(3) T. Higuchi and L. Lachman, *J. Amer. Pharm. Ass., Sci. Ed.*, **44**, 521(1955).
(4) J. C. Lach and W. A. Pauli, *Drug Stand.*, **27**, 104(1959).
(5) L. Lachman and T. Higuchi, *J. Amer. Pharm. Ass., Sci. Ed.*, **46**, 32(1957).
(6) G. Levy and T. Matsuzawa, *J. Pharm. Sci.*, **54**, 1003(1965).
(7) G. Levy and E. J. Mroszczak, *ibid.*, **57**, 235(1968).
(8) P. Singh, J. K. Guillory, T. D. Sokoloski, L. Z. Benet, and Y. N. Bhatia, *ibid.*, **55**, 63(1966).
(9) B. Idson, in "Topics in Medicinal Chemistry," vol. 4, J. L. Rabinowitz and R. M. Myerson, Eds., Wiley–Interscience, New York, N.Y., 1971, p. 207.
(10) P. Grasso and A. B. G. Lansdown, *J. Soc. Cosmet. Chem.*, **23**, 481(1972).
(11) J. Adriani and H. Dalili, *Anesth. Analg.*, **50**, 834(1971).
(12) J. W. Ayers and P. A. Laskar, *J. Pharm. Sci.*, **63**, 1402(1974).
(13) G. M. Ghali, A. M. Saleh, and M. M. Motawi, in "XII Conference of Pharmaceutical Sciences," Cairo, U.A.R., Nov. 1971, p. 117.
(14) G. M. Ghali, A. M. Saleh, and M. M. Motawi, in *ibid.*, p. 118.
(15) A. M. Saleh and P. York, *Pharm. Ind.*, in press.
(16) A. C. Bratton and E. K. Marshall, Jr., *J. Biol. Chem.*, **128**, 537(1939).
(17) T. Higuchi, *J. Soc. Cosmet. Chem.*, **11**, 85(1960).
(18) W. I. Higuchi, *J. Pharm. Sci.*, **51**, 802(1962).

ACKNOWLEDGMENTS AND ADDRESSES

Received April 4, 1975, from the *Department of Pharmaceutics, Faculty of Pharmacy, University of Khartoum, Khartoum, Sudan.*

Accepted for publication May 13, 1975.

* 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

Table I—Test Solutions

Solution	pH	Volume, ml	Hydrochloric Acid, mEq
1	1.2	50	4.2[a]
2	1.2	50	4.2
3	2.2	50	0.37
4	2.2	100	0.74
5	3.2	50	0.05
6	3.2	100	0.1

[a] With pepsin.

erythromycin (and erythromycin) dissolve in gastric juice and quickly lose their antibiotic activity. Carboxylic acid salts of these substances, even though water insoluble, behave similarly because the hydrochloric acid of gastric juice displaces the carboxylic acid and dissolves the antibiotic as the soluble hydrochloride salt. However, the estolate is a salt of the very strong acid, lauryl sulfuric acid, and gastric acid is not strong enough to displace the acid radical from the insoluble estolate; hence, it remains undissolved and potent for prolonged periods in gastric acid.

The following study was designed to expand on the observation by Stephens *et al.* (9) by examining *in vitro* the effect of acidity conditions on erythromycin stearate and solid pharmaceutical formulations of it. The purposes were to clarify conflicting published statements and to find a basis for understanding reported blood level results.

EXPERIMENTAL

Design—The study was divided into three parts: Study 1, the effect of hydrochloric acid on pure (unprocessed) erythromycin stearate, *i.e.*, the rate of dissolution of erythromycin from the stearate as hydrochloride; Study 2, the rate of inactivation of erythromycin when dissolved in hydrochloric acid; and Study 3, the rate of dissolution of erythromycin from commercial solid dosage forms when treated with a range of simulated gastric fluids.

Test Solutions—Approximately 4 mEq of hydrochloric acid was selected as a realistic simulation of the amount of gastric acid likely to be present over a 30-min period in a fasting adult, *i.e.*, the acid level expected to be present in the resting stomach contents (1–2 mEq) plus the average amount generated during 30 min without stimulation (~ 1 mEq every 15 min). In practice, larger amounts of hydrochloric acid could be present if the dose had been taken shortly before or after food. In selecting this amount of acid, several reference sources were used (10–12).

The effect of lower amounts of acid was also studied, including the very low level of 0.05 mEq to represent the situation in subjects markedly deficient in acid. The pH range of the test solutions was 1.2–3.2. A volume of 50 ml was selected for most tests, although in some cases 100 ml was used to obtain the desired balance of pH *versus* total acidity.

