Table II—Absorption of Clindamycin from the Buccal Cavity at Various pH Values and Time Intervals

Subject	Buffer	pH	Time Interval in Mouth, min.	Absorbed Clindamycin, %
1	Citrate	4.0	5	0
1	Phosphate	7.5	5	2
1	Phosphate	8.5	5	0
1	Phosphate	8.5	15	12
1	Deionized H_2O	6.9[a]	15	6
2	Phosphate	8.5	5	4

[a] pH at end of absorption experiment.

was used to calculate clindamycin in the assay. Table I gives the peak area ratios of clindamycin–internal standard for various known amounts of clindamycin and is typical of the GLC quantitation.

The results of buccal absorption of clindamycin for two subjects are presented in Table II. One milligram of clindamycin base per 25 ml. solution was used for each experiment. Within experimental error, no clindamycin was absorbed buccally in 5 min. at pH 4, 7.5, or 8.5. A small amount of clindamycin may have been absorbed after 15 min. at pH 8.5, or this indicated absorption may have been due to the swallowing of a portion of the solution during the longer time interval. In contrast to the poor buccal absorption, clindamycin is well absorbed from the gastrointestinal tract (4–6).

The data of Bickel and Weder (3) indicated that at pH 7.4 the buccal absorption of imipramine and similar compounds could be related to lipid solubility as measured by partition values. At this pH, imipramine with an apparent partition coefficient (diethylether–water) of 140 was absorbed to the extent of approximately 60%. The true partition coefficient,[2] k, for clindamycin between diethylether and water is 9.8 at 25° (10). The apparent partition coefficient of clindamycin at pH 7.4 was calculated (11) to be 3 from the above k and the pKa. This indicates that the lower lipid solubility of clindamycin relative to imipramine could partially account for the poor buccal absorption of clindamycin. However, it does not explain the difference between the poor buccal absorption and the excellent gastrointestinal absorption of clindamycin. This difference in absorption may be due to the differences in surface area, transport mechanisms, and/or mucous membrane pH between the buccal cavity and the gastrointestinal tract.

[2] The true partition coefficient, k, equals the concentration of unionized species in the organic phase per the concentration of the unionized species in the aqueous phase.

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Effect of Polysorbate 80 and Oleic Acid on Drug Absorption from the Rat Intestine

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Abstract □ Low concentrations of polysorbate 80 and oleic acid, which enhance drug absorption across the external membranes of goldfish, have no apparent effect on the absorption of salicylate, salicylamide, and 4-aminoantipyrine from the *in situ* rat small intestine.

Keyphrases □ Polysorbate 80, oleic acid—drug absorption rate, effects, rat intestine □ Absorption rate, rat intestine—polysorbate 80, oleic acid, effects □ Drugs, absorption—polysorbate 80, oleic acid, effects, rat intestine □ Oleic acid, polysorbate 80—drug absorption rate, rat intestine, effects

Polysorbate 80 and oleic acid enhance the rate of drug absorption by goldfish immersed in drug solutions containing low concentrations of one of these substances (1–4). The purpose of this study was to determine if polysorbate 80 and oleic acid can also increase the absorption rate of certain drugs from the small intestine of the rat.

EXPERIMENTAL

Drug absorption was studied by the *in situ* rat gut technique of Doluisio *et al.* (5) with the following modifications: (*a*) Sprague-Dawley rats (weighing approximately 220 g.) were anesthetized with 1.5 mg. urethan/g. body weight (rather than 1 mg./g.); (*b*) the animals were hydrated immediately after urethan administration by an intraperitoneal injection of 5 ml. normal saline solution; (*c*) the gut was first rinsed with the perfusion solution (5) and then with the drug solution; and (*d*) 7 ml. (rather than 10 ml.) of the drug solution was placed in the intestine for the absorption experiment.

The drug solutions contained 200 or 400 mg.% salicylic acid, 150 or 300 mg.% salicylamide, or 50 or 100 mg.% 4-aminoantipyrine in Sorensen's buffer of pH 6.0. Solutions containing the low concentra-

Table I—Effect of Polysorbate 80 and Oleic Acid on the Intestinal Absorption of Salicylate, Salicylamide, and 4-Aminoantipyrine in Rats

Drug	Concentrations Used, mg./100 ml.	Mean[a] Absorption Half-Life, min. (*SD*)			
		High Conc.	Low Conc.	With Polysorbate 80[b]	With Oleic Acid[c]
Salicylic acid	200; 400	8.2 (0.7)	8.9 (1.7)	8.5 (1.5)	8.6 (2.4)
Salicylamide	150; 300	9.5 (2.9)	9.2 (2.0)	9.5 (2.5)	8.7 (0.7)
4-Aminoantipyrine	50; 100	12.9 (1.4)	13.4 (1.6)	14.0 (0.8)	15.3 (1.9)

[a] Mean of 3 to 5 experiments. [b] The solutions contained the low drug concentration and 0.03% polysorbate 80. [c] The solutions contained the low drug concentration and 0.1% oleic acid.

tions of drug and 0.03% polysorbate 80 or 0.1% oleic acid were also prepared. The concentrations of salicylic acid and salicylamide were determined in suitably diluted and acidified samples by the method of Trinder (6). The concentration of 4-aminoantipyrine was determined by the method of Brun (7), as modified by Levy and Miller (8).

RESULTS AND DISCUSSION

The results of the absorption experiments are summarized in Table I. In agreement with Doluisio *et al.* (5), it was found that the concentration of salicylic acid in the intestinal solution decreased exponentially for at least two half-lives. The absorption half-life of salicylic acid was 8–9 min. in this study, compared to 8 min. reported by Doluisio *et al.* Contrary to the observations of those workers, the authors of this study noted considerable (≃50%) net absorption of water, which was reduced somewhat by hydrating the animals and reducing the volume of the solution in the intestine from 10 to 7 ml.[1]

The absorption of salicylamide from the rat intestine was somewhat slower than that of salicylate (even though the former was essentially nonionized while the latter was almost fully ionized), and the absorption of 4-aminoantipyrine was even slower. Polysorbate 80 and oleic acid had no apparent effect on the absorption of these three drugs, on water absorption, and on the gross appearance of the small intestine. The concentration of oleic acid used in this study was slightly in excess of solubility in order to maintain a reasonably constant concentration during the experiment.

The lack of effect of polysorbate 80 and oleic acid on drug absorption from the small intestine of the rat is in contrast to the pronounced absorption-enhancing effect of similar low concentrations of these substances in goldfish (1–4). The absorption and exsorption rate constants of 4-aminoantipyrine in goldfish are increased almost twofold by 0.01% polysorbate 80 (3). The absorption of barbiturates by goldfish is enhanced appreciably by polysorbate 80 and oleic acid in low concentrations (1, 2, 4). However, while the external membranes of goldfish and the rat intestine have the characteristics of a lipoid barrier and yield qualitatively similar (*i.e.*, the same rank order) results in their respective permeability to a series of drugs with different lipoid–water partition coefficients (9), the two types of membranes do differ in their response to certain additives. Thus, the goldfish membranes are exquisitely sensitive to such substances as sodium lauryl sulfate and salicylic acid (unpublished observations), and become more permeable when exposed to polysorbate 80 and certain other surface-active substances (1–4). On the other hand, the *in situ* rat small intestine appears to be much more resistant to these substances.

[1] In more recent studies in this laboratory, the volume of intestinal solution is maintained essentially constant by adding drug-free solvent at each sampling time. Absorption rate constants obtained under these conditions are somewhat smaller than the rate constants obtained by the method used in this study.

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