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Ex vivo oral mucosal permeation of lidocaine hydrochloride with sucrose fatty acid esters as absorption enhancers

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Abstract

The ex vivo permeation of lidocaine hydrochloride, a model drug, was studied in two different regions of the oral mucosa: pig palate (keratinized) and cheek (non-keratinized). The enhancing effect of a series of sucrose fatty acid esters (nonionic surfactants), which have the advantage of reduced irritation potential relative to other enhancers, was investigated. Among the sucrose esters tested, an increase in the passage of lidocaine through buccal and palatal mucosae was observed only for sucrose laurate (L-1695) (enhancement ratio (ER) ~ 22 for buccal and ~ 14 for palatal mucosa). The other sucrose esters (S-1670, O-1570 and P-1670), did not show any promoting effect. The type of fatty acid sucrose ester, was found to be a key factor for promoting the absorption of lidocaine. The contribution of sucrose esters was compared with that of other enhancers, such as ethanol, oleic acid and Transcutol®. A significant enhancing effect was observed with oleic acid/hydroalcoholic solution, for both buccal and palatal mucosa (ER ~ 13 and ~ 61, respectively). However, there was no promotion when the hydroalcoholic solution was applied in the absence of oleic acid. A synergic effect between oleic acid and ethanol is very probable. A slight promoting effect was obtained when Transcutol/water (50:50) was used as the vehicle.

Keywords: Lidocaine; Oral mucosal enhancement; Nonionic surfactant; Sucrose ester; Fatty acid

1. Introduction

The oral mucosa offers a number of advantages not only as a local, but as a systemic drug delivery

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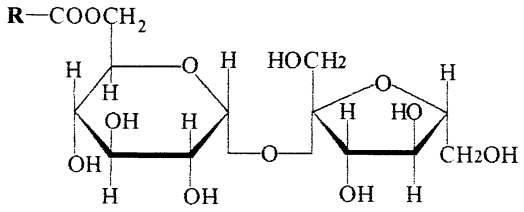

Fig. 1. Chemical structure of a sucrose monoester (R = fatty acid).

site. The absorption of numerous compounds through this tissue, has drawn the attention of many different research groups. However, most of the studies carried out in this field, had one aspect in common: the need to coadminister a penetration enhancer in order to improve drug absorption. The most commonly studied enhancers for oral mucosal application are non-ionic and ionic surfactants, and steroidal detergents (Aungst, 1996). The principal problem with formulations containing absorption enhancers, is that membrane irritation severely limits their clinical application. Typically, both cationic and anionic surfactants are more potent enhancers than non-ionic compounds, but they are also considered more toxic, as they can damage the permeability barrier at relatively low concentrations (Siegel and Gordon, 1985, 1986). Therefore, there is a need to find safe and effective new mucosal absorption enhancers.

In this respect, an interesting possibility is offered by sucrose fatty acid esters (SE), which are nonionic surfactants, with a sugar substituent, sucrose, as the polar head group (Fig. 1). An advantage of using SE as absorption promoters is reduced irritation potential relative to other enhancers, such as bile salts or sodium lauryl sulphate (Nakada et al., 1988). Furthermore, they are legally approved as food additives owing to their high safety. Being non-irritant to mucous membranes and skin, they are suitable not only for foods but also for medication and cosmetics (Mitsubishi-Kasei Food Corporation, 1987). Some physicochemical characteristics of the SE used in this study are shown in Table 1.

The purpose of this work was to compare the effects of a series of SE with different fatty acid moieties, and some vehicles normally used as promoter agents, such as ethanol, Transcutol® and oleic acid, on the in vitro rate of transfer of a substance, across oral mucosa. Two regions of pig oral mucosa were chosen, because of their different histological and permeability characteristics: the palate (keratinized) and the cheek (non-keratinized). Porcine tissue was chosen as a model for the human oral mucosa, based on the similarity in permeability and morphology of their epithelia (Merkle and Wolany, 1992). Lidocaine hydrochloride, typically used as a local oral mucosal anaesthetic, as well as an antiarrhythmic agent, administered intravenously for the management of ventricular arrhythmias, was chosen as a model hydrophilic drug, which has shown poor penetration through intact stratum corneum when administrated topically (Tachibana and Tachibana, 1993).

