Modification of Diffusion Rates of Benzocaine from Topical Vehicles Using Sodium Salicylate as Complexing Agent

PETER YORK ˣ and ABDEL AZIS M. SALEH *

Abstract □ The release of benzocaine from various topical vehicles containing benzocaine, alone and in the presence of a complexing agent, sodium salicylate, was measured at 37° using dialysis through a cellulose membrane. Sodium salicylate had a marked effect on the release of benzocaine, depending upon the type of vehicle, with the largest increase observed for the water-miscible base, polyethylene glycol (macrogol ointment BPC). The amount of drug released from preparations containing 1% (w/w) and 2% (w/w) benzocaine in this vehicle depended upon the sodium salicylate concentration. Results are discussed in terms of the differing physical properties of the complexes formed.

Keyphrases □ Benzocaine—diffusion from topical vehicles, effect of sodium salicylate as complexing agent □ Sodium salicylate—effect on diffusion of benzocaine from topical vehicles □ Complex formation—effect on diffusion of benzocaine from topical vehicles, sodium salicylate as complexing agent □ Topical vehicles—effect of sodium salicylate on diffusion of benzocaine

Complexes result from donor–acceptor interactions between molecules and are used in pharmaceutical formulations in several ways. Certain complexes can solubilize otherwise insoluble material in a solvent [*e.g.*, the solubilization of xanthines by aromatic hydroxy acids (1)], and surfactants are widely used to solubilize pharmaceutical drugs (2). Improved stability of drugs can also result from complexation, as illustrated by the stabilization of solutions of certain local anesthetics by complexation with caffeine (3–5).

Drug–complex formation can also either improve or impair drug absorption and bioavailability, depending upon such factors as the oil–water partition coefficients of the drug and drug complex, the change in drug solubility, and the change in the diffusion rate of the drug through membranes when complexed (6–8). Absorption studies have generally related to GI absorption, and such effects in topical preparations have not been widely investigated.

There are two generally recognized methods for modifying drug release from topical preparations: (*a*) inclusion of a material in the base to modify the epidermal absorption barrier, and (*b*) alteration of the physical properties of the semisolid vehicle (9). Rates of drug release from such preparations can be followed by various *in vitro* and *in vivo* techniques (10), although prediction of release patterns is unreliable (10).

In a recent *in vivo* study, local anesthetic preparations were tested for their effectiveness in preventing itching and pain induced by an electric current. Only one of the 30 commercial formulations studied was efficient (11), and this preparation contained 20% (w/w) benzocaine. *In vitro* diffusion tests of ointment preparations of benzocaine also indicated significant variation of drug release from different types of vehicle (12).

In view of these reported variations and since many official and commercial benzocaine preparations contain less than 20% (w/w) of drug, the release of benzocaine from official and nonofficial semisolid topical vehicles was examined. The effect of adding sodium salicylate, which is known to form molecular complexes with benzocaine (13–15), also was studied to establish whether the *in vitro* release rate of benzocaine, measured using a dialysis cell, could be improved.

EXPERIMENTAL

Materials—Benzocaine[1] and sodium salicylate[2], official grades, were sieved through a 53-μm (300-mesh) sieve. Polyethylene glycol (macrogol) 300[3] and 4000[3], white soft paraffin[4], cetomacrogol emulsifying ointment[4], wool alcohols[4], hard paraffin[4], liquid paraffin[4], and wool fat[4], all official grades, were used as supplied.

The assay materials were 32% (w/w) hydrochloric acid[5], sodium nitrite[2] (analar), ammonium sulfamate[2] (laboratory reagent), and *N*-(1-naphthyl)ethylenediamine dihydrochloride[2] (laboratory reagent).

The cellulose dialysis cell membrane, prepared by splitting dialysis sacks[6] (inflated diameter 1.57 cm), was washed before use in distilled water.

Preparation of Bases—The vehicles studied are listed in Table I, and all constituents were incorporated on a weight per weight basis. No preservatives were included in the vehicles.

For Vehicles A and B, benzocaine and sodium salicylate, when present, were dissolved in polyethylene glycol 300, with the percentage of polyethylene glycol 300 being reduced appropriately. The ointment then was prepared by fusing the constituents at 60° and stirring until cold.

