Surface Tension Lowering and Dissolution Rate of Hydrocortisone from Solid Solutions of Selected *n*-Acyl Esters of Cholesterol

KWON HO KIM and CHARLES I. JAROWSKI ˣ

Abstract □ The dissolution of hydrocortisone into simulated intestinal fluid from lipid delivery systems followed second-order kinetics. As the ratio of hydrocortisone to lipid was increased from 1:1 to 1:6, the dissolution rate decreased. Solvent deposition of solid solutions of hydrocortisone and lipid on lactose resulted in the enhancement of the dissolution rate. For the 1:1 hydrocortisone–lipid solid solutions, the rank order of the dissolution rate was hydrocortisone–cholesteryl stearate, hydrocortisone, hydrocortisone–cholesterol, hydrocortisone–cholesteryl acetate, hydrocortisone–cholesteryl palmitate, hydrocortisone–cholesteryl *n*-butyrate, hydrocortisone–cholesteryl laurate, and hydrocortisone–cholesteryl *n*-decylate. A direct correlation was found between the dissolution rate of hydrocortisone and the surface tension lowering of simulated intestinal fluid by the corticoid and various lipids.

Keyphrases □ Hydrocortisone—dissolution into simulated intestinal fluid from solid solutions with cholesterol or various esters, effect on surface tension □ Cholesterol and various esters—solid solutions with hydrocortisone, dissolution into simulated intestinal fluid, effect on surface tension □ Dissolution—hydrocortisone into simulated intestinal fluid from solid solutions with cholesterol or various esters □ Surface tension—simulated intestinal fluid, effect of solid solutions of hydrocortisone and cholesterol or various esters □ Solid solutions—hydrocortisone and cholesterol or various esters, dissolution into simulated intestinal fluid, effect on surface tension □ Glucocorticoids—hydrocortisone, dissolution into simulated intestinal fluid from solid solutions of cholesterol or various esters, effect on surface tension □ Lipids—cholesterol and various esters, solid solutions with hydrocortisone, dissolution into simulated intestinal fluid, effect on surface tension

The utility of lipid drug delivery systems has been amply demonstrated. Griseofulvin bioavailability was improved when micronized particles were administered in a corn oil-in-water emulsion (1). Oral progesterone administration gave higher blood levels when the hormone was solvent deposited on lactose as a solid solution with cholesterol or its acetate ester (2). Significant improvement in the *in vitro* stability of the potassium salts of penicillins G and V was achieved when they were coated with cholesterol, its acetate ester, or β-sitosterol (3). The oral administration of such coated penicillins, as well as erythromycin lactobionate, resulted in an increase in the urinary recovery of antibiotic activity (3). The urinary excretion of unchanged salicylate was increased when salicylic acid was given as a solid solution in cholesteryl *n*-decylate (4).

The purpose of this investigation was to study the *in vitro* dissolution rate of hydrocortisone (I) from solid solutions containing cholesterol (II) or one of the following cholesteryl esters: acetate (III), *n*-butyrate (IV), *n*-decylate (V), laurate (VI), palmitate (VII), and stearate (VIII). In addition, the hydrocortisone dissolution rate was determined after solvent deposition of such solid solutions on powdered lactose (IX). The surface tension-lowering effect of selected candidates was measured to ascertain if a direct correlation with the dissolution rate could be made. An additional objective was to treat the accumulated data mathematically to determine the kinetic order followed by hydrocortisone dissolution from such solid solutions.

EXPERIMENTAL

Materials—The following were obtained from commercial sources: hydrocortisone[1], cholesterol[2], cholesteryl acetate[2], cholesteryl butyrate[2], cholesteryl *n*-decylate[2], cholesteryl laurate[2], cholesteryl palmitate[2], cholesteryl stearate[2], lactose powder USP[3], methanol[4], absolute chloroform NF[3], sodium hydroxide[4] (ACS), and monobasic sodium phosphate[5] (laboratory grade).

Equipment—The following equipment was used: a capillary melting-point apparatus[6], a constant-temperature shaker bath[7], a tensiometer[8], a pH meter[9], a dissolution basket stirrer[10], and a spectrophotometer[11].

Hydrocortisone–Lipid Solutions with and without Lactose—Powdered hydrocortisone and the various lipids were weighed in ratios of 1:1, 1:3, and 1:6. The mixture of hydrocortisone and lipid was dissolved in a minimal quantity of 50% (v/v) chloroform in methanol. The solutions were stirred with a magnetic stirrer, and the solvent was evaporated in a stream of air. The residues were completely dried in an oven set at 40° and then ground in a mortar and passed through an 80-mesh screen. After blending to ensure homogeneity, duplicate aliquots were assayed. Only samples containing 100 ± 5% of the theoretical quantity of hydrocortisone were used in the dissolution studies. Assays outside the 5% limits were rare.

