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Comparison of the effects of various transmucosal absorption promoters on buccal insulin delivery

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Summary

We have evaluated the effects of various classes of transmucosal and transdermal absorption promoters on buccal insulin absorption in rats. Insulin absorption was estimated from the cumulative response of plasma glucose concentrations and by comparison to an i.m. dose/response curve. In the absence of an absorption promoter, buccal insulin was less than 4% as effective as i.m. insulin. All steroidal detergents examined as absorption promoters markedly improved buccal insulin absorption, using aqueous vehicles containing 5% adjuvant. Concentrations greater than 1% were required. The non-ionic surfactant, laureth-9, was also an effective absorption promoter and was effective at lower concentrations. Ester non-ionic surfactants had no effects. The effect of pH was evaluated for sodium fusidate and laureth-9 vehicles, and with both adjuvants buccal insulin absorption was lower at pH 5.4 than at pH 3.4 or pH 7.4. Other effective absorption promoters included sodium lauryl sulfate, sodium laurate (at pH 8.9), palmitoyl carnitine, and a lauric acid/propylene glycol vehicle. With the most effective absorption-promoting vehicles, buccal insulin was one-fourth to one-third as effective as i.m. insulin.

Introduction

Transmucosal delivery (e.g. nasal, rectal, buccal, sublingual) has been shown to be useful for peptide and protein drugs because the oral bioavailability of these drugs is usually negligible and there is a need for alternatives to injections. Transmucosal delivery is especially germane for drugs that are administered chronically and by the patient. Insulin typifies these attributes, and transmucosal insulin by the nasal and rectal routes has shown promise in initial clinical trials (Moses et al., 1983; Pontiroli et al., 1982; Yamasaki et al., 1981). One of the problems confronting transmucosal delivery of proteins and peptides is that bioavailability may be low because of metabolism at the absorption site or because of poor membrane permeability. Therefore, there exists a need for methods to improve transmucosal bioavailability by inhibiting metabolism or by increasing membrane permeability. A further advantage of transmucosal delivery, in contrast to oral dosing, is that the effects of absorption promoters can be localized to a small area.

The majority of previous work on transmucosal absorption enhancers has focused on the nasal

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and rectal routes. However, administration via the buccal mucosa may have certain advantages over nasal or rectal dosing. Rectal dosage forms are generally not well accepted in the U.S. Nasal drug administration raises concerns about local toxic effects, including slowed ciliary movements (Hermens and Merkus, 1987) and irritation caused by absorption enhancers (Hersey and Jackson, 1987). In addition to the patient acceptance and local toxicity considerations, there are also differences among the nasal, rectal, and buccal absorption sites in membrane morphology. The buccal membrane is a stratified squamous epithelium, similar to skin, wherein the intercellular spaces are filled with a matrix of cellular extrusion products. In contrast, the nasal and rectal epithelia are single cell layers with tight junctions providing the barrier to paracellular diffusion. As a consequence of these morphologic differences, there are differences in the effects of absorption promoters on these membranes. We previously showed that the non-ionic surfactant, laureth-9, markedly increased nasal, rectal, and buccal insulin absorption in rats, but sodium salicylate and disodium EDTA were more specific for enhancing rectal absorption (Aungst and Rogers, 1988). Sodium glycocholate increased insulin absorption after nasal, rectal, and buccal administration (Aungst et al., 1988). An adhesive patch containing a core of 10% sodium glycocholate in cocoa butter has been administered buccally to dogs, but the percentage of insulin absorbed was only about 0.5% relative to i.m. (Ishida et al., 1981). But there have been few other studies evaluating the effects of transmucosal absorption enhancers on the oral mucosa. Therefore, we have examined the effects of various adjuvants on buccally administered insulin in rats. The goals were to determine which adjuvants are the most potent absorption promoters for buccal insulin and to compare structure/activity relationships for buccal absorption promoters with literature data for other mucosal membranes. The adjuvants selected for evaluation were from various classes of known transmucosal absorption enhancers (bile salts and non-ionic and ionic surfactants), as well as agents not in these classes. In addition, some previously unreported penetration enhancers were evaluated. We also evaluated non-aqueous vehicles, as well as absorption promoters which have been more commonly used to affect skin permeability.