The solid materials were incorporated into Vehicle C at 50°, and the ointment then was stirred until cold.

For Vehicles D–G, benzocaine powder was suspended in the oily phase. Sodium salicylate, when present, was dissolved in the aqueous phase, with the proportions of the phase constituents being reduced appropriately. The two phases were heated separately to 50° and then mixed and stirred until cold.

Dialysis Equipment—The vehicle sample under test was tightly packed into a shallow steel dish, 3.12 cm in diameter and 0.62 cm in depth, fitted with a small flange. The surface of the vehicle was made smooth before applying the dialysis membrane to ensure intimate contact and removal of air. The membrane was secured by solidified hard paraffin wax above and below the small flange and then checked for leakage. The dish was located centrally, by means of a magnet, on the base of a 600-ml glass beaker containing 200 ml of distilled water (pH 5.2) at 37 ± 0.5°. This volume of water provided sink conditions for the diffusing benzocaine.

The distilled water was stirred at 75 rpm using a polytetrafluoroethylene plastic rectangular blade, 4.5 × 1.7 cm, connected by a glass rod, 6 mm in diameter, to a constant-speed motor[7]. The blade was positioned centrally in the beaker with the top of the 4.5-cm edge at the surface of the water.

[1] Hopkins and Williams Ltd., Chadwell Heath, Essex, England.
[2] B.D.H. Chemicls Ltd., Poole, England.
[3] Koch Light Laboratories Ltd., Colnebrook, England.
[4] Evans Medical Ltd., Speke, Liverpool, England.
[5] Merck Chemicals, Darmstadt, Germany.
[6] Sigma Chemicals, St. Louis, Mo.
[7] Citenco constant-speed motor K2.606, Citenco Ltd., Boreham Wood, Herts., England.

Table I—Composition and Type of Topical Vehicles Studied

Code	Name of Vehicle	Type of Vehicle	Benzocaine, % (w/w)	Sodium Salicylate, % (w/w)
A	Polyethylene glycol (macrogol ointment BPC)	Water miscible	1	0.0, 0.1, 0.25, 0.5, 1, 1.5, 2, 5, 10, 20
			2	0.0, 0.25, 0.5, 1, 2, 5, 10
B	Polyethylene glycol (macrogol ointment BPC), 90% (w/w), and distilled water, 10% (w/w)	Water miscible	1	0, 10
C	White soft paraffin BP	Oleaginous	1	0, 10
			5	0
D	Cetomacrogol cream BP	Oil-in-water emulsion cream	1	0, 10
E	Aqueous cream BP	Oil-in-water emulsion cream	1	0, 10
F	Wool alcohol cream[a]	Water-in-oil emulsion cream	1	0, 10
G	Hydrous wool fat BP	Water-in-oil emulsion cream	1	0, 10

[a] Composition: liquid paraffin, 30% (w/w); wool alcohols, 5% (w/w); white soft paraffin, 55% (w/w); and distilled water, 10% (w/w). For vehicle containing 1% (w/w) benzocaine and 10% (w/w) sodium salicylate, 44% (w/w) white soft paraffin was used.

Samples, 1 ml, were removed from time zero to 3 hr at 30-min intervals. A minimum of two diffusion experiments was performed for each vehicle composition.

Analytical Method—The assay for benzocaine was carried out using the diazo-coupling method of Bratton and Marshall (16) with minor modifications. A 1-ml sample was added to a 100-ml volumetric flask containing 50 ml of distilled water and 0.5 ml of 32% (w/w) hydrochloric acid; then 0.5 ml of 1% (w/v) sodium nitrite solution was added, and the contents were shaken for 3 min. Then 0.5 ml of 5% (w/v) ammonium sulfamate solution was added, and the solution was shaken for another 1 min. Then 1 ml of 0.5% (w/v) *N*-(1-naphthyl)ethylenediamine dihydrochloride solution was added, and the solution was diluted to volume with distilled water. After 10 min, the percentage transmission of the developed red color was determined at 545 nm[8] and the concentration of benzocaine was estimated from a calibration curve.

RESULTS AND DISCUSSION

Figure 1 shows the release of drug from plain vehicles containing 1% (w/w) benzocaine. Individual points are included for Vehicle A to illustrate the observed scatter of results. The points on the other curves represent averaged values. Similar scatter of results was observed for all subsequent experiments.