Table 1
Physicochemical characteristics of sucrose fatty acid esters (SE)

SE	Fatty acid [carbon skeleton]	HLB	Ester composition (%)		Solubility in water (%)	mp (°C)
			Mono ester	Di, tri, poly ester		
S-1670	Stearic acid [18:0]	16	75	25	0.1	50–56
O-1570	Oleic acid [18:1(Δ^9)]	15	70	30	10	25–45
P-1670	Palmitic acid [16:0]	16	80	20	0.1	45–54
L-1695	Lauric acid [12:0]	16	80	20	>50	35–50

Mitsubishi-Kasei Food Corporation, 1987.

Table 2
Flux of lidocaine across buccal and palatal mucosa with different vehicles

Vehicle[c]	Flux ± S.D.[a] (mg/cm^2/h)		ER[b]	
	Buccal	Palatal	Buccal	Palatal
Transcutol®/water (50:50)	0.3932 ± 0.0393	0.2959 ± 0.1230	2.34	10.97
Ethanol/water (50:50)	0.2104 ± 0.0202	0.0934 ± 0.0255	1.25	3.46
Oleic acid/ethanol/water (1:49:50)	2.1552 ± 0.1609	1.6498 ± 0.3283	12.85	61.20
L-1695 (1.5% w/v)	3.7269 ± 0.9516	0.3917 ± 0.0383	22.22	14.53
P-1670[d] (1.5% w/v)	0.2001 ± 0.0279	0.0272 ± 0.0102	1.19	1.01
S-1670[d] (1.5% w/v)	0.1261 ± 0.0226	0.0307 ± 0.0129	0.75	1.14
O-1570 (1.5% w/v)	0.2087 ± 0.0135	0.0301 ± 0.0205	1.24	1.12
Water (control)	0.1677 ± 0.0090	0.0269 ± 0.0118	1	1

[a] S.D., standard deviation.
[b] ER, flux of penetrant from test solution/flux of penetrant from control solution (Kushla and Zatz, 1991).
[c] All solutions containing 10% (w/v) of lidocaine hydrochloride.
[d] At room temperature they were incompletely soluble, although clear solutions were attained at 37°C.

2. Materials and methods

2.1. Chemicals

All chemicals were of analytical grade and used as obtained from the manufacturer, without further purification. Lidocaine hydrochloride (lid-HCl), oleic acid and acetone were purchased from Sigma (St. Louis, MO); butanol, glacial acetic acid, ethanol and sodium chloride were obtained from Fluka (Buchs, Switzerland); Transcutol® was kindly provided by Gattefossé (Saint-Priest, France). Sucrose stearate (Ryoto Sugar Ester® S-1670), sucrose oleate (Ryoto Sugar Ester® O-1570), sucrose palmitate (Ryoto Sugar Ester® P-1670) and sucrose laurate (Ryoto Sugar Ester® L-1695), were a generous gift from Selectchemie AG (Zürich, Switzerland). Aqueous solutions were prepared using deionized water supplied by a Milli-Q water purification system (Millipore, Bedford, MA).

2.2. Animals

Palatal and buccal (cheek) tissues from male or female pigs were obtained from the slaughterhouse and transported in isotonic saline solution. After detachment from the bone, the submucosal tissue of the palate was removed with a manual dermatome. The buccal epithelium was carefully isolated with scissors. The tissues were then kept at −20°C before use (no more than 2 weeks).