Materials and Methods

Materials

Studies were performed using bovine insulin (Sigma Chemical Co.) of 22-24 I.U. per mg activity and approximately 0.5% zinc. The adjuvants were from the following sources: sodium glycocholate, sodium deoxycholate, sodium fusidate, sodium lauryl sulfate, sodium laurate, lauric acid, glyceryl monolaurate, octoxynol-9 (polyoxyethylene (9) octyl phenyl ether), palmitoyl-D,L-carnitine chloride, laureth-9 (polyoxyethylene (9) lauryl ether), laureth-4 (polyoxyethylene (4) lauryl ether), L-α-phosphatidylinositol (crude, from soybean), L-α-phosphatidylcholine (type IV-S, from soybean), and hyaluronidase (type I-S, from bovine testes) (Sigma); CHAPS (3-(3-cholamidopropyl)-dimethylammonio-1-propanesulfonate) (Pierce); BigCHAP (*N*,*N*-bis-(3-D-gluconamidopropyl)-cholamide) (Calbiochem); PEG-4 laurate (Emerest 2620, Emery); PEG-8 laurate (Lipopeg 4L, Lipo); polysorbate 20 (Tween 20) and sorbitan laurate (Span 20) (ICI); propylene glycol laurate (Pfaltz and Bauer); cocomorpholine (Baircat NCM, Lonza); lauroamphoglycinate (Monateric LMM-30) and lauramidopropyl betaine (Monateric LMAB) (Mona); 6-aminocaproic acid (Aldrich); polyacrylic acid (Carbopol 934P, B.F. Goodrich); chondroitinase ABC (ICN Biomedicals); z-Gly-Pro-Leu-Gly-Pro (Z = carbobenzoxy) (Serva); propylene glycol N.F. (Fisher); N-methylpyrrolidone (M-Pyrol, GAF); decylmethylsulfoxide (Wateree); dimethylsulfoxide (EM Science).

Methods

All vehicles were prepared by first dissolving or dispersing the adjuvant in the solvent, adjusting the pH if necessary, and then adding the insulin with the vehicle warmed to approximately 40 °C. Most adjuvants were evaluated using 0.1 M phosphate buffer at pH 7.4 as the solvent. Laureth-9 and sodium fusidate were also administered in vehicles at pH 3.4 and pH 5.4. Several water-

insoluble adjuvants were tested using various non-aqueous vehicles which were also prepared by first dissolving the adjuvant and then insulin. The vehicles were prepared to contain adjuvants on an equal % concentration basis, but molar concentrations are reported in the tables for comparison of the most effective adjuvants. Some adjuvants which were effective in enhancing insulin absorption at 5% concentrations were also tested at lower concentrations. Among the miscellaneous adjuvants evaluated were polyacrylic acid, enzymes, and a peptide. These were administered in concentrations less than 5%.

Male Lewis rats (Charles River) were fasted at least 16 h before dosing. The esophagus was surgically ligated, under ether anesthesia, to prevent swallowing of the dosing solution. After a 1.5–2.5 h recovery period the rats were anesthetized with urethane (700 mg/kg, i.p.). A predose blood sample was taken and insulin was administered using a microliter syringe. The dosing volume was 0.2 ml/kg. The jaws were held closed and the rats were maintained in a prone position. The anesthesia, small dosing volume, and esophageal ligation minimized leaking of the dosing solution from the buccal cavity. Serial blood samples (0.3–0.4 ml) were collected at 0.25, 0.5, 1, 1.5, 2, 3, and 4 h by cutting the tip of the tail and were anticoagulated with heparin. Plasma was separated and frozen. Plasma glucose determinations were made on an autoanalyzer, using a method based on the phosphorylation of glucose by hexokinase.