Six test solutions were selected (Table I). Several of these solutions were used for all three studies, depending on the pH and amount of hydrochloric acid required in each case. Solution 1 was simulated gastric fluid USP, containing pepsin and sodium chloride. Solution 2 was simply hydrochloric acid at the same pH and concentration for comparison with Solution 1 to assess whether pepsin contributed to breakdown. Solutions 3–6 were also dilutions of hydrochloric acid.

Exposure Times—There are ample references to stomach emptying times and to the $t_{1/2}$ (time for half the gastric contents to be emptied) following a meal. Buckler (13) quoted 2–6 hr for the former, and the latter was measured at slightly more than 1 hr (14, 15). However, times for which a single dose of medicament could be exposed to the gastric contents in the fasting state were more difficult to define. Based on previous work (16, 17), 30 min was selected as a conservatively realistic simulation of the time a solid dose would remain in an empty stomach. However, longer exposure times were also studied since doses could sometimes be taken in the presence of food and probably retained longer in the stomach.

Test Method—A test method was devised to give relatively quiescent conditions of exposure of the dose to the continuously moving solution, with no direct agitation applied to the dose itself.

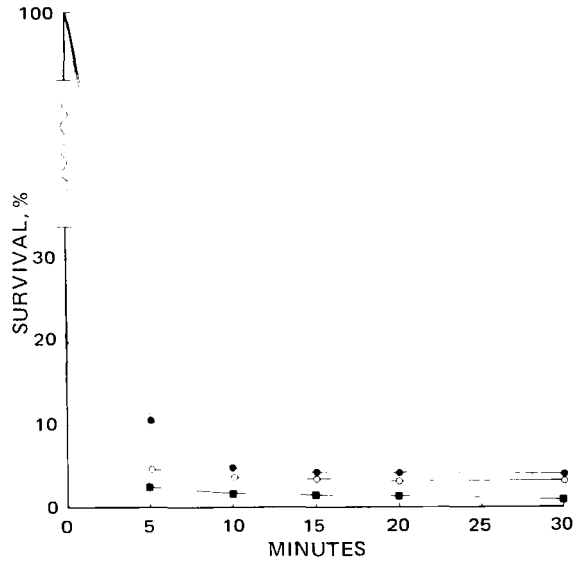


Figure 1—*Inactivation of erythromycin (250 mg, 0.34 mEq) in hydrochloric acid at different pH values. Key:* ■, *pH 1.2, 4.2 mEq;* ○, *pH 2.35, 0.74 mEq; and* ●, *pH 2.9, 0.45 mEq.*

For Studies 1 and 3 (see *Design*), the test solution was placed in a 100- or 200-ml round-bottom flask[1] and warmed to 37°. Erythromycin stearate (392 mg, equivalent to 250 mg of erythromycin), or a dose unit, was added and the stoppered flask was inclined at 45° and rotated at 30 rpm in a water bath controlled at 37 ± 0.5°. Capsules were prevented from floating by means of a glass loop made from a capillary tube.

For Study 3, the time of the first disruption of the shell and the appearance of the contents was recorded as the "disintegration time." Exposure periods were timed from the same point. After the appropriate exposure period, the solution was decanted quickly from the solid through Whatman 541 filter paper, the contents of the flask were washed with 15 ml of cold (18–20°) distilled water, and the washings were decanted through the filter. Four more washings were performed, *i.e.*, until free from acid, and the solid residue in the flask was transferred to the filter. The residue on the filter was dried to constant weight at 20° under vacuum. In Study 3, each residue was well mixed in an agate mortar to ensure homogeneity.

For Study 2, erythromycin base (250 mg, 0.34 mEq) was dissolved in the test solutions in a stoppered flask immersed in a 37° constant-temperature water bath. At intervals up to 30 min, 1-ml samples were removed and immediately diluted with 19 ml of pH 8.0, 0.8 *M* phosphate buffer. Solutions 2 and 4 were used (4.2 and 0.74 mEq of acid, respectively), and their final pH values were 1.2 and 2.35, respectively. A special solution also was used containing 0.45 mEq of hydrochloric acid in 100 ml. This was the lowest acidity–volume system capable of dissolving 250 mg of erythromycin, the final pH being 2.9.

Assays—Biological assays were performed on the dose residues and test solutions according to the cylinder-plate method of USP XVIII (p. 858), using *Sarcina lutea* as the test organism. The assay has the lower detectable limit of approximately 0.02 μg/ml.