The curves in Fig. 1 indicate that the various vehicles exhibited differing rates of *in vitro* release of benzocaine. Their efficiency for releasing benzocaine was in the following order: water miscible > oil-in-water emulsion creams > white soft paraffin > water-in-oil emulsion creams.

All vehicles showed a curvilinear relationship between the total amount of benzocaine released and time. Vehicles A and B had an initial convex-upward section, while Vehicles C–G exhibited an initial concave-upward section.

With Vehicles A and B, slight swelling of the membrane occurred during the diffusion experiment due to water uptake into the dialysis cell. This result can be accounted for by the high osmotic pressure of the polyethylene glycol base, initially inducing water molecules to penetrate the membrane and enter into the cell. This effect would explain the "lag" period of approximately 60 min before the drug release rate became constant (Fig. 1). This effect was substantiated by the shorter period of slow release of 30 min for Vehicle B, the polyethylene glycol vehicle containing 10% (w/w) water.

In contrast, Vehicles C–G exhibited a faster initial release rate, which decreased to a constant rate after 60 min. This change in rate can be ascribed to the benzocaine in the layers adjacent to the membrane at the beginning of the experiment readily diffusing through the membrane. Subsequent availability of benzocaine for release depended upon diffusion of the drug through the vehicle to the membrane, and this diffusion was a slower process.

The benzocaine release data for Vehicles C–G all conformed to the mathematical relationship developed (17, 18), based on Fick's law, to describe the release of drugs from ointment bases in that straight-line relationships existed between the total amount of drug released and the square root of time.

It can be seen from Fig. 1 that the vehicles providing optimum release of benzocaine were the polyethylene glycol vehicles, A and B. The increase in solubility of benzocaine in the presence of polyethylene glycol 300 (15) and the water miscibility of the polyethylene glycol vehicle may be contributing factors in achieving improved release rates compared with the other vehicles. The drug release data for these two bases do not conform to the reported mathematical model (17, 18).

The effect of adding 10% (w/w) sodium salicylate, a material

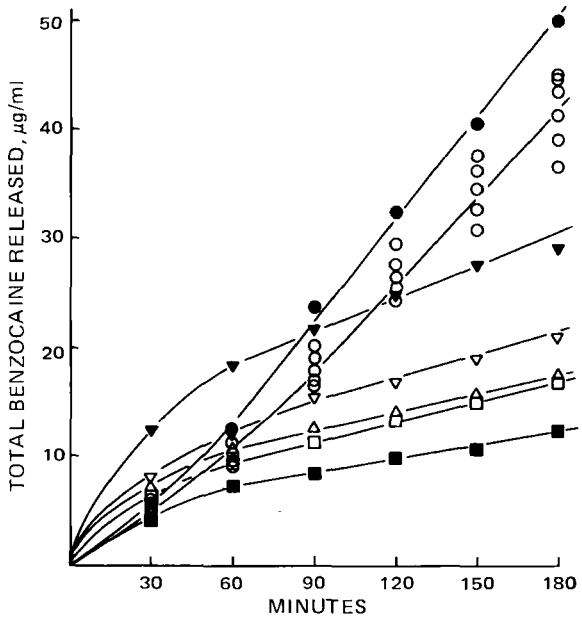

Figure 1—*Effect of type of topical vehicle on release of drug from preparations containing 1% (w/w) benzocaine. Key: ○, Vehicle A; ●, Vehicle B; △, Vehicle C; ▽, Vehicle D; ▼, Vehicle E; □, Vehicle F; and ■, Vehicle G. (To avoid confusion, individual experimental points are illustrated only for Vehicle A. Other points represent averaged values).*

[8] Eel 197 spectra colorimeter, Evans Electroselenium Ltd., Halstead, Essex, England.