Data analysis

The method for calculating the efficacy of buccally administered insulin, relative to i.m. insulin, was described previously (Aungst et al., 1988). For each rat, plasma glucose concentrations were expressed as a percentage of the initial (predose) glucose concentration. These were plotted vs time, and the area between the 100% baseline and the glucose concentration (% of initial) vs time curve was calculated from 0 to 4 h. The log dose vs response curves for i.m. insulin were reported before (Aungst et al., 1988). Those rats were treated as these were, including the esophageal ligation. The response was a linear function of log dose, within a limited range (0.125 U/kg to 5 U/kg i.m. doses). In some cases where very effective promoters of buccal insulin absorption were administered, the normally administered dose (50 U/kg) gave a response outside this linear range, so lower doses were administered. All data presented here are expressed as the percentage efficacy of buccal insulin relative to i.m. insulin. There were at least 6 rats in each treatment group, and the data represent mean ± S.E.M.

Results

Buccal insulin efficacy in the absence of coadministered absorption promoters was very low relative to i.m. insulin. At 10 U/kg and 50 U/kg doses, using pH 7.4 solutions, buccally administered insulin was 3.6 ± 2.8% and 0.7 ± 0.3%, respectively, as effective as i.m. insulin. Several steroidal detergents were evaluated as buccal absorption promoters. Their structures are shown in Fig. 1. These adjuvants were initially tested using 50 U/kg insulin doses. But in the presence of absorption promoters the response to absorbed insulin was in the plateau region when compared to an i.m. insulin dose/response curve, so lower doses were given. At 5% (w/v) concentrations all significantly improved the efficacy of buccal 10 U/kg insulin doses (Table 1). On a molar concentration basis, CHAPS and BigCHAP may be the most potent of this class of enhancers. The effects of sodium glycocholate were examined using a range of insulin doses. The values of relative efficacy, which are indicative of buccal bioavailability, were similar for 5, 10, and 20 U/kg insulin doses, but that for the 2 U/kg dose was lower. The response after the 2 U/kg dose was approaching the minimum detectable level. The effects of sodium glycocholate were concentration dependent, and concentrations greater than 1% were required to significantly increase buccal insulin absorption. Sodium fusidate and CHAPS similarly were not effective insulin absorption promoters at 1% concentrations.

The non-ionic surfactants tested as buccal absorption promoters are shown in Fig. 2. Previous structure/effect studies of non-ionic surfactants

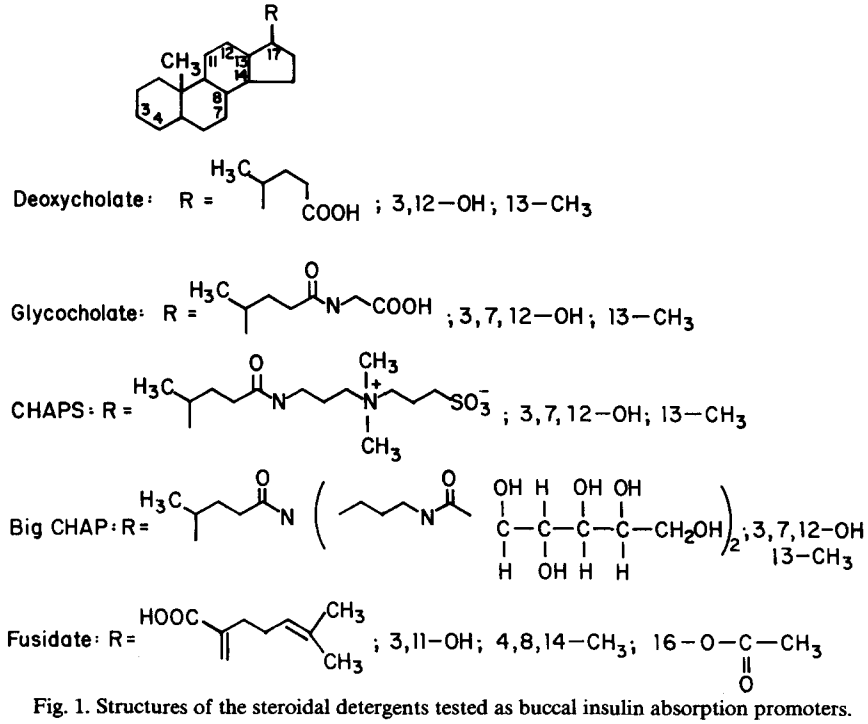

Fig. 1. Structures of the steroidal detergents tested as buccal insulin absorption promoters.