Products Tested—A range of products was tested: nonenteric Capsule A from Source X, nonenteric Capsule B from Source Y, nonenteric Capsule C from Source Z, nonenteric film-coated Tablet A from Source X, and enteric-coated Tablet B from Source Y.

The same batch of each product was used throughout except for enteric-coated Tablet B; several batches of Tablet B were examined to check the reproducibility of its resistance to coat shedding in an acid medium. A separate dose unit was required for each individual experiment, *i.e.*, for each exposure period in each test solution. Thus, in addition to the normal limitations in experimental and assay reproducibility, each result contained a "deviation potential" because of the permitted variation in drug content between individual doses.

[1] Quickfit.

Table II—Erythromycin Surviving in Residues after Treatment of Erythromycin Stearate (392 mg, 0.34 mEq) with Solutions 2, 3, and 5

Exposure Time, min	Solution 2 (4.2 mEq)			Solution 3 (0.37 mEq)			Solution 5 (0.05 mEq)		
	Residue, mg	Surviving Erythromycin, mg	Survival, %	Residue, mg	Surviving Erythromycin, mg	Survival, %	Residue, mg	Surviving Erythromycin, mg	Survival, %
5	117	Nil	Nil	205	79	32	—	—	—
10	119	Nil	Nil	168	42	17	310	184	74
15	118	Nil	Nil	157	31	12	—	—	—
20	117	Nil	Nil	151	25	10	312	186	74
40	119	Nil	Nil	126	Nil	Nil	314	188	75
60	118	Nil	Nil	127	Nil	Nil	308	182	74

RESULTS

Study 1: Rate of Dissolution of Erythromycin from Unprocessed Erythromycin Stearate—The weights of the dried residues are given in Table II, together with weights and percentages of surviving erythromycin after treatment with Solutions 2, 3, and 5. All residues after testing against Solution 2 (pH 1.2, 4.2 mEq) and the 40- and 60-min residues after treatment with Solution 3 (pH 2.2, 0.37 mEq) were identified as pure stearic acid from their IR spectra (potassium bromide disk). The remaining residues were mixtures of erythromycin (stearate) and stearic acid.

The theoretical weight of stearic acid in each 392-mg sample of erythromycin stearate was 142 mg. The bulk of the stearic acid was deposited as an insoluble residue with part of it remaining in solution. Taking the undissolved portion as 126 mg (*vide* the final residue after treatment with Solution 3), the amount of erythromycin in the other residues was calculated by difference. Assays were not done for this series of tests, since this study was simply a pilot as a guide to the study on dosage forms.

In Solution 2, the acid represented a 12-fold stoichiometric excess. At this pH and excess acidity, full dissolution had occurred within 5 min. In Solution 3, which represented only about a 10% excess of acid, full dissolution of the erythromycin required 30–40 min. However, approximately 70% had been dissolved in 5 min. In Solution 5 (pH 3.2, 0.05 mEq), the amount of acid represented only about 15% of the stoichiometric equivalent of the test sample (0.34 mEq).

Although full dissolution of the erythromycin could not occur under these conditions, the actual proportion dissolved was in excess of the theoretical (26 *versus* 15%), with equilibrium being reached within 10 min. This finding can be explained on the basis of the intrinsic solubility of erythromycin base and some degree of catalytic behavior by the small level of hydrochloric acid. This particular experiment indicates the rapidity at which a trace of acid at relatively high pH could destroy at least its own equivalent of the stearate.

Study 2: Rate of Inactivation of Erythromycin at Three pH Values—The rates of inactivation of the erythromycin under the three test conditions are given graphically in Fig. 1. Under each condition, 90% or more of the antibiotic was inactivated in the first 5 min. The pH 1.2 condition (4.2 mEq) represented a relatively large excess of acid, but one that would not be abnormal *in vivo* even in the fasting state. The pH 2.35 (0.74 mEq) and pH 2.9 (0.45 mEq) conditions represented acidity levels appreciably lower than the average *in vivo* fasting situation with a relatively small excess of acid over antibiotic; but even under these conditions, the destruction of the antibiotic was almost as rapid as at pH 1.2.

If it is assumed that 0.34 mEq of hydrochloric acid displaces the stearic acid component and dissolves the erythromycin (Study 1), it is apparent that considerably less than 1 mEq of hydrochloric acid can concurrently dissolve and destroy at least two-thirds of a dose in 5 min.