2.3. Permeation experiments

Pieces of palatal or buccal tissue were defrosted in isotonic saline solution and clamped into position between the donor and the receptor compartment of a static vertical diffusion cell, based on the Franz design (exposed area = 0.78 cm^2). The receptor medium, consisting of 2.2 ml of isotonic saline solution, was maintained at 37°C by a circulating water pump, and constantly stirred with a teflon-coated magnetic bar. The donor side of the tissue was hydrated for 30 min with the receptor medium and subsequently dried with a cotton swab. The donor was then filled with 1 ml of the solution under test. The test solutions contained lid-HCl 10% (w/v) in different vehicles (Table 2). Samples of 100 μl were withdrawn each hour from the receptor compartment over a period of 8 h (replacing them with an equivalent volume of fresh solution). The results were corrected for dilution effect. The steady-state flux of lid-HCl was calculated from the slope of the linear portion of plots of cumulative amount penetrated versus time. At the end of the experiments, lid-HCl was extracted overnight at room temperature, by soaking the tissues in 2 ml of 20% (w/v) sodium chloride solution, and subsequently in 2

ml of distilled water. The extraction suspensions were centrifuged and the supernatant filtered through a membrane filter (0.45 μm, polypropylene micro-centrifuge tube filters, Whatman, Maidstone, England). All the samples were analysed by high performance thin-layer chromatography (HPTLC) for lid-HCl content. Experiments were generally performed in hextuplicate.

2.4. High performance thin-layer chromatography (HPTLC)

First, 2 μl of the samples (aqueous receptors, lid-HCl extracted from the tissue and unpenetrated donors at the end of the experiment), was spotted on HPTLC plates (silica gel 60, 10×20 cm without concentration zone), obtained from Merck (Darmstadt, Germany), using a Linomat IV (CAMAG, Muttenz, Switzerland). Separations were carried out in developing chambers (CAMAG), presaturated with the developing solvent system, consisting of butanol/acetone/glacial acetic acid/water (7:5:2:1 v/v). The solvent front was allowed to migrate to 4.0 cm above the origin. After drying the plates at 60°C on a hotplate (CAMAG) for 40 min, they were scanned with a CAMAG TLC Scanner II at 225 nm, in the Refl-Abs mode, and the signals were integrated with a CAMAG SP4290 integrator. Standard solutions were applied on each plate for mass calibration purposes. Total recovery of lid-HCl typically exceeded 90%.

3. Results and discussion

The cumulative profiles of drug amount diffused across pig buccal and palatal mucosae into the receptor compartments, from the different vehicles, are shown in Figs. 2 and 3. As expected, all the vehicles gave higher fluxes for buccal than for palatal mucosa, because of the presence of a keratinized layer in the case of palatal mucosa, which confers to this region, a more efficient permeability barrier. A marked increase in both the buccal and palatal permeation of lid-HCl was observed with the oleic acid/hydroalcoholic solution. In fact, as shown in Table 2, among the vehicles tested, the greatest enhancement effect for palatal mucosa was obtained with this solution. The omission of oleic acid from the hydroalcoholic solution, i.e. the use of a 50% ethanol/water mixture, led to a dramatic decrease in the passage of lid-HCl, obtaining fluxes similar to those from the pure aqueous solution. This may suggest a synergic action between oleic acid and ethanol, an effect that has been already reported (Francoeur

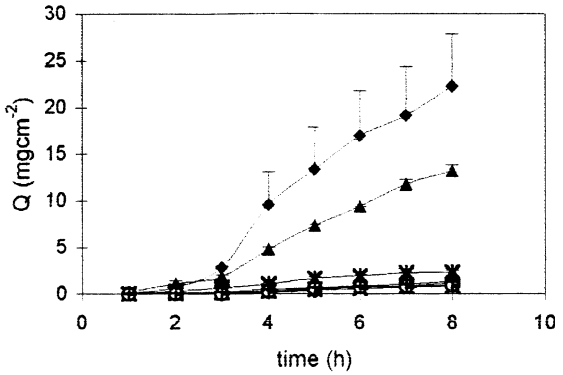

Fig. 2. Permeation profile of lidocaine through pig buccal mucosa. (◇) P-1670; (▲) oleic acid/ethanol/water; (◆) L-1695; (×) S-1670; (∗) Transcutol/water; (○) ethanol/water; (+) O-1570; (−) control. In some cases, S.D. are smaller than symbols. The profiles of (◇), (○), (×), (+), (−) are superposed.