as absorption promoters for nasal (Hirai et al., 1981a), rectal (Ichikawa et al., 1980), and transdermal (Aungst et al., 1986) routes have shown

TABLE 1

Effects of steroidal adjuvants in pH 7.4 vehicles on buccal insulin efficacy in rats

Adjuvant	Adjuvant concentration	Insulin dose (U/kg)	Efficacy relative to i.m. insulin (%)
Sodium glycocholate	5% (0.103 M)	20	19.5±4.2
Sodium glycocholate	5%	10	25.5±7.5
Sodium glycocholate	5%	5	18.3±6.6
Sodium glycocholate	5%	2	9.5±4.1
Sodium glycocholate	2.5% (0.053 M)	10	8.4±4.9
Sodium glycocholate	1% (0.021 M)	10	1.8±1.4
Sodium deoxycholate	5% (0.120 M) [a]	10	20.6±5.0
Sodium fusidate	5% (0.093 M) [a]	10	16.9±4.7
Sodium fusidate	1% (0.019 M)	10	6.0±4.6
CHAPS	5% (0.081 M)	10	29.6±6.2
CHAPS	1% (0.016 M)	10	1.2±0.4
BigCHAP	5% (0.057 M)	10	17.8±4.2

[a] Soluble when warmed to 40 °C but gelled at room temperature.

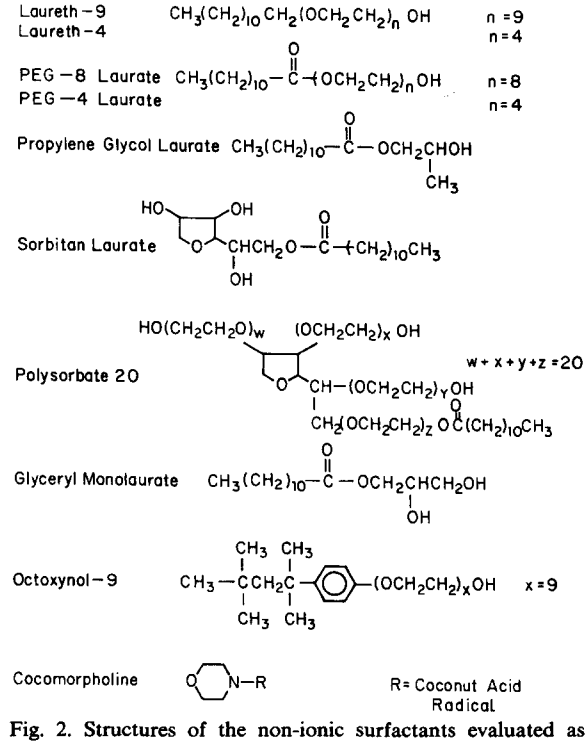

Fig. 2. Structures of the non-ionic surfactants evaluated as buccal insulin absorption promoters.

TABLE 2

Effects of non-ionic surfactant adjuvants in pH 7.4 vehicles on buccal insulin efficacy in rats

Adjuvant (HLB value)	Adjuvant concentration	Insulin dose (U/kg)	Efficacy relative to i.m. insulin (%)
Laureth-9 (11.5)	5% (0.086 M)	10	27.2 ± 10.3
Laureth-9	2.5%	10	9.7 ± 6.6
Laureth-9	1% (0.017 M)	10	11.4 ± 4.9
Laureth-9	0.5%	10	3.7 ± 1.9
Laureth-4 (9.7)	5% [a]	50	2.7 ± 1.0
PEG-8 laurate (13.0)	5%	10	3.4 ± 2.9
PEG-4 laurate (9.3)	5% [a]	50	2.6 ± 0.4
Propylene glycol laurate (4.5)	5% [a]	50	1.6 ± 0.9
Sorbitan laurate (8.6)	5% [a]	50	1.3 ± 0.5
Polysorbate 20 (16.7)	5%	50	0.7 ± 0.2
Glyceryl monolaurate (4.9)	5% [a]	10	1.6 ± 0.6
Octoxynol-9 (13.5)	5% (0.077 M)	10	14.8 ± 4.7
Cocomorpholine	5% [a]	50	1.6 ± 0.2

[a] Adjuvant not completely soluble in vehicle.