Study 3: Rate of Dissolution of Erythromycin from Commercial Solid Dosage Forms—All products, except Tablet B, started to disintegrate at varying times in the test solutions. Tablet B had not shed its coat after 2 hr at 37° in the pH 1.2 medium. This product was checked for disintegration in simulated intestinal fluid BP, and disintegration was complete in times ranging from 10 to 22 min for 20 samples from different production batches. For the other products, the times of incipient disintegration are given in Table III.

Because it resisted disintegration in the acid medium, Tablet B was excluded from further study. All four of the remaining products were tested against pepsin-containing simulated gastric fluid USP (Solution 1, pH 1.2), but only Capsules A and B were tested against the nonpepsin-containing pH 1.2 medium (Solution 2) to obtain the comparative data on the effect of pepsin. All four products were tested against Solutions 3 and 4, but Solution 5 was excluded from this study. Only Capsule B was tested with Solution 6 (pH 3.2) since the very small amount of acid (0.1 mEq) made this information of minor interest.

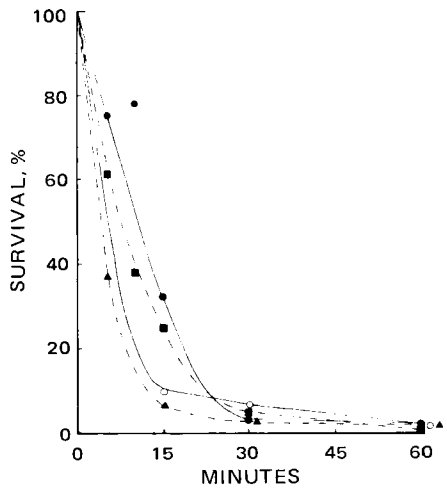


Figure 2—*Dissolution of erythromycin from nonenteric erythromycin stearate dosage forms treated with Solution 1 (pH 1.2, 4.2 mEq of hydrochloric acid, plus pepsin and sodium chloride). Key:* ●—●, *Capsule A;* ■- - - -■, *Capsule B;* O——O, *Capsule C; and* ▲- - - -▲, *Tablet A.*

Table III—Times of First Rupture of Shells or Coats of Nonenteric Dosage Forms

Product	Minutes					Mean Time, min
	Solution 1	Solution 2	Solution 3	Solution 4	Solution 6	
Capsule A	6, 4, 2, 2, 2	2, 3, 2, 2, 2	3, 3, 3, 6	4, 9, 3, 10, 10, 10	—	4.4
Capsule B	2, 2, 1, 2, 2	2, 2, 2, 2, 2	3, 2, 2, 2, 2, 2	2, 3, 2, 2, 2, 3	4, 2, 2, 2, 2, 2	2.1
Capsule C	2, 2, 2	—	3, 2, 3, 3	2, 3, 3, 3	—	2.5
Film-coated Tablet A	22, 20, 16, 11	—	13, 6, 7, 14, 10	7, 11, 3, 14	—	12.2

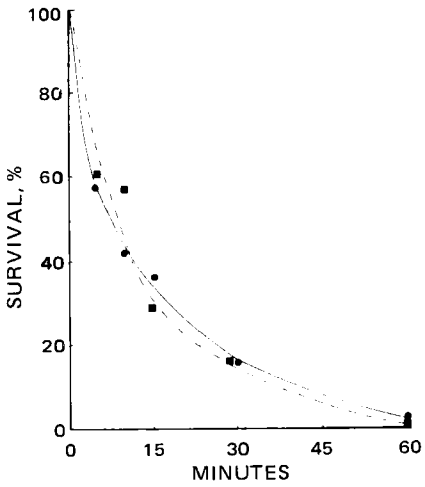


Figure 3—*Dissolution of erythromycin from nonenteric erythromycin stearate dosage forms treated with Solution 2 (pH 1.2, 4.2 mEq of hydrochloric acid, no pepsin). Key:* ●——●, *Capsule A; and* ■- - - -■, *Capsule B.*

The amounts of erythromycin surviving in the residues are given in Figs. 2–6. The percentage survival of erythromycin is quoted to the nearest 1% and relative to the nominal content of 250 mg/dose.

Solution 1 (pH 1.2, 4.2 mEq Acid with Pepsin)—Figure 2 shows that under these conditions all four nonenteric products were destroyed to degrees ranging from 70 to 90% in the first 15 min after the acid reached the contents. The most sensitive products were Capsule C and Tablet A, probably due to a lower proportion of buffering agent in these products. This amount of acid is approximately the amount likely to be available during a 30-min period in the resting stomach contents of adults.

