

Table 2
Apparent permeability coefficients (P_{app}) and steady state fluxes for lidocaine through porcine ear skin in the absence and in the presence of L-TC and O-TC

pH	Control		2% L-TC			2% O-TC		
	J	Papp	*J*	Papp	ER	*J*	Papp	ER
5.0	0.14 ± 0.03	1.55 ± 0.31	1.78 ± 0.52	18.46 ± 5.60	11.95 ± 3.62	0.55 ± 0.06	5.83 ± 0.65	3.77 ± 0.48
7.0	0.17 ± 0.10	1.81 ± 1.1	1.82 ± 0.35	19.58 ± 3.82	10.84 ± 2.11	0.58 ± 0.03	6.24 ± 0.31	3.45 ± 0.17
9.0	0.51 ± 0.14	5.65 ± 1.52	0.30 ± 0.02	3.34 ± 0.22	0.59 ± 0.04	1.36 ± 0.21	15.08 ± 2.30	2.67 ± 0.41

J: Flux (mg/h cm^2); Papp: apparent permeability coefficients (cm/h × 10^4); ER: enhancement ratio (lidocaine flux with enhancer/lidocaine flux without enhancer); control: untreated skin.

was very similar, and far greater than at pH 5.0 (0.83 ± 0.16 mg), the equivalent slopes at pH 5.0 and 7.0 yielded similar fluxes and permeability coefficients (Table 2). With respect to the skin permeation experiments with the enhancers, they were immensely affected by both pH and the type of sucrose ester. Moreover, the effect was dictated by the nature of the ester derivative, as shown in Fig. 2 and Table 2. When 2% L-TC was employed, drug permeation increased at pH 5.0 and pH 7.0, but was significantly decreased at pH 9.0. Actually, the analysis of variance ($F = 63.55$; $F_{0.05,2.8} = 4.46$) and Duncan's procedure revealed differences in the total amount permeated at pH 5.0 and 9.0, and at pH 7.0 and 9.0. Significant differences were found in the amount permeated after 2% L-TC treatment when compared to the control at pH 5.0 ($F = 55.54$; $F_{0.05,2.7} = 4.46$) and at pH 7.0 ($F = 271.52$; $F = F_{0.05,2.7} = 4.74$).

A completely different trend was observed when the skin was treated with 2% O-TC; the flux (*J*) was greater at pH 9.0, where the unionized species was predominant. Duncan's test showed only significant differences in the amount permeated after the treatment with 2% O-TC and the control at pH 9.0 ($F = 44.87$; $F_{0.05,2.10} = 4.10$).

In order to verify that the SE were able to selectively modify the permeability coefficient (P_{app}) of a specific lidocaine species, the ratio of the permeability coefficients of unionized (P_{un}) and ionized (P_i) forms was calculated (Fig. 3). P_{un} and P_i are, respectively, the slope and the intercept of the linear relationship between Papp/f_i (apparent permeability coefficient of lidocaine/ionized fraction) versus f_{un}/f_i. As can be seen, 2% L-TC treatment dramatically reduces the P_{un}/P_i ratio, which implies that the diffusion of the ionized species through the skin was significantly increased, and that the transport of the unionized form was not favoured. Subsequently to the 2% O-TC treatment, although P_{un}/P_i was lower than that for the control, it remained >1, suggesting that the passage of the unionized species was predominant.

Investigations from our own group (Ayala-Bravo et al., 2003) have shown that 2% L-TC, in contact with human skin, produces significant SC lipid extraction and fluidization. Therefore, insertion of the sucrose esters alkyl chain into the SC lipid bilayers is expected to provoke structural disorder of the intercellular lipids, allowing the passage of the drug through the skin. Membrane disordering may occur at two levels: (a) perturbation of the 'lipoidal domain' and (b) alteration of the polar regions. The results of several percutaneous penetration studies (Hatanaka et al., 1994; Yamashita et al., 1994; Sznitowska et al., 1998) have alluded to the presence of aqueous intercellular micro-channels within the lipoidal "matrix" comprising aqueous regions, which are formed by lipids with hydrophilic groups; if this is the case, we can assume that the