Solvent deposition of the various hydrocortisone–lipid combinations on lactose was conducted similarly. Weight ratios of hydrocortisone–lipid–lactose of 1:1:6, 1:3:6, and 1:6:6 were prepared. Again, assays outside the 5% limits were rare.

Dissolution Studies—The hydrocortisone dissolution rate in simulated intestinal fluid USP, without pancreatin, was determined by the Short *et al.* (5) beaker method. Simulated intestinal fluid, 200 ml, was placed in a 300-ml beaker and maintained at 37 ± 0.5° in a constant-temperature water bath. The dissolution medium was stirred with the basket recommended for the USP dissolution test. The stirrer was vertically centered and lowered to a depth of 1 cm above the bottom of the beaker. The stirrer was attached to a synchronous motor set to rotate at 150 rpm.

Accurately weighed samples, equivalent to 60 mg of pure drug, were spread over the surface of the dissolution medium. Any aggregates that formed at this stage were lightly broken up with a microspatula within 10 sec after sample addition. Subsequently, the surface was not disturbed except when 10-ml aliquots were withdrawn at 15, 30, 45, 60, 90, 120, and 150 min. The samples were withdrawn through a sintered-glass filter of medium porosity and filtered again through a membrane filter[12] (0.45 μm). Dissolution medium, 10 ml, was replaced immediately after removal of the aliquot.

The filtrate was diluted to an appropriate concentration in a volumetric flask, and the absorbance was measured at 250 nm. A cumulative correction was made for the previously removed samples in determining the total quantity of hydrocortisone dissolved (6). The data are summarized in Table I, and selected combinations are shown in Fig. 1. Each data point represents the average of at least two determinations. There was no interference from the various lipids or lactose on the hydrocortisone assay by the spectrophotometric procedure.

[1] Pfizer & Co., New York, N.Y.
[2] K and K Laboratories, Plainview, N.Y.
[3] Matheson, Coleman and Bell, Norwood, Ohio.
[4] J.T. Baker Chemical Co., Phillipsburg, N.J.
[5] Fisher Scientific Co., Fair Lawn, N.J.
[6] Thomas–Hoover, Arthur H. Thomas Co., Chicago, Ill.
[7] Model WBR, New Brunswick Scientific Co., New Brunswick, N.J.
[8] Du Nouy, Central Scientific Co., Chicago, Ill.
[9] Zeromatic, Beckman Instruments Co., Fullerton, Calif.
[10] Model 53, Hanson Research Corp., Northridge, Calif.
[11] Coleman Hitachi-124 double-beam model, Coleman Instruments Co., Maywood, Ill.
[12] Millipore Corp., Bedford, Mass.

Table I—Dissolution Rate of Hydrocortisone in Simulated Intestinal Fluid from Hydrocortisone–Lipid and Hydrocortisone–Lipid–Lactose Combinations