Solution 2 (pH 1.2, 4.2 mEq Acid, No Pepsin)—Capsules A and B showed an almost identical destruction pattern (Fig. 3). Comparison with Fig. 2 does not suggest that pepsin significantly contributed to degradation, certainly not within the first 15 min by which time 70% of the erythromycin had been dissolved.

Solutions 3 and 4 (pH 2.2, 0.37 and 0.74 mEq Acid, Respectively)—The results in Figs. 4 and 5 show that degradation was again very rapid even at this higher pH and these low levels of acidity. On the average, it was of the order of 40 and 70%, respectively, in the first 15 min, apart from Capsule A which contained the highest amount of buffering agent. At these very low levels of acid, the presence of significant amounts of buffering agent could hinder degradation appreciably, since the amount of acid used was only slightly in excess of the chemical equivalent of erythromycin stearate. However, these levels of acid are well below those normally found even in the fasting stomach. The results using Solutions 1 and 2 show that with more normal amounts of acid, the quantity of buffers that can be incorporated in capsules or tablets fails to inhibit degradation significantly.

Solution 6 (pH 3.2, 0.1 mEq Acid)—The results on Capsule B (Fig. 6) were very erratic, but this is understandable with such a small amount of acid. Factors such as the rate of penetration of acid into the individual capsules used in each test would affect the results significantly, as would the permitted variation in content between individual capsules. Nevertheless, the figures indicate that approximately 30% of the erythromycin had been dissolved in about 15 min. Since the amount of acid represented 29% of the stoichiometric equivalent of erythromycin stearate, even a trace of acid at relatively high pH can rapidly dissolve approximately its own equivalent of erythromycin from the stearate, even in a dose containing a proportion of buffering agent.

DISCUSSION

The results show that erythromycin stearate is very sensitive to gastric acid *in vitro*, and any reduction in the rate and degree of inactivation is due to the nature of the pharmaceutical formulation. The 4.2 mEq of hydrochloric acid produced 70–90% destruction of all nonenteric products tested within 30 min, which included the time for disintegration of the shells. The period of most rapid degradation was the first 5 min after rupture of the shells. Furthermore, 0.74 mEq, which *in vivo* would represent a very low amount of gastric acid even in the fasting state, produced an average of 50–60% destruction within 15 min of shell disintegration.

It is difficult to relate these results directly to the *in vivo* situation. However, the study was designed to simulate as realistically