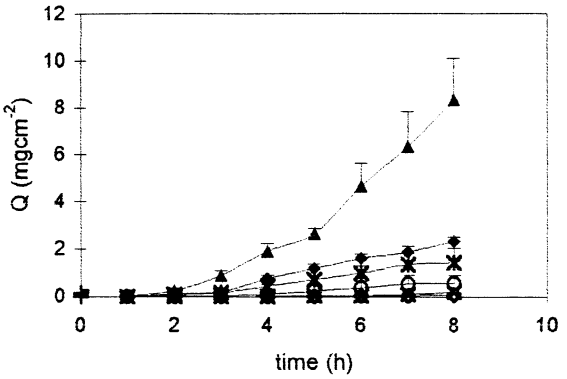

Fig. 3. Permeation profile of lidocaine through pig palatal mucosa. (◇) P-1670; (▲) oleic acid/ethanol/water; (◆) L-1695; (×) S-1670; (∗) Transcutol/water; (○) ethanol/:water; (+) O-1570; (−) control. In some cases, S.D. are smaller than symbols. The profiles of (◇), (×), (+), (−) are superposed.

et al., 1990; Clancy et al., 1994). Different studies have suggested that the insertion of ethanol between endogenous lipids may have a 'fluidisation' effect, provoking an increase in structural disorder. This effect has been reported to occur at low ethanol concentrations (Kim et al., 1992). An increasing extraction of membrane lipids with increasing ethanol concentration, has also been reported (Kurihara-Bergstrom et al., 1990; Kim et al., 1992; Manabe et al., 1996). In fact, lipid extraction has been proposed by some authors (Bommannan et al., 1991), as the major mechanism by which ethanol enhances permeation. In previous work carried out in our laboratory, we found that a 50% ethanolic solution, in contact with the palatal mucosa, produced significant extraction of the membrane lipids, even for short contact times (e.g. 10 min) (Ganem-Quintanar et al., 1998). However, according to our results, even though ethanol may alter the lipid composition of the membrane by removing a substantial percentage of the total lipids, this effect was not enough, in the case of the ethanol/water solution, to improve significantly the passage of lid-HCl. It has been previously found that oleic acid/ethanol treatment led to extensive lipid extraction (Clancy et al., 1994), but we do not believe that this was the principal action of the oleic acid/hydroalcoholic solution. The efficacy of oleic acid has been typically related to its *cis* double bound which increases lipid fluidity, by preventing the formation of well-ordered compact structures (White et al., 1988; Gay et al., 1989). The insertion of oleic acid between the alkyl chains of the membrane lipids may form separate domains, creating regions of disorder, due to differences in lipid packing (Clancy et al., 1994; Tanojo et al., 1997). In human buccal epithelial cells, oleic acid has also been shown to disrupt strongly the polar head group and the hydrophobic region of the membrane lipids (Turunen et al., 1994). This effect, may be increased by the presence of ethanol, which was reported (Francoeur et al., 1990) to increase the amount of oleic acid taken up by the stratum corneum and silastic membranes, reaching a maximum value when a 40% ethanolic solution was used. Penetration enhancement may result from diffusion of the drug across these fluid domains or the permeable interfacial 'defects' (Clancy et al., 1994; Tanojo et al., 1997). Transcutol/water (50:50 v/v) was used as vehicle because it has been previously found (Ganem-Quintanar et al., 1997), that Transcutol can influence the partitioning behaviour of a drug because it penetrates into the tissue, and would favour the permeation of a drug due to its own passage. Transcutol produced a greater enhancement effect through palatal (ER = 10.97) than through buccal mucosa (ER = 2.34) (Table 2).