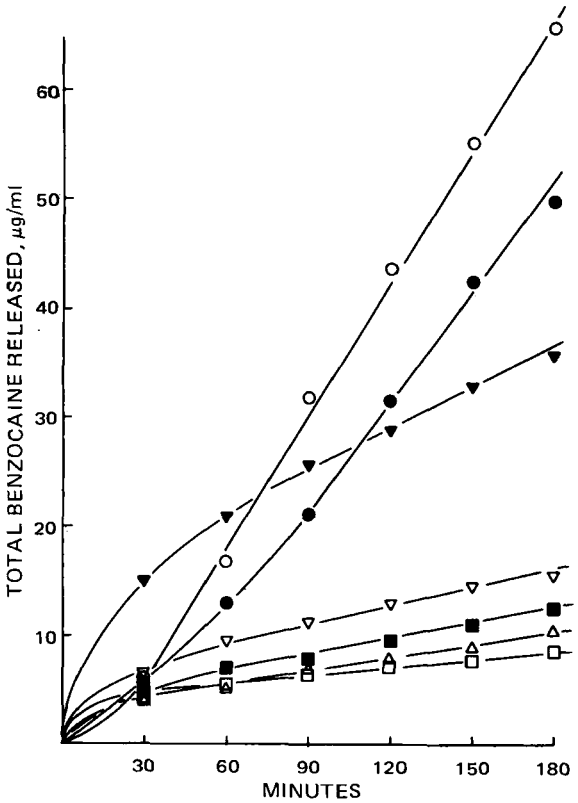

Figure 2—*Effect of type of topical vehicle on release of drug from preparations containing 1% (w/w) benzocaine and 10% (w/w) sodium salicylate. Key: see Fig. 1.*

known to complex with benzocaine (13–15), on the release rate of benzocaine from each vehicle is shown in Fig. 2. Three vehicles, A, B, and E, exhibited improved release profiles, while Vehicles C, D, and F showed decreased release profiles. For Vehicle G, the release rate remained unchanged. These differences can be attributed to possible changes in the partition coefficient of benzocaine in the vehicles containing sodium salicylate, the nonsolubility of sodium salicylate in the oily phases, and other factors such as solubility changes of the drug and drug complex (6–8).

The most significant increase occurred with Vehicle A, with an increase in amount of drug released of more than 60% after 2 hr compared with the plain vehicle. Since in this study the desired effect was to improve drug availability, this vehicle, polyethylene glycol (macrogol ointment BPC), was studied further, using two concentrations of benzocaine, 1 and 2% (w/w), with a series of concentrations of sodium salicylate (Table I).

Figure 3 shows graphs of the release of benzocaine from Vehicle A containing 1% (w/w) benzocaine and differing concentrations of sodium salicylate. To linearize these graphs and similar curves for 2% (w/w) benzocaine in Vehicle A, it was necessary to plot logarithm$_{10}$ of the total amount of benzocaine released *versus* logarithm$_{10}$ of the time in minutes (Fig. 4). Least-squares regression was carried out for all graphs, and the statistical data are given in Table II.

From these data, estimates of the total amount of benzocaine released after 2 hr from each studied preparation were made (Table II). Figure 5 shows the relationship between the total amount of drug released after 2 hr and the percent (w/w) sodium salicylate in Vehicle A for the 1 and 2% (w/w) benzocaine concentrations, together with the standard error of the individual points. Both curves exhibited a maximum at 0.25% (w/w) sodium salicylate followed by minima at 1.5 and 0.5% (w/w) sodium salicylate for Vehicle A containing 1 and 2% (w/w) benzocaine, respectively. A plateau section was then observed at higher sodium salicylate concentrations in both graphs.

A number of molecular complexing interactions took place within the polyethylene glycol vehicle containing both benzocaine and sodium salicylate since complexation reactions are known to occur