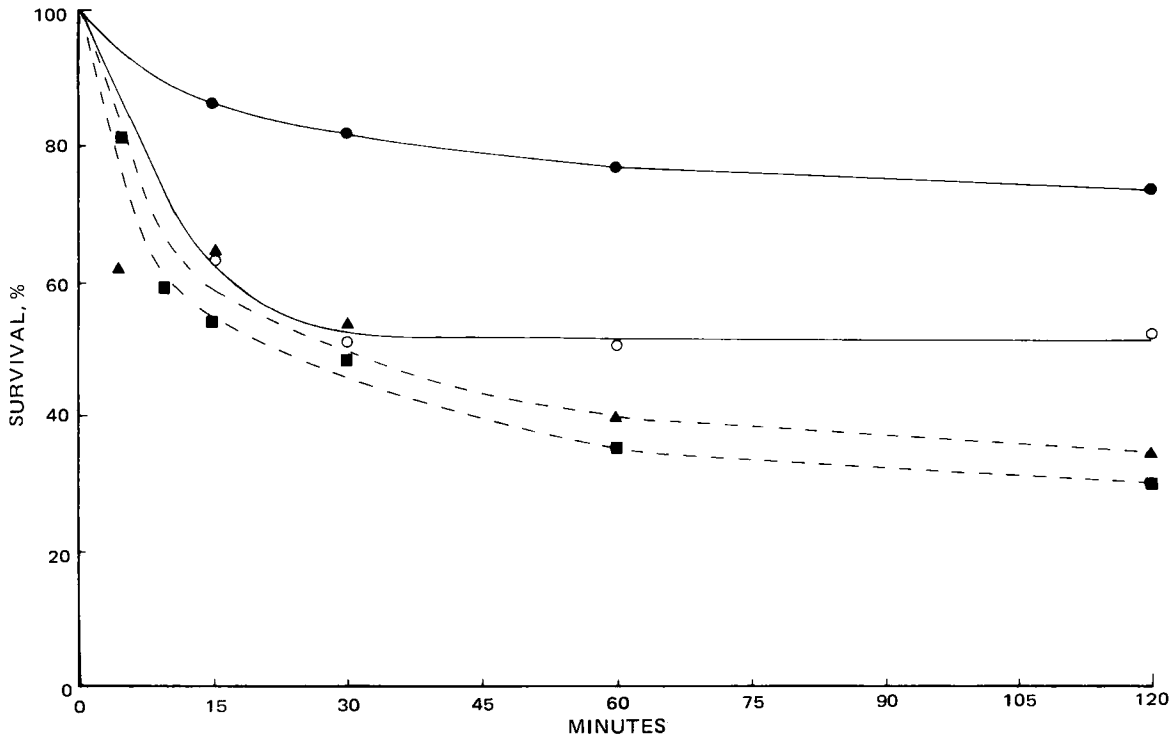


Figure 4—*Dissolution of erythromycin from nonenteric erythromycin stearate dosage forms treated with Solution 3 (pH 2.2, 0.37 mEq of hydrochloric acid). Key:* ●——●, *Capsule A;* ■- - - -■, *Capsule B;* O—O, *Capsule C; and* ▲- - - -▲, *Tablet A.*

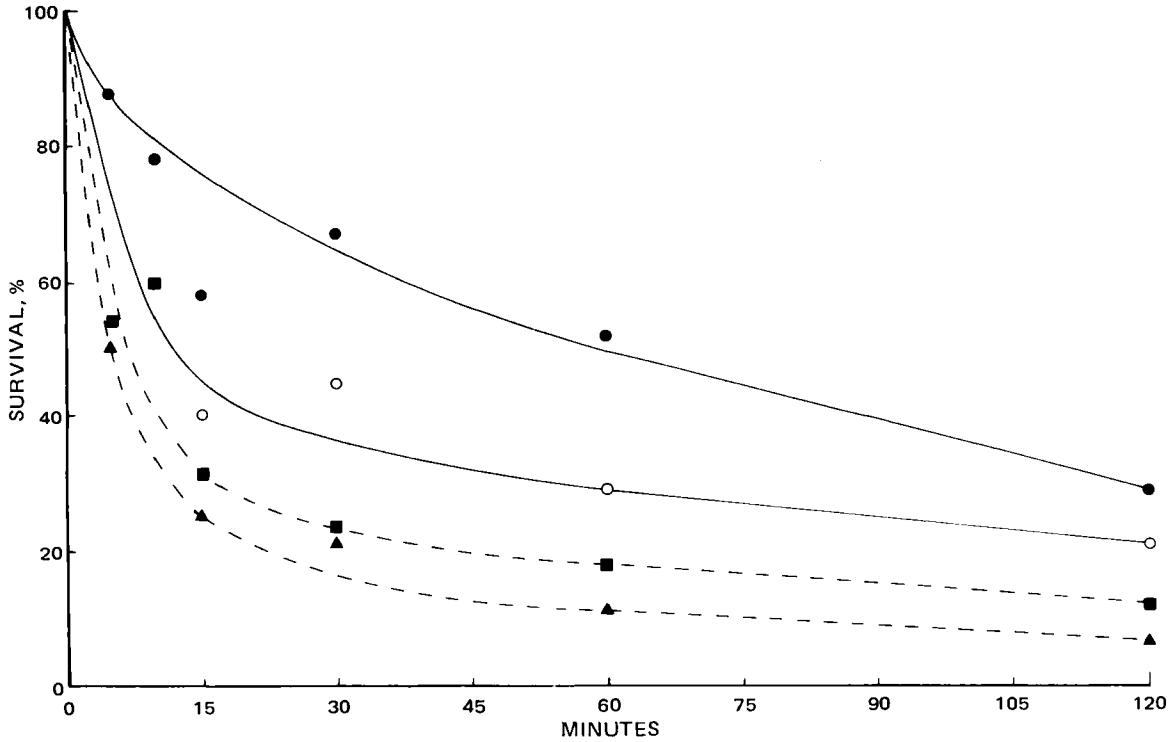


Figure 5—*Dissolution of erythromycin from nonenteric erythromycin stearate dosage forms treated with Solution 4 (pH 2.2, 0.74 mEq of hydrochloric acid). Key: ●——●, Capsule A; ■- - - -■, Capsule B; ○——○, Capsule C; and ▲- - - -▲, Tablet A.*