Nakada et al. (1988) found that SE having an HLB between 11 and 16 were effective in increasing the absorption of human calcitonin through rat buccal mucosa. Therefore, for this study we chose SE with similar HLB values between 15 and 16 (Table 1). The results show that the chain length of the fatty acid moiety of the sucrose esters, was an important factor for promoting the absorption of lid-HCl. In previous studies, it has been found that among the homologous series of saturated straight-chain fatty acids, lauric acid (C_{12}) was effective in promoting the absorption of drugs, e.g. propranolol through hamster cheek pouch (Coutel-Egros et al., 1992) and insulin through rat oral mucosa (Aungst and Rogers, 1989). Longer ($C_{>14}$), as well as shorter fatty chains (C_6–C_{10}) were generally less effective than the medium-chain fatty acids (Ogiso and Shintani, 1990). Previous structure/effect studies of surfactants have shown that maximal effects were attained with adjuvants having lauryl hydrophobic groups (García Domínguez et al., 1977; Aungst and Rogers, 1989). Peak surfactant enhancement effects for lidocaine were reported at alkyl chain lengths of 12–14 carbons (Kushla and Zatz, 1991). As shown in Figs. 2 and 3 and in Table 2, among the series of SE tested, only sucrose laurate (L-1695) enhanced lid-HCl permeation through buccal mucosa (ER = 22.22), obtaining a 2-fold greater flux than with the oleic acid/hydroalcoholic solution. In contrast, L-1695 was less effective in enhancing lid-HCl passage through palatal mucosa (ER = 14.53). Sucrose stearate (S-1670), sucrose palmitate (P-1670) and sucrose oleate (O-1570), did not show any promoting effect, either in buccal or palatal mucosa. These results were not in accord with those of Nakada

et al. (1988), who studied the absorption of human calcitonin in rat oral mucosa in vivo. The authors did not find any promoting effect with L-1695, but observed a marked effect with P-1670. However, it should be considered that the effects of sucrose esters can vary depending, on the drug being studied, the site of application, the particular differences among the animal models chosen for the experiments and the experimental conditions (e.g. in vitro or in vivo studies). It is interesting to note that the oleate moiety of sucrose oleate (O-1570), did not have the same effect as that observed with the free fatty acid. As mentioned above, no enhancement effect was observed with this additive. In this respect, some authors have previously observed that the type of functional group present in the enhancer agent, may have an influence on the extent of penetration enhancement. For example, the replacement of the carboxyl group by either a hydroxyl group (e.g. oleyl alcohol), a methyl ester group, or the use of sodium salts (sodium oleate) brought about a decrease in the enhancing effect (Yamada and Uda, 1987). It is known that sucrose esters are hydrolysed to sucrose and fatty acid under physiological conditions (Berry and Turner, 1960). However, we cannot be certain that this transformation could take place in our in vitro experiments. Furthermore, as mentioned above, it may also be that there is the possibility of a synergic effect between ethanol and oleic acid (this was not tested for in the case of sucrose oleate).

Extraction from the tissue at the end of the experiment showed a maximum lid-HCl content for the vehicles that produced the greatest enhancement effects, i.e. oleic acid/hydroalcoholic solution and L-1695 (Fig. 4). A curious observation was that the amount of lid-HCl found in the tissue with L-1695 was about twice for palatal than for buccal mucosa. This is interesting, considering that the flux of lid-HCl with this additive was about 10-fold smaller for palatal than for buccal mucosa (Table 2). This may suggest a depot effect with L-1695 in the palatal mucosa, probably due to the presence of the stratum corneum, which may retard the passage through the membrane. It was determined that when using L-1695, about 16% of the total amount of lid-HCl

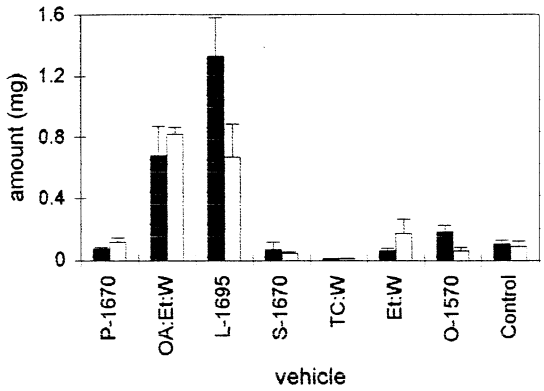

Fig. 4. Lidocaine extracted from the tissue. (■) Palatal mucosa; (□) buccal mucosa. OA:Et:W = oleic acid/ethanol/water; Et:W = ethanol/water; TC:W = Transcutol/water.

found in the tissue remained in the stratum corneum, against only about 7% in the case of oleic acid/hydroalcoholic solution. Therefore, it might be possible that the presence of surfactant in the tissue minimises the energy barrier of the partition step, promoting in this way the penetration of a greater amount of drug into the tissue.