Sample	Ratio	Hydrocortisone Dissolved, %						
		15 min	30 min	45 min	60 min	90 min	120 min	150 min
I	—	35.0	51.8	65.1	73.1	78.3	82.6	86.1
I–II	1:1	20.8	35.2	48.1	58.3	66.5	73.1	80.0
	1:3	10.2	16.6	22.7	31.6	40.8	51.6	63.0
	1:6	9.3	14.9	20.2	25.9	34.1	41.0	48.0
I–III	1:1	15.1	22.0	26.4	28.6	29.8	30.9	31.5
	1:3	8.2	12.9	15.7	19.9	22.7	25.8	28.0
	1:6	3.2	3.6	4.0	4.4	5.6	6.2	6.8
I–IV	1:1	11.8	15.6	18.5	20.6	22.3	23.8	25.5
	1:3	4.2	5.4	5.8	6.2	6.8	7.8	8.2
	1:6	0.8	1.0	1.1	1.3	1.5	1.7	1.9
I–V	1:1	5.8	8.7	10.9	12.1	13.0	13.8	14.6
	1:3	2.4	3.6	3.8	4.2	4.5	4.8	5.1
	1:6	0.6	0.8	0.8	0.9	1.0	1.2	1.4
I–VI	1:1	6.0	9.5	12.6	14.5	16.6	17.8	19.4
	1:3	3.0	4.2	5.0	5.8	6.9	7.7	8.3
	1:6	2.0	2.3	2.4	2.6	3.2	3.7	4.3
I–VII	1:1	12.1	15.9	18.8	20.9	22.5	24.6	26.8
	1:3	4.8	7.7	9.1	10.0	11.7	13.1	14.3
	1:6	2.0	2.3	2.5	2.6	3.2	3.7	4.3
I–VIII	1:1	78.3	88.8	90.8	92.3	93.3	93.6	93.8
	1:3	49.7	55.0	62.3	69.8	75.4	82.9	88.2
	1:6	29.2	44.1	50.5	55.1	58.4	61.8	64.1
I–IX	1:6	63.8	79.1	85.6	88.0	92.8	94.0	95.8
I–II–IX	1:1:6	95.5	96.4	97.7	99.0	99.0	99.0	99.0
	1:3:6	72.2	91.7	95.6	97.7	98.3	98.8	99.0
	1:6:6	64.8	81.8	86.0	90.7	92.7	94.1	94.8
I–III–IX	1:1:6	24.8	36.2	44.3	49.8	54.1	60.4	63.9
	1:3:6	16.8	23.2	28.5	32.8	36.5	41.4	45.3
	1:6:6	9.8	11.3	13.8	16.2	19.5	22.9	27.1
I–IV–IX	1:1:6	11.7	16.2	19.0	21.3	23.1	25.1	26.9
	1:3:6	7.0	7.9	8.3	8.7	9.4	9.9	10.3
	1:6:6	3.2	5.4	6.5	7.4	8.9	9.9	10.1
I–V–IX	1:1:6	9.1	12.9	14.0	16.4	17.1	17.8	18.5
	1:3:6	4.7	6.3	7.2	8.1	9.0	9.8	10.6
	1:6:6	3.1	4.0	4.5	5.2	6.2	7.1	7.7
I–VI–IX	1:1:6	14.6	19.8	22.3	24.6	26.1	27.1	28.2
	1:3:6	19.0	22.5	23.2	24.5	25.9	26.9	28.3
	1:6:6	3.2	5.2	6.0	6.2	7.6	9.1	9.3
I–VII–IX	1:1:6	16.1	21.1	25.2	28.4	30.2	31.8	33.7
	1:3:6	19.0	21.6	22.7	23.3	25.9	28.2	30.9
	1:6:6	5.0	8.3	9.1	9.9	11.9	13.5	14.7
I–VIII–IX	1:1:6	85.2	94.9	97.5	99.0	99.0	99.0	99.0
	1:3:6	79.5	89.9	92.3	93.5	94.6	95.5	96.3
	1:6:6	57.0	63.3	66.2	68.9	71.1	73.2	74.5

The addition of the equivalent of 60 mg of hydrocortisone to 200 ml of simulated intestinal fluid ensured that the dissolution test was being conducted under sink conditions. Hydrocortisone solubility in simulated intestinal fluid at 37° was 861 μg/ml. Consequently, approximately 172 mg of hydrocortisone would be required to saturate 200 ml of this medium. Furthermore, saturated solutions of the various lipids in simulated intestinal fluid exerted an insignificant effect on hydrocortisone solubility.

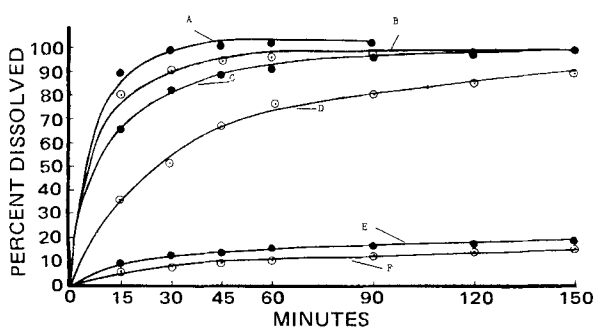

Figure 1—*Dissolution rate of hydrocortisone from selected lipid combinations, with and without lactose, in simulated intestinal fluid at 37°. Key: A, hydrocortisone–cholesteryl stearate–lactose (1:1:6); B, hydrocortisone–cholesteryl stearate (1:1); C, hydrocortisone–lactose (1:6); D, hydrocortisone; E, hydrocortisone–cholesteryl* n*-decylate–lactose (1:1:6); and F, hydrocortisone–cholesteryl* n*-decylate (1:1).*