that maximal effects are attained with adjuvants having laurate hydrophobic groups. Therefore, in these studies surfactants with laurate hydrophobic groups were usually selected. Results are summarized in Table 2. Of the non-ionic surfactants tested, only laureth-9 and octoxynol-9 significantly improved buccal insulin absorption. The effects of the non-ionic surfactants were not related to their hydrophil-lipophil balance (HLB) values, which are also listed in Table 2. Rather, they suggest that non-ionic surfactants wherein the hydrophobic and hydrophilic portions are joined through an ether linkage can be effective buccal absorption promoters, but that those with ester bonds are not. Specifically, laureth-9, an ether, was a very effective promoter but PEG-8 laurate, an ester, was not. The HLB values for these are similar.

One difference between the steroidal detergents and the non-ionic surfactants is that the steroidal detergents generally have at least one ionizable group. The pH dependence of buccal insulin absorption and the effects of laureth-9 and sodium fusidate at various pHs were compared. Fusidic acid is a weak acid with pKa of 5.7 (Reeves, 1987). The isoelectric point of insulin is pH 5.4. A pH effect was not apparent in the absence of an absorption promoter; the efficacy of buccal insulin relative to i.m. insulin was consistently very low (Table 3). Insulin was less soluble at pH 5.4 and pH 3.4 than at pH 7.4. In the presence of 5% laureth-9, the vehicles were clear solutions at pH 3.4 and pH 7.4, but insulin was not completely soluble at pH 5.4. Insulin absorption was also lowest at pH 5.4. At room temperature, 5% sodium fusidate was incompletely soluble at each pH, although at pH 7.4 a clear solution was attained at greater than 40 °C. Insulin solubility could not be visually determined in these vehicles. Insulin absorption from sodium fusidate vehicles was lowest at pH 5.4, as with laureth-9 vehicles.

The effects of some miscellaneous adjuvants as buccal absorption promoters are summarized in Table 4. The ionic surfactants sodium lauryl sulfate and palmitoyl carnitine significantly increased buccal insulin efficacy. Sodium laurate was not effective at pH 7.4, but this could have been due to its very limited solubility at that pH. A clear 5% sodium laurate solution was made at pH 8.9, and this vehicle increased buccal insulin delivery. Neither of the amphoteric surfactants, lauroamphoglycinate and lauramidopropyl betaine, increased insulin absorption. Of the phospholipids studied, phosphatidylinositol vehicles provided good insulin absorption in some rats and the average efficacy of buccal, relative to i.m., was

TABLE 3

Efficacy of buccally administered insulin and the effects of laureth-9, sodium fusidate, and vehicle pH

Adjuvant	Insulin dose (U/kg)	Efficacy relative to i.m. insulin (%)		
		pH 3.4	pH 5.4	pH 7.4
None	50	1.0 ± 0.3 [a]	1.2 ± 0.4 [a]	0.7 ± 0.3
None	10			3.6 ± 2.8
Laureth-9	10	31.7 ± 8.4	15.3 ± 4.3 [a]	27.2 ± 10.3
Sodium fusidate	10	16.4 ± 7.1 [b]	8.6 ± 2.7 [b]	16.9 ± 4.7 [b]

[a] Insulin was not completely soluble.

[b] Adjuvant and possibly insulin were not completely soluble.

increased. None of the other adjuvants listed in Table 4 improved buccal insulin efficacy.

Finally, some vehicles and absorption promoters which have been shown to enhance transdermal drug absorption were evaluated. The difference in this approach is that the vehicles were non-aqueous and the adjuvants were water-insoluble. Initially, insulin solubility in various non-aqueous vehicles was evaluated. Insulin solubilities in propylene glycol, glycerin, isopropanol, and ethanol were less than 2 mg/ml, whereas concentrations greater than 10 mg/ml were attained in dimethylsulfoxide (DMSO) and *N*-methylpyrrolidone (NMP). Buccal insulin absorption from DMSO and NMP vehicles was very low, however, as shown in Table 5. Vehicles containing 5% decylmethylsulfoxide or 5% lauric acid in NMP gave only slightly increased insulin absorption. Lauric acid apparently increased insulin solubility in propylene glycol (PG); insulin solubility in 10% lauric acid/PG was greater than 2 mg/ml. This vehicle provided as high a level of pharmacologic effect as any of the other vehicles and enhancers we evaluated. A 5% lauric acid/PG vehicle was much less effective, however.

