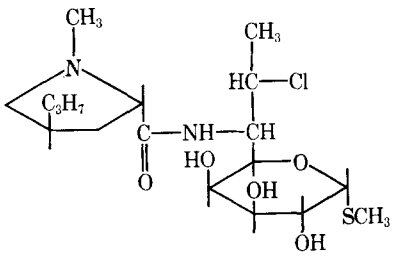
Absorption of Clindamycin from the Buccal Cavity

MILDRED J. TARASZKA

Abstract □ Clindamycin, which is known to be absorbed from the gastrointestinal tract, was absorbed extremely slowly, or possibly not at all, from the buccal cavity at various pH values. This finding indicates that buccal absorption alone cannot be used to predict the gastrointestinal absorption of a compound.

Keyphrases □ Clindamycin—buccal absorption □ Drug absorption, buccal—clindamycin □ GLC—analysis

Recently, several investigators (1–3) have proposed the method of buccal absorption as an example of an *in vivo* model of drug partitioning into, or passive drug transfer through, a lipid membrane. They also proposed the buccal absorption test for predicting the relative absorption and excretion of compounds in biological systems. Since clindamycin (I)[1] is well absorbed from the human gastrointestinal tract (4–6), it was of interest to determine the pH profile for buccal absorption of clindamycin. Clindamycin is an antibiotic which is synthetically derived from lincomycin (7, 8).



clindamycin

I

EXPERIMENTAL

Absorption Studies—The buccal absorption procedure was essentially the same as that used by Beckett and Triggs (1). The subjects were instructed to hold 25 ml. of buffer containing 1 mg. of the base form of the compound in their mouths for a given time interval. During this interval they kept the solution in constant movement with tongue-and-cheek action. At the end of the time interval, the solution was expelled into a 60-ml. Teflon-stoppered, separatory funnel. Immediately the mouth was given a 10-sec. rinse with 10 ml. of deionized water. The water rinse was combined with the previously expelled solution. The amount of compound unabsorbed was measured by extraction and GLC.

Standards were prepared by having the subjects hold plain buffer in their mouths. Various amounts of compound were then added to the expelled solution in the separatory funnels and used as standards.

To ensure that the buccal-absorption methodology was in agreement with that used in the literature, a 1-mg. sample of benzphetamine base in 25 ml. of pH 8.5 phosphate buffer was tested. In two separate experiments, 76 and 79% of the benzphetamine samples were buccally absorbed in 5 min.; these results are in agreement with the data presented by Beckett and Triggs (1).

Assay for Clindamycin—The pH of the buffer solution in the separatory funnel was adjusted to pH 11 with NaOH, and 2 ml. of a water-saturated chloroform solution containing 0.3 mg./ml. of cholesteryl acetate as an internal standard was added. The separatory funnel was shaken vigorously for 1.5 min., and the cloudy chloroform layer collected in a centrifuge tube. The tubes were centrifuged at 10° for 10–15 min. at 12,000 r.p.m. to break the suspension. Approximately 1 ml. of the chloroform layer was transferred to a 2-ml. volumetric flask and evaporated to dryness under a dry stream of air. Then 0.4 ml. of hexamethyldisilazane was added and the flask was shaken to dissolve the residue. One-tenth milliliter of trifluoroacetic acid was added, and the flask was allowed to stand for 1 hr. for complete reaction. Gas chromatography of clindamycin *tris*-trimethylsilyl ether was carried out using glass columns 50.80 cm. × 1.27 cm. (20 in. × 0.5 in.) packed with Gas Chrom Q, 80–100 mesh, and coated with 1% OV-1. The oven temperature was 210° and the carrier gas (He) flow was 60 ml./min.

Assay for Benzphetamine—The assay for benzphetamine is similar to that for clindamycin, except 3 ml. of chloroform solution containing 0.75 μl. nicotine as an internal standard was added to the separatory funnel. The collected chloroform layer was gas chromatographed using glass columns packed with Diaport S, 60–80 mesh, and coated with 6% LAC-728. The oven temperature was 180° and the carrier gas (He) flow was 50 ml./min.