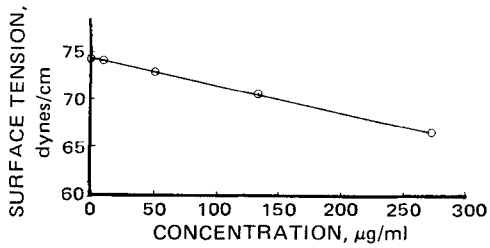

Figure 2—*Surface tension* versus *hydrocortisone concentration in simulated intestinal fluid at 30°. Surface tension = −0.0263C + 73.72.*

Spectrophotometric Absorption, Calibration Curves, and Assay Procedures for Hydrocortisone—A plot of absorbance *versus* wavelength for the hydrocortisone solution in simulated intestinal fluid, without enzymes (20 μg/ml), showed a maximum value at 250 nm. At this wavelength, a linear relationship was found between absorbance and concentration (range of 1–20 μg/ml). A plot of absorbance *versus* wavelength for hydrocortisone in 50% (v/v) chloroform in methanol showed a maximum at 245 nm. At this wavelength, a linear relationship was found between absorbance and concentration (range of 1–20 μg/ml). The slopes for the Beer's plot of the organic and aqueous solutions of hydrocortisone were identical, 4.31×10^{-2} absorbance unit/ml/μg.

Hydrocortisone stability in simulated intestinal fluid at 37° during the 2-hr dissolution study was satisfactory. Even after 48 hr at 37°, only a 0.54% drop in potency occurred. The calibration curve for hydrocortisone in 50% (v/v) chloroform in methanol was of value in the assay of hydrocortisone–lipid and hydrocortisone–lipid–lactose preparations. Thus, an accurately weighed sample was treated with sufficient solvent to dissolve the lipid and the hydrocortisone. Undissolved lactose, in the latter case, was filtered off by passage of the suspension through a 0.45-μm membrane filter. After appropriate dilution with additional solvent, the absorbance of the solution was determined. The pure solvent combination was used as the blank.

Measurement of Surface Tension of Hydrocortisone and Hydrocortisone–Lipid Solutions in Simulated Intestinal Fluid—The surface tension of various concentrations of hydrocortisone in simulated intestinal fluid, without pancreatin, was measured with a tensiometer at 30° using a 4-cm platinum–iridium ring. Correction factors were determined by graphical extrapolation of the values published by Harkins and Jordan (7). The densities of the various solutions were measured with a 10-ml pycnometer. The density values were required in the calculation of the correction factor. The results are summarized in Table II and Fig. 2.

The effect of selected lipids on the surface tension lowering of simulated intestinal fluid was then determined. The powdered hydrocortisone–lipid solid solutions (120 mg) were stirred at 150 rpm in 200 ml of simulated intestinal fluid at 37° for 60 min. The suspensions were filtered through a 0.45-μm filter, and the hydrocortisone concentrations of the filtrates were determined spectrophotometrically. The density of each filtrate was measured for computation of the correction factors (Table III).

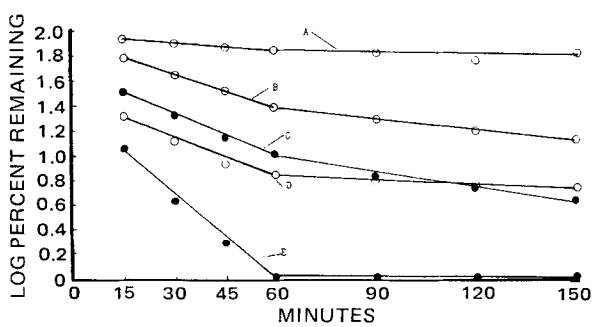

Figure 3—*Dissolution rate of hydrocortisone from selected lipid combinations, with and without lactose, in simulated intestinal fluid at 37° plotted in first-order fashion. Key: A, hydrocortisone–cholesteryl* n*-decylate (1:1); B, hydrocortisone; C, hydrocortisone–lactose (1:6); D, hydrocortisone–cholesteryl stearate (1:1); and E, hydrocortisone–cholesteryl stearate–lactose (1:1:6).*

Table II—Effect of Hydrocortisone Concentration on the Surface Tension of Simulated Intestinal Fluid at 30°

Sample	Hydrocortisone Concentration, μg/ml	Dial Reading[a]	Uncorrected Surface Tension, dynes/cm	Density	R^3/V[b]	Correction Factor	Corrected Surface Tension, dynes/cm
Simulated intestinal fluid	0.0	36.13	75.157	1.0346	0.437	0.981	73.72
Simulated intestinal fluid plus hydrocortisone	13.7	36.07	75.018	1.0346	0.438	0.980	73.50
Simulated intestinal fluid plus hydrocortisone	55.0	35.70	74.258	1.0347	0.442	0.979	72.69
Simulated intestinal fluid plus hydrocortisone	137.0	34.70	72.037	1.0348	0.455	0.976	70.30
Simulated intestinal fluid plus hydrocortisone	275.0	32.90	68.484	1.0349	0.479	0.970	66.42

[a] Average of three readings. Dial scale is 16.64 dynes/dial division. [b] R is the radius of the ring measured from the center of the ring to the center of the wire. The volume of liquid raised above the free surface of the liquid is V.