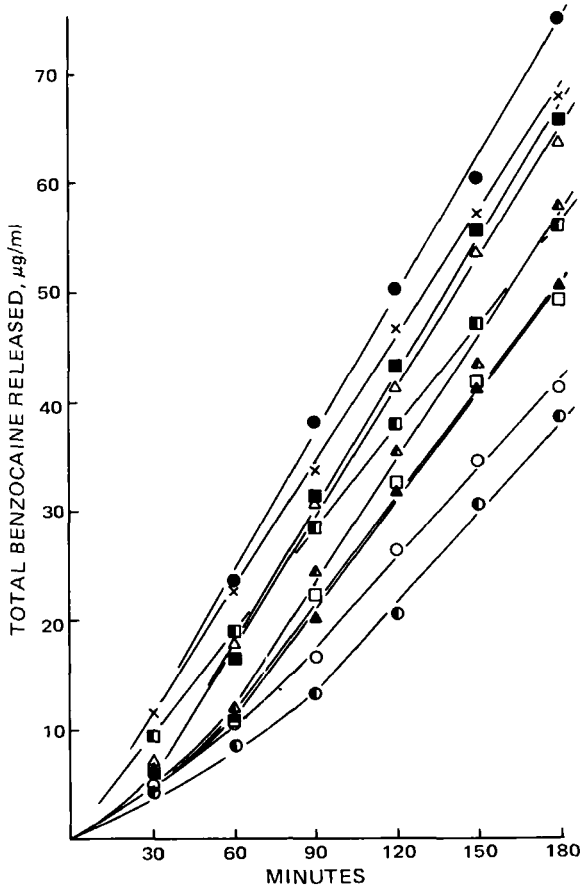

Figure 3—*Effect of increasing sodium salicylate concentration on release of drug from Vehicle A containing 1% (w/w) benzocaine. Key [sodium salicylate concentrations (1% w/w)]: ○, 0.0; ◐, 0.1; ●, 0.25; △, 0.5; ▲, 1.0; ▲, 1.5; □, 2.0; ◧, 5.0; ■, 10.0; and ×, 20.0.*

between both benzocaine and polyethylene glycol and benzocaine and sodium salicylate (15). Indeed, in concentrations of 5% of both complexing agents, benzocaine showed increased solubility compared with the presence of either polyethylene glycol or sodium salicylate alone, suggesting the possible formation of a multicomplex of the three different constituent molecules (15).

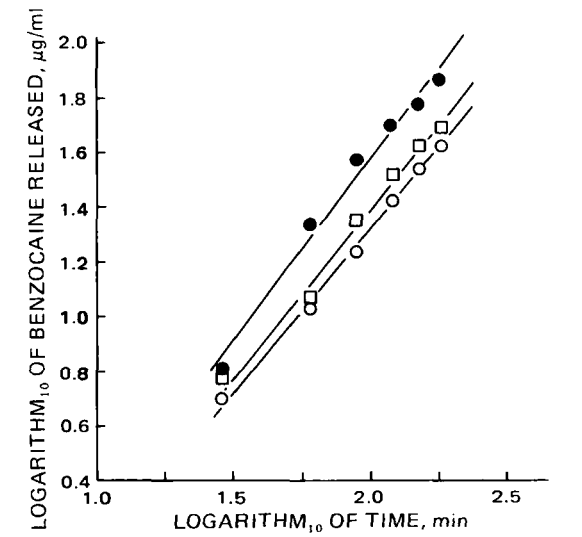

Figure 4—*Correlation between logarithm$_{10}$ of total benzocaine released and logarithm$_{10}$ of time for Vehicle A preparations containing 1% (w/w) benzocaine and different concentrations of sodium salicylate. Key: see Fig. 3.*

Table II—Summary of Calculated Statistical Parameters for Logarithm$_{10}$ Total Benzocaine Released *versus* Logarithm$_{10}$ Time in Minutes for Linear Regression

Vehicle	Sodium Salicylate, % (w/w)	Slope	Intercept	Correlation Coefficient	Calculated Total Amount of Benzocaine Released after 2 hr ± *SE*, μg/ml (p = 0.95, df = 4)[a]
Vehicle A + 1% (w/w) benzocaine	0.0	1.14	−0.960	0.970	25.76 ± 1.73
	0.1	1.09	−0.905	0.959	23.01 ± 2.02
	0.25	1.33	−1.084	0.991	48.08 ± 4.07
	0.5	1.28	−1.040	0.982	41.88 ± 3.47
	1.0	1.21	−0.987	0.997	33.88 ± 1.40
	1.5	1.12	−0.840	0.990	30.90 ± 1.40
	2.0	1.26	−1.130	0.998	30.97 ± 2.71
	5.0	0.98	−0.460	0.997	37.84 ± 2.29
	10.0	1.30	−1.082	0.965	42.07 ± 2.30
	20.0	0.95	−0.313	0.976	46.03 ± 1.61
Vehicle A + 2% (w/w) benzocaine	0.0	1.48	−1.276	0.998	63.39 ± 2.51
	0.25	1.19	−0.611	0.996	73.11 ± 1.06
	0.5	1.21	−0.907	0.992	40.74 ± 1.30
	1.0	1.28	−0.866	0.995	62.52 ± 1.83
	2.0	1.33	−0.984	0.939	60.39 ± 2.29
	5.0	1.42	−1.186	0.987	58.34 ± 1.76
	10.0	1.16	−0.612	0.989	63.24 ± 1.44