TABLE 4

Effects of other types of adjuvants on buccal insulin efficacy using aqueous pH 7.4 vehicles

Adjuvant	Adjuvant concentration	Insulin dose (U/kg)	Efficacy relative to i.m. insulin (%)
Sodium lauryl sulfate	5% (0.173 M)	10	20.3±5.6
Sodium laurate (pH 7.4)	5% [a]	10	2.6±1.1
Sodium laurate (pH 8.9)	5%	10	22.4±6.8
Palmitoyl carnitine	5% [a]	10	13.8±3.5
Lauroamphoglycinate	5%	50	2.6±0.8
Lauramidopropylbetaine	5%	50	1.8±1.1
Phosphatidylinositol	5% [a]	10	11.3±6.4
Phosphatidylcholine	5% [a]	10	1.1±0.4
Aminocaproic acid	5%	50	1.7±0.5
Polyacrylic acid (in water)	0.25% [a]	10	0.2±0.2
Hyaluronidase	2900 U/ml	50	2.0±1.0
Hyaluronidase	2900 U/ml	10	0.8±0.3
Chondroitinase	5 U/ml	10	Negligible
Z-Gly-Pro-Leu-Gly-Pro	0.08 M [a]	10	1.0±0.2

[a] Adjuvant was not completely soluble.

TABLE 5

Efficacy of buccally administered insulin using non-aqueous vehicles with or without adjuvants

Vehicle	Insulin dose (U/kg)	Efficacy relative to i.m. insulin (%)
Dimethylsulfoxide (DMSO)	50	2.8±1.2
N-methylpyrrolidone (NMP)	50	1.7±0.9
5% Decylmethylsulfoxide in NMP	10	9.9±3.3
5% Lauric acid in NMP	10 [a]	5.2±3.0
5% Lauric acid in propylene glycol (PG)	10 [a]	9.0±1.9
10% Lauric acid in PG	10	27.9±5.6

[a] Insulin was not completely soluble.

Discussion

The buccal membranes lining the oral cavity are potential sites for delivering protein and peptide drugs. Low molecular weight drugs are often well absorbed, and absorption through the buccal mucosa has been shown to bypass intestinal and hepatic first-pass metabolism (Hussain et al., 1986). Furthermore, absorption promoters can be easily coadministered to a specific area of membrane. These agents are often necessary for transmucosal protein and peptide delivery. However, there is very little information available on the effects of absorption promoters on the buccal mucosa. The main objectives of this study were (1) to identify adjuvants that can be used to promote buccal absorption of insulin, a model protein drug, and (2) to compare the characteristics of the buccal mucosa with other mucosal membranes and

with skin in regard to the effects of absorption promoters. Insulin absorption was estimated by measuring its cumulative effect on plasma glucose concentrations and relating that to a previously established dose/response curve for i.m. insulin.

The most effective absorption promoters in the studies using aqueous vehicles at pH 7.4 were the steroidal detergents, laureth-9, and sodium lauryl sulfate. All steroidal detergents examined markedly increased buccal insulin absorption (Table 1). Sodium glycocholate and sodium deoxycholate have been previously used as absorption promoters for insulin administered nasally in clinical trials (Pontiroli et al., 1982; Moses et al., 1983). These were effective at 1% concentrations nasally, but in our studies concentrations greater than 1% were required to improve buccal insulin absorption. This difference of membrane susceptibility to permeability enhancement may reflect differences in mechanisms of absorption promotion. The bile salts were suggested to increase nasal insulin absorption by solubilization of insulin monomers in micelles and formation of reverse micelles, which function as aqueous channels within the membrane (Gordon et al., 1985). The latter effect would be less likely with a stratified membrane like the buccal mucosa. As detergents, these agents solubilize lipids, and they are used to solubilize membrane proteins, so solubilization of membrane components probably is involved in their actions on buccal insulin absorption. Their practical use via any route will depend on their membrane irritation potential. Fusidates are of interest because they are claimed to be less lytic than bile salts or laureth-9 (Longenecker et al., 1987).