In general, surfactants have shown a concentration-dependence in improving the absorption of substances across the oral mucosa (Siegel and Gordon, 1985, 1986). This is dependent on different variables, among them concentration. Therefore, the effect of concentration of L-1695 on the passage of lid-HCl was also investigated. Three concentrations were compared: 0.15, 1.5 and 15%

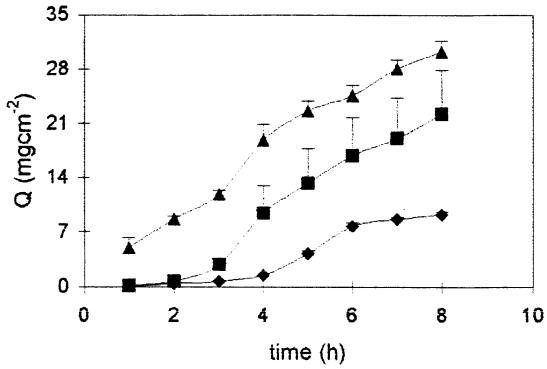

Fig. 5. Influence of L-1695 concentration on lidocaine permeation across buccal mucosa. (◆) 0.15% ($t_{lag} \sim 3.5$ h); (■) 1.5% ($t_{lag} \sim 1.1$ h); (▲) 15% ($t_{lag} \sim 0$ h).

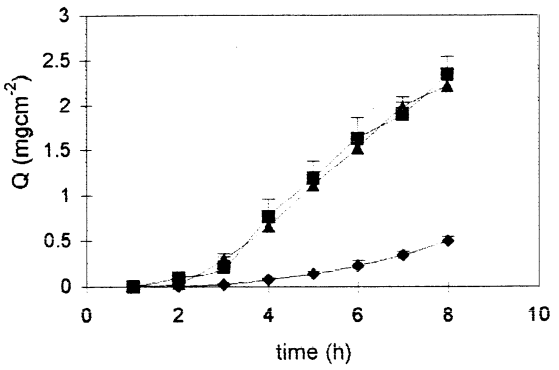

Fig. 6. Influence of L-1695 concentration on lidocaine permeation across palatal mucosa. (◆) 0.15%; (■) 1.5%; (▲) 15%.

w/v. As shown in Figs. 5 and 6, there was only a small increase in flux for both buccal and palatal mucosae, at a concentration of 0.15%. Indeed, the enhancement effect for palatal mucosa was almost negligible at this concentration ($ER_{(0.15\%)} = 2.60$; see, $ER_{(1.5\%)} = 14.53$; $ER_{(15\%)} = 12.96$). There was no statistically significant difference ($0.05 < p$) in the flux between the sucrose ester concentrations of 1.5 and 15% for palatal mucosa. Thus, no further increase in lid-HCl flux through palatal mucosa was obtained with the 10-fold increase in surfactant concentration (Fig. 6). On the contrary, as shown in Fig. 5, the cumulative amount permeated through buccal mucosa was significantly different at every sampling point, increasing with the concentration of surfactant. It is noteworthy that the same permeation profile was obtained for the three concentrations, with a progressive decrease in the lag time, which was negligible at 15% w/v surfactant. This increase in the passage of lid-HCl with surfactant concentration should be considered carefully, because it is difficult to distinguish between an enhancement effect and an enhancement due to a toxic effect, mainly in excised tissue which has decreased vital functions in relation to in vivo situations.

The results of the present study showed that, in the presence of surfactants such as SE, particularly L-1695, the in vitro oral mucosal absorption of lid-HCl was significantly enhanced. Nevertheless, this does not mean that L-1695 is the only SE effective via the oral mucosa, effectiveness depends on different factors, such as concentration, vehicle, and the type of drug. However, animal species and anatomical application sites are also factors that must be considered. The interaction of SE with biological membranes and with drugs merits further investigation.

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