The relative solubility of benzocaine in its different complexed forms will differ, as will the rate of diffusion of the various complexes across the dialysis membrane, due to the different oil–water partition coefficients and size and charge changes of the complexes compared with the original form of the drug (7). Such changes in drug solubility in topical vehicles produce modification in drug availability, with slow release rates for drugs readily soluble in the base and faster release rates when the drug is less soluble (9). In addition, competition takes place between the complexing agents for the benzocaine molecules; the proportions of different complexes formed depend upon the relative affinities and binding strengths of the various complexes.

The summation of these interactions, solubility changes, competition, and other effects could account for the observed changes in the release rate of benzocaine with increasing concentrations of sodium salicylate.

The advantages of the polyethylene glycol vehicle and the presence of a complexing agent are shown by Fig. 6, which compares the release of benzocaine from two preparations. Vehicle C, containing 5% (w/w) benzocaine, is similar to an official benzocaine ointment preparation; Vehicle A, containing 1% (w/w) benzocaine and 0.25% (w/w) sodium salicylate, is the preparation that exhibited the optimum release of benzocaine for this concentration of drug. Although the latter system contained only one-fifth of the concentration of drug compared with the former, the total amount of benzocaine released after 2 hr was approximately 2.5 times greater than that observed for the preparation using white soft paraffin. The clinical significance of these findings using *in vivo* experiments is being established and will be presented in a future report.

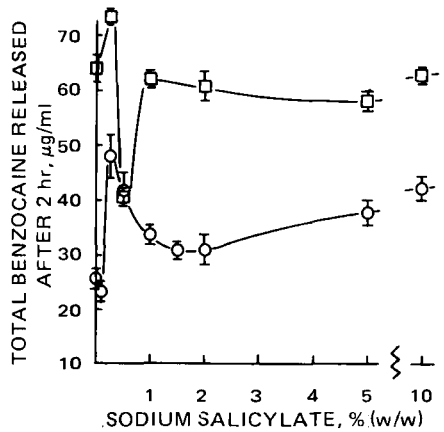

Figure 5—*Effect of increasing sodium salicylate concentration on the total amount of benzocaine released after 2 hr from Vehicle A. Key:* ○, *Vehicle A containing 1% (w/w) benzocaine; and* □, *Vehicle A containing 2% (w/w) benzocaine. (The bar lines represent ± 1* SE *from the calculated value.)*

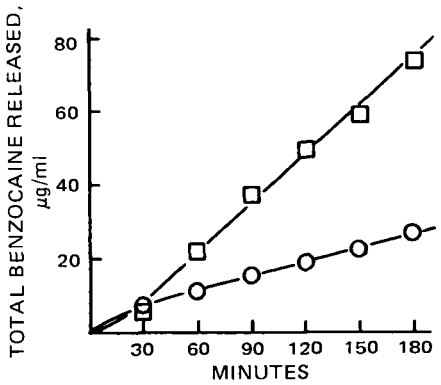

Figure 6—*Comparison of the release of benzocaine from two preparations. Key:* □, *Vehicle A containing 1% (w/w) benzocaine and 0.25% (w/w) sodium salicylate; and* ○, *Vehicle C containing 5% (w/w) benzocaine.*

CONCLUSIONS

1. The diffusion of benzocaine from various topical vehicles was studied using a dialysis cell fitted with a cellulose membrane. The rate of release for preparations containing 1% (w/w) benzocaine was in the following order: water-miscible vehicles > oil-in-water emulsion cream vehicles > white soft paraffin > water-in-oil emulsion cream vehicles.

2. The effect of sodium salicylate, an agent that complexes with benzocaine, on the rate of diffusion of drug was also investigated. The water-miscible base and aqueous cream vehicles exhibited increased release profiles.