In contrast to the steroidal detergents, laureth-9 was an effective promoter of buccal insulin absorption at 1% concentration (Table 2). The effects of the non-ionic surfactants on buccal absorption were very similar to those on nasal insulin absorption described by Hirai et al. (1981a). They showed maximal effects for ether (vs. ester) non-ionics with HLB values in the 8–14 range. The anionic surfactants sodium lauryl sulfate and potassium laurate enhanced nasal insulin absorption in the study by Hirai, and sodium lauryl sulfate showed similar effects in our study on buccal insulin absorption. Sodium laurate was insoluble at pH 7.4 and increased buccal insulin absorption only at pH 8.9, where it was more soluble.

Other adjuvants were tested because it was suspected that they might promote buccal insulin absorption. Palmitoyl carnitine increased the absorption of various poorly absorbed drugs from the small intestine and rectum of rats and dogs (Fix et al., 1986). This also increased buccal insulin absorption (Table 3), but not to as great an extent as the previously discussed agents. Interestingly, this was the only ester adjuvant that we examined which significantly enhanced buccal absorption. Polyacrylic acid gels have been reported to enhance the rectal absorption of insulin (Morimoto et al., 1980) and calcitonin (Morimoto et al., 1985a) as well as the nasal absorption of both of these proteins (Morimoto et al., 1985b). However, we saw no improvement in buccal insulin absorption using similar polymer concentrations. Although the mechanism of enhanced absorption with polyacrylic acid is not known, it apparently primarily involves the paracellular spaces (Morimoto et al., 1987). In this way it is similar to EDTA, which also had little effect on buccal insulin absorption (Aungst and Rogers, 1988). We looked at the effects of hyaluronidase and chondroitinase because there were indications that these enzymes could digest the materials packed in the intercellular spaces of the buccal epithelium (Squier, 1984). In the presence of these agents very little insulin was absorbed. The peptide listed in Table 3 was studied as a potential inhibitor of insulin metabolism. Hori et al. (1983) reported that 0.008 M Z-Gly-Pro-Leu-Gly significantly inhibited the degradation of s.c. injected insulin (0.2 U/kg) in rats. In our studies a 0.08 M concentration of Z-Gly-Pro-Leu-Gly-Pro had no effect on the buccal absorption of 10 U/kg insulin.

Finally, because the buccal mucosa is morphologically similar to skin, we examined non-aqueous vehicles and known skin penetration enhancers. Dimethylsulfoxide and *N*-methylpyrrolidone are generally recognized as providing good skin penetration of low molecular substances, but not for those of molecular weight greater that 3000 (Barry, 1983). Similarly, al-

though both were good solvents for insulin, the buccal absorption of insulin from these vehicles was very low (Table 5). Propylene glycol vehicles containing decylmethylsulfoxide or lauric acid also allow good skin penetration rates for low molecular weight drugs (Aungst et al., 1986). These improved buccal insulin absorption slightly at 5% adjuvant concentrations, and at 10% concentration lauric acid was quite effective.

All of the adjuvants that increased buccal insulin efficacy are known from numerous studies on other membrane systems to affect membrane permeability. It is possible that these agents could enhance absorption by other mechanisms as well. It has been previously shown that 1% sodium glycocholate and 1% laureth-9 slowed the rates of insulin metabolism in rat nasal mucosa homogenates (Hirai et al., 1981b). These adjuvants could have also affected the physicochemical properties of insulin in the dosing solutions. These possibilities should be investigated.

It is hoped that this work will provide a basis for understanding how to improve the buccal absorption of proteins and peptides. We have shown that the absorption of insulin can be markedly increased using adjuvants which are known to enhance nasal, rectal, or transdermal absorption rates. Although there are similarities in the effects of some absorption promoters on these diverse membranes, it is important to also realize that the buccal mucosa is structurally different from other mucosal membranes and skin. These differences emerge when comparing the effects of salicylates (Aungst and Rogers, 1988), polyacrylic acid, and low concentrations of bile acids; these promote rectal or nasal, but not buccal, insulin absorption.

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