Ionization Constant for Clindamycin—Twenty-milliliter samples of clindamycin (1.5×10^{-3} *M*) were titrated with 0.1 *M* KOH in a radiometer type SBR2/SBU1 titrigraph. A pKa of 7.72 ± 0.04 ($\bar{X} \pm \sigma$) was evaluated from the continuously recorded titration curves at 25°.

Table I—Standard Samples

Weight of Clindamycin, mg.	Peak Area Ratio Clindamycin–Internal Standard
1.0	1.080
0.9	0.898
0.6	0.606
0.4	0.395
0.2	0.224
0.1	0.092

RESULTS AND DISCUSSION

A typical gas chromatogram of clindamycin from buffered saliva solutions is shown in Fig. 1. An impurity extracted from saliva is present (Peak 4 in Fig. 1) but does not interfere with the assay. The 4′-ethyl analog of lincomycin (Peak 2 in Fig. 1) is an antibiotic produced at about the 3% level in the microbiological synthesis of lincomycin (9). Since clindamycin is synthesized from lincomycin, the 4′-ethyl analog of clindamycin was present in small amounts in the clindamycin samples. The total area under Peaks 1, 2, and 3

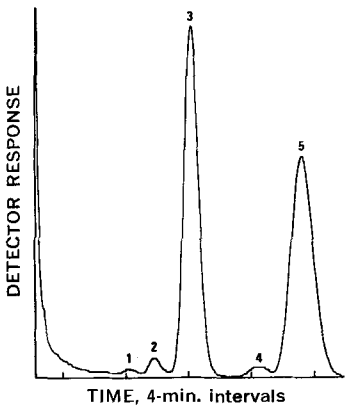


Figure 1—*Typical gas chromatogram of a silanized clindamycin buccal solution. Key: Peak 1, column-thermal degradation product of clindamycin; Peak 2, 4′-ethyl analog of clindamycin; Peak 3, clindamycin; Peak 4, saliva impurity; and Peak 5, internal standard cholesteryl acetate.*

[1] Cleocin, The Upjohn Co., Kalamazoo, Mich.

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.

REFERENCES

(1) A. H. Beckett and E. J. Triggs, *J. Pharm. Pharmacol.*, **19,** Suppl. 31S(1967).

(2) A. H. Beckett and A. C. Moffat, *ibid.*, **20,** Suppl. 239S (1968).

(3) M. H. Bickel and H. J. Weder, *ibid.*, **21,** 160(1969).

(4) J. G. Wagner, E. Novak, N. C. Patel, C. G. Chidester, and W. L. Lummis, *Amer. J. Med. Sci.*, **256,** 25(1968).

(5) R. F. McGehee, Jr., C. P. Smith, C. Wilcox, and M. Finland, *ibid.*, **256,** 279(1968).

(6) E. Novak, J. G. Wagner, and D. J. Lamb, to be published.

(7) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *Antimicrob. Ag. Chemother.*, **1966,** 727(1967).

(8) H. Hoekema, B. Bannister, R. D. Birkenmeyer, F. Kagan, B. J. Magerlein, F. A. MacKellar, W. Schroeder, G. Slomp, and R. R. Herr, *J. Amer. Chem. Soc.*, **86,** 4223(1964).

(9) A. D. Argoudelis, J. A. Fox, and T. E. Eble, *Biochemistry*, **4,** 698(1965).

(10) W. Morozowich, to be published.

(11) A. N. Martin, "Physical Pharmacy," Lea and Febiger, Philadelphia, Pa., 1960, pp. 380–388.

ACKNOWLEDGMENTS AND ADDRESSES

Received September 29, 1969, from the *Pharmacy Research Unit, The Upjohn Co., Kalamazoo, MI 49001*

Accepted for publication January 27, 1970.

The author expresses her appreciation to Mr. William Woltersom for his assistance with the assays.

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

GERHARD LEVY and AINO PERÄLÄ*

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-