3. The extent of the modifying effect on the release rate of drug by the complexing agent depended upon the concentration of sodium salicylate in the polyethylene glycol vehicle containing 1 and 2% (w/w) benzocaine. This result has been attributed to the formation of different types of complexes and to the differing solubilities and physical properties of these complexes.

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* Present address: Department of Pharmaceutics, Faculty of Pharmacy, Alexandria University, Alexandria, U.A.R.

[x] To whom inquiries should be directed. Present address: Department of Pharmacy, Faculty of Medicine, University of Dar es Salaam, P.O. Box 20693, Dar es Salaam, Tanzania.

Gastric Acid Inactivation of Erythromycin Stearate in Solid Dosage Forms

B. G. BOGGIANO [x] and M. GLEESON

Abstract □ The effect of hydrochloric acid at pH 1.2–3.2 on erythromycin stearate and commercial dosage forms of erythromycin stearate was studied. Under all conditions examined, erythromycin was readily dissolved from the stearate as hydrochloride, and rapidly lost its biological activity in solution. The inclusion of pepsin in the test systems did not affect the results. Although formulation differences somewhat affected the rate of destruction, acid lability was exhibited by all products examined, except enteric-coated tablets. Amounts of acid considered to be normal in the fasting stomach contents of adults during the time likely for a dose to remain in the stomach caused 70–90% destruction within 15 min after the shells started to rupture. Amounts of hydrochloric acid appreciably less than 1 mEq, representing abnormally small quantities even in the fasting state, caused destruction ranging from 30 to 70% of the doses in 15 min. These results are not reconcilable with published statements that the sensitivity of erythromycin to gastric acid is overcome by providing the antibiotic in the form of stearate salt.

Keyphrases □ Erythromycin stearate—effect of hydrochloric acid at gastric pH, commercial dosage forms □ Gastric acid inactivation—erythromycin stearate, effect of hydrochloric acid at gastric pH, commercial dosage forms □ Antibiotics—erythromycin stearate, effect of hydrochloric acid at gastric pH, commercial dosage forms

Current knowledge appears to have rationalized most bioavailability issues with erythromycin. However, there remains the perplexing question of erratic blood levels from the stearate, particularly in the nonfasting stage. In a four-way crossover study on 12 subjects, the average peak serum level of erythromycin from the stearate was less than half that from the estolate following single 250-mg doses in fasting subjects (1). In the presence of food, the estolate showed no decrease in average peak serum levels but the levels from the stearate were greatly decreased, seven of the 12 subjects failing to show any absorption. Similar results were later found in a crossover study of 30 subjects in the nonfasting state (2).

BACKGROUND

The reduction in serum levels from the stearate in the presence of food could be due to increased gastric acidity or to the food *per se*. In one study (1), the presence of food did not reduce the absorption of the estolate; this finding suggests that the more likely reason for the reduced stearate levels could be increased gastric acidity.

The destructive effect of gastric acidity on unprotected erythromycin base has been known since Josselyn and Sylvester (3) reported an *in vivo* study in 1953. In the same year, they also reported a study on the stearate salt of erythromycin taken in suspension form, buffered with sodium citrate (4). They found that food did not reduce the absorption of erythromycin from the stearate and concluded that the less soluble stearate salt was resistant to gastric acid when taken in this form. Since then, unprotected solid dosage forms of erythromycin stearate have been marketed extensively.

The literature contains conflicting statements on the effect of gastric acidity on the stearate. In 1970 the *Medical Letter* (5) and in 1971 Wade (6) stated that erythromycin stearate is acid labile. However, more recently, Garrod and O'Grady (7) and Tolhurst *et al.* (8) claimed that the stearate is stable in the presence of gastric acid and that the base is liberated from it in the duodenum where it is absorbed. This divergence of published opinion and the low and erratic blood levels reported for solid dosage forms of the stearate suggested that an *in vitro* study of the effect of gastric acid on a range of solid pharmaceutical formulations of erythromycin stearate was warranted.

There has been no reported study on this topic. However, Stephens *et al.* (9) reported a measurement showing that unprocessed erythromycin stearate was rapidly inactivated by gastric acid. This finding contrasted markedly with their results on propionyl erythromycin lauryl sulfate (erythromycin estolate), which retained virtually full activity after prolonged exposure to gastric acid. The authors summarized the chemistry by explaining that propionyl