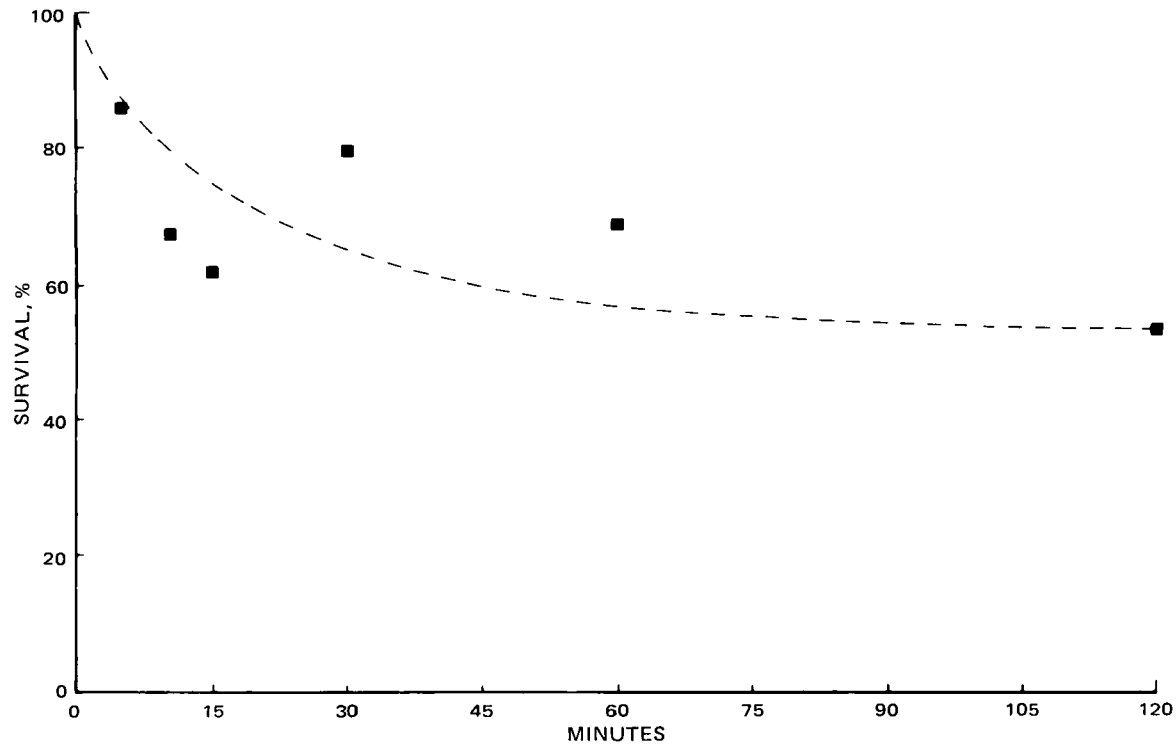


Figure 6—*Dissolution of erythromycin from Capsule B treated with Solution 6 (pH 3.2, 0.1 mEq of hydrochloric acid).*

as possible the range of acidity conditions found in the human stomach in the fasting state. The data show clearly that published statements on the acid stability of erythromycin stearate have been in error, and it is likely that a comparable degree of acid destruction occurs *in vivo*. This situation could account for the low serum levels found by Griffith and Black (1) compared to the estolate in fasting subjects and the much lower, or nonexistent, levels found by the same authors (1) and Bell (2) in nonfasting subjects.

REFERENCES

(1) R. S. Griffith and H. R. Black, *Amer. J. Med. Sci.*, **247**, 69(1964).

(2) S. M. Bell, *Med. J. Aust.*, **2**, 1280(1971).

(3) L. E. Josselyn and J. C. Sylvester, *Antibiot. Chemother.*, **1953**, 63.

(4) J. C. Sylvester and L. E. Josselyn, *ibid.*, **1953**, 930.

(5) *Med. Lett.*, **12**, 35(1970).
(6) D. N. Wade, *New Ethicals*, 12(10), 9(1971).
(7) L. P. Garrod and F. O'Grady, *Antibiot. Chemother.*, **1971**, 169.
(8) J. C. Tolhurst, G. Buckle, and S. W. Williams, "Chemotherapy with Antibiotics and Allied Drugs," 3rd ed., N.H.M.R.C., Australian Government Publishing Service, p. 78.
(9) V. C. Stephens, J. W. Conine, and H. W. Murphy, *J. Amer. Pharm. Ass., Sci. Ed.*, **48**, 620(1959).
(10) H. Varley, "Practical Clinical Biochemistry," William Heinemann Books Ltd., London, England, 1963, p. 258.
(11) G. F. Stening, *Mod. Med. Aust.*, **16**(5), 15(1973).
(12) F.D.A. Antacid Monograph, First Proposal, F.D.C. Reports, Special Supplement, Apr. 9, 1973.
(13) K. G. Buckler, *Gut*, **8**, 138(1967).
(14) G. H. Griffith, G. M. Owen, H. Campbell, and R. Shields, *Gastroenterology*, **54**, 1(1968).
(15) M. R. Colmer, G. M. Owen, and R. Shields, *Brit. Med. J.*, **2**, 448(1973).
(16) T. M. Feinblatt and E. A. Ferguson, *N. Engl. J. Med.*, **256**, 331(1957).
(17) J. Nimmo, R. C. Heading, P. Tothill, and L. F. Prescott, *Brit. Med. J.*, **1**, 587(1973).