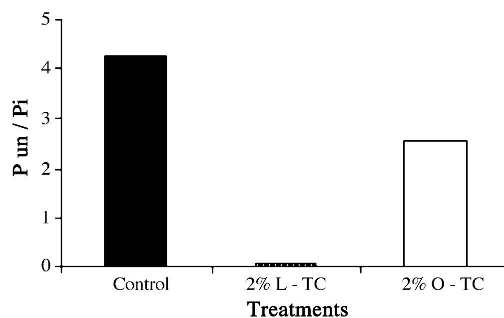

Fig. 3. Effect of 2% L-TC and 2% O-TC treatments on the apparent permeability coefficient of lidocaine. P_{un}/P_i: permeability coefficient of unionized form/permeability coefficient of ionized form.

structural disordering of these lipids increases the volume and number of micro-pores resulting in a greater penetration of ions. This theory can explain the enhanced passage of lidocaine at pH 5 and 7 when the skin was treated with 2% L-TC. Nevertheless, this disordering effect does not allow to explain the retarding effect on the passage of lidocaine at pH 9.0. The unexpected results found with 2% L-TC, may be compared with those reported by Walters et al. (1984), who suggested that the effect of 10-dodecyl-polyoxyethylene ether (a non-ionic surfactant) on nicotinic acid skin permeation was much greater for the anion (pH 4.7–5.0) than for the free acid (pH 4.3). When surfactant was employed, an increase in the permeability constants of the ionized species was observed. This may suggest that 10-dodecyl-polyoxyethylene ether preferentially promotes the transport of the ionized species of a drug through the skin.

It is known that the movement of ionizable drugs across membranes can also be facilitated by ion pair formation (IPF). However, the ability of IPF to influence the behavior of drugs depends strongly on the physicochemical properties of both the drugs and the counter ions (Valenta et al., 2000). Improved lipophilicity and transport by IPF can be achieved through hydrophilic ionizable drugs and suitable lipophilic counter ions (high lipophilicity, sufficient solubility, physiological compatibility and metabolic stability). In the present study, it is highly unlikely that the transport of lidocaine in the presence of SE depends on IPF, based on the fact that SE do not act as lipophilic counter ions. Furthermore, treatment of the skin with 2% O-TC increases the penetration of the drug at all pH values, including at pH 9.0, when lidocaine is not charged (Table 2).

Enhancer-drug and drug–SC interactions at different pH conditions must be studied, since they are crucial to clarify the exact mechanism of action of sucrose esters.

It is important to consider that the effect of SE can vary depending on the drug under study, the site of application, the characteristics of the animal models chosen for the experiments and the experimental conditions. It is interesting to note that the oleate moiety (O-1570) did not have the same effect as that previously observed with palatal and buccal (cheek) tissues (Ganem-Quintanar et al., 1998b). With respect to this, some authors (Chattaraj and Walker, 1995) have seen that the type of functional group present in the enhancer agent may have an influence on the extent of penetration enhancement. The efficacy of sucrose oleate may be related to its fatty acid *cis* double bond, which is known to increase lipid fluidity. The insertion of this molecule between the alkyl chains of the membrane lipids may strongly disrupt the polar head groups and the hydrophobic region, creating regions of disorder and therefore, increasing the passage of both ionized and unionized species (Table 2).

Francouer et al. (1990) suggest that enhanced transport of piroxicam ($pK_a = 1.8, 5.2$) induced by oleic acid is dependent on the increasing concentration of the ionized form in the donor phase, suggesting that diffusion occurs by a mechanism different from the classical pH-partition theory. DSC studies demonstrated that oleic acid reduces the transition temperatures and cooperativity associated with the phase properties of the SC lipid structure. Therefore, the increased permeability for the anion could be the result of diffusion across the phase boundaries or permeable interfacial “defects” (Francouer et al., 1990).

Although this fatty acid may alter the lipid structure leading to the passage of the polar species, the effect may also be dependent on the type of ion. In our study, the promoted transport of lidocaine by sucrose oleate was lower at pH 5.0, when the molecule was positively charged, unlike that reported for diffusion of the negatively charged piroxicam species.

As shown in Fig. 4, the highest average amount of lidocaine was extracted from the control experiments irrespectively of the solution’s pH. The analysis of variance and Duncan’s test showed only a significant difference ($F = 11.66$; $F_{0.05,2.10} = 4.10$) between the amounts

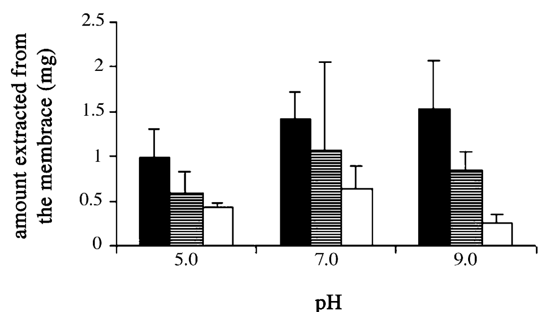

Fig. 4. Amount of lidocaine extracted from the tissue. (■) Control (buffer solution); (▤) 2% L-TC solution; (□) 2% O-TC solution.