ACKNOWLEDGMENTS AND ADDRESSES

Received November 7, 1973, from the *Research Division, F. H. Faulding & Co. Ltd., 48 Beans Road, Thebarton, South Australia, 5031.*

Accepted for publication June 11, 1975.

The authors thank D. R. Best of Hawthorn Park Research Laboratories Pty Ltd., Mittagong, New South Wales, Australia, for performing the biological assays.

[x] To whom inquiries should be directed.

Release and Elimination of ^{14}C-Fluphenazine Enanthate and Decanoate Esters Administered in Sesame Oil to Dogs

JACQUES DREYFUSS [x], JOHN J. ROSS, Jr., JAMES M. SHAW, IRVING MILLER, and ERIC C. SCHREIBER

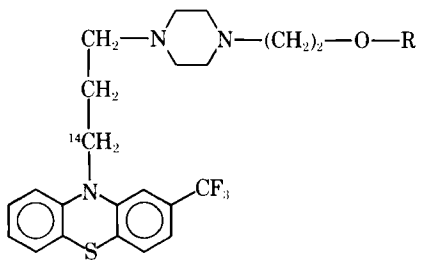
Abstract □ The rates of release of ^{14}C-fluphenazine enanthate and ^{14}C-fluphenazine decanoate were compared in two groups of five male dogs. Each dog was given a single dose (2 mg/kg im) of either the enanthate or decanoate ester in sesame oil. The times required to attain maximum concentrations of radioactivity in plasma were 3.8 ± 0.5 days (±*SE*) for the enanthate ester and 10.6 ± 1.1 days for the decanoate ester ($p < 0.001$); maximum concentrations of radioactivity in the plasma at these times were 16.7 ± 1.1 and 11.1 ± 1.2 ng/ml, respectively ($p < 0.01$). However, 35 days after dosing, the concentrations of radioactivity in plasma were greater for the decanoate ester than for the enanthate ester. The times required for 50% of the dose to be excreted in the urine and feces were 7.8 ± 0.5 days for the enanthate ester and 22.6 ± 4.4 days for the decanoate ester ($p < 0.05$). The total amounts excreted in 35 days were 85.4 ± 1.8 and 68.8 ± 6.6% of the dose for the enanthate and decanoate esters, respectively; the average half-times for the rates of release of radioactivity from depot and body, as calculated from the data for total excretion, were 5.55 days for the enanthate ester and 15.4 days for the decanoate ester. Thirty-five days after dosing, the amount of the dose present in the injection site was 4.6 ± 1.6% for the enanthate ester and 18.6 ± 5.7% for the decanoate ester. Two groups of six dogs each were protected against the emetic effects of apomorphine more than twice as long by the decanoate ester than by the enanthate ester after the subcutaneous administration of single 8-mg/kg doses of either drug in sesame oil ($p < 0.05$). Based on measurements of total radioactivity, it was concluded that the decanoate ester was released from the depot at less than one-half the rate of the enanthate ester.

Keyphrases □ Fluphenazine—enanthate and decanoate esters, rates of release and elimination in urine and feces, dogs □ Elimination—renal and GI, fluphenazine enanthate and decanoate esters, dogs

Although many studies conducted in humans have demonstrated the clinical efficacy of long-acting esters of fluphenazine, there is little objective evidence to enable one to quantitate their slow-release characteristics. Such studies are difficult to conduct in humans for the following reasons:

1. Sufficient radioactivity cannot be administered to humans to allow for the detection of the low concentrations of the drug or its metabolites present in the circulation during a prolonged time.
2. It is generally not feasible, even under the best of circumstances, to collect excreta quantitatively over a month, especially when most radioactivity is excreted in the feces as it is with fluphenazine and its esters (1–3).
3. At the conclusion of the study, it is not possible to determine the amount of drug remaining in the depot at the injection site.

The relative rates of release of the enanthate (I*a*) and decanoate (I*b*) esters of ^{14}C-fluphenazine were compared in dogs because this species could be given



I*a*: R = $-C(=O)-(CH_2)_5CH_3$

I*b*: R = $-C(=O)-(CH_2)_8CH_3$