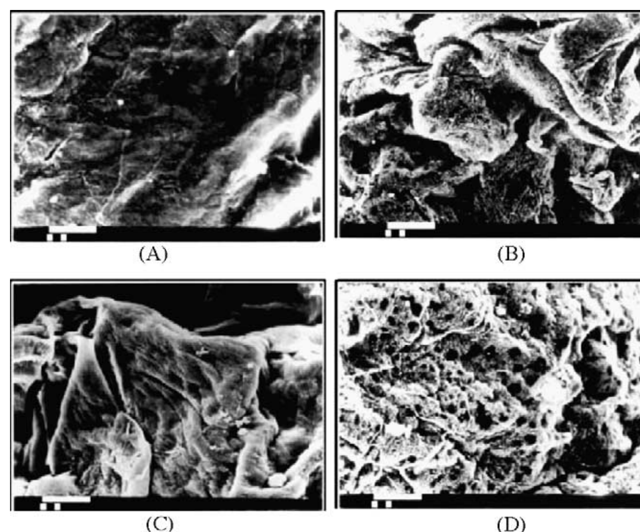

Fig. 5. Scanning electron micrographs of porcine ear skin surface corneocytes: (A) untreated skin; (B) skin treated with Transcutol for 1 h; (C) skin treated with 2% L-TC for 1 h; (D) skin treated with 2% O-TC for 1 h. Bar = 10 μm (1500×).

extracted from the tissue treated with 2% L-TC and 2% O-TC when compared to the control at pH 9.0 (Fig. 4). This may suggest that at pH 9.0, the presence of SE–TC in the membrane reduces the accumulation of free drug in the tissue.

In general, SE have shown a pH-dependent enhancement of lidocaine absorption across the skin. However, it should be mentioned that the efficacy of SE is also related to the nature of the vehicle. As mentioned above, the addition of a cosolvent promotes the penetration of a surfactant into the skin, favouring its interaction with the stratum corneum lipids. Transcutol has been used as a cosolvent because it can influence the partitioning behaviour of a drug or a co-enhancer into the tissue (Ganem-Quintanar et al., 1997; Mura et al., 2000). The penetration of the solvent can temporarily alter the barrier properties by the replacement of water molecules in the stratum corneum with those of TC (Zatz and Dalvi, 1983; Barry, 1987). Furthermore, the combination SE–TC at concentrations below the CMC was shown to be effective for enhancing 4-cyanophenol permeation across human SC (Ayala-Bravo et al., 2003). In order to determine the physical effect of SE and this cosolvent on the skin, a SEM study was performed. The visual appearance of corneocytes following application of different treatments is shown in Fig. 5. It can be clearly seen that the skin treated with TC was contracted, with respect to untreated skin, which is attributed to tissue dehydration. Transcutol is a hygroscopic solvent that can absorb water not only from the air, but also from the skin (change in vehicle composition) improving the skin penetration of certain drugs, by maximizing their thermodynamic activity due to a change in drug solubility (Ritschel and Hussain, 1988; Bialik et al., 1993; Ganem-Quintanar et al., 1997). When the skin was treated with SE–TC, the epithelium did not appear to be contracted, very probably due to the ability of the hydroxyl groups of the sucrose ring to form hydrogen bonds with water, thus preventing skin dehydration.

4. Conclusions

The results presented demonstrated that the diffusion of lidocaine, an ionizable molecule, significantly improved when the skin was pretreated with both 2% L-TC and 2% O-TC. However, the effect of the two esters on the penetration of the ionized and unionized forms is quite distinct. Sucrose laureate favoured the diffusion of the ionized species (pH 5.0 and 7.0) but reduced the passage of the uncharged base (pH 9.0). In contrast, sucrose oleate enhanced the permeation of both the ionized and unionized species of lidocaine,

albeit to a modest extent. The enhanced transport of ionic species across permeable interfacial boundaries, as may be created in the stratum corneum in the presence of amphiphilic enhancers, is an acknowledged phenomenon. However, the mechanism of selectivity exhibited by these sucrose esters remains to be elucidated. Clearly, the configuration of their alkyl chain length and level of unsaturation, the physical chemistry of the permeant, and carrier vehicle can play an important role.

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