Table III—Effect of Hydrocortisone plus Lipids on the Surface Tension of Simulated Intestinal Fluid at 30°

Sample[a]	Hydrocortisone Concentration, μg/ml	Percent Dissolved	Dial Reading[b]	Correction Factor	γ_1[c]	γ_2[d]	$\frac{\gamma_2 - \gamma_1}{\gamma_2} \times 100$, %[e]
Hydrocortisone plus cholesterol	208.0	69.3	31.9	0.966	64.15	68.25	6.00
Hydrocortisone plus cholesteryl acetate	80.0	26.6	34.3	0.973	69.41	71.61	3.07
Hydrocortisone plus cholesteryl *n*-decylate	26.0	8.6	34.9	0.976	70.84	73.03	2.99
Hydrocortisone plus cholesteryl stearate	218.0	72.6	31.5	0.965	63.22	67.98	7.00

[a] Hydrocortisone–lipid ratios were 1:1. [b] Average of three readings. [c] Surface tension of the solution containing both hydrocortisone and lipid. [d] Surface tension of the solution containing only hydrocortisone. [e] Percent of surface tension lowering by the lipid.

RESULTS AND DISCUSSION

Several generalizations can be made about the data in Table I. As the ratio of lipid to drug was increased, the hydrocortisone dissolution rate decreased. The only exception to this generalization was hydrocortisone–cholesteryl laurate–lactose in the weight ratio of 1:3:6. Solvent deposition of the hydrocortisone–lipid solid solutions on lactose invariably resulted in more rapid dissolution. This enhancement of the dissolution rate can be attributed to the increased surface attained by such molecular dispersions on lactose.

An unexpected observation was the rapid dissolution of hydrocortisone from hydrocortisone–cholesteryl stearate (1:1). Within 15 min, 78.3% of the hydrocortisone had dissolved, whereas only 35% had dissolved when the pure drug was used. The hydrocortisone dissolution rate from a 1:3 weight ratio of hydrocortisone–cholesteryl stearate was equivalent to that for the pure drug. Unexpectedly, the *n*-decylate ester of cholesterol was the most effective deterrent to the hydrocortisone dissolution.

The rank order in hydrocortisone dissolution was as follows for the 1:1 hydrocortisone–lipid solid solutions: hydrocortisone–cholesteryl stearate, hydrocortisone, hydrocortisone–cholesterol, hydrocortisone–cholesteryl acetate, hydrocortisone–cholesteryl palmitate, hydrocortisone–cholesteryl *n*-butyrate, hydrocortisone–cholesteryl laurate, and, finally, hydrocortisone–cholesteryl *n*-decylate. The solvent deposition of solid solutions on the surface of lactose resulted in improved dissolution rates, whereas increases of 1:3 and 1:6 in drug–lipid ratios resulted in reduced dissolution rates. The superiority of the solid solutions containing the stearate ester of cholesterol was unexpected. It was anticipated that the rapid hydrocortisone release from such solid solutions might be explained by surface tension lowering.

The data in Table II and Fig. 2 show that a linear relationship existed between hydrocortisone concentration in simulated intestinal juice and surface tension lowering. The data in Table III clearly show a direct relationship between the hydrocortisone release rate and surface tension lowering brought about by the lipid. Thus, hydrocortisone–cholesteryl stearate (1:1) released the drug most rapidly. The surface tension of a solution containing both cholesteryl stearate and the corticoid was 7% lower than a solution containing only the corticoid. With hydrocortisone–cholesteryl *n*-decylate (1:1), the surface tension of the aqueous

Table IV—Dissolution Rate Data for Hydrocortisone–Lipid (1:1) and Hydrocortisone–Lipid–Lactose (1:1:6) Expressed as the Parameters of Apparent First-Order Kinetics

Sample	K'[a], $\times 10^{-4}$ min^{-1}	K''[b], $\times 10^{-4}$ min^{-1}	t_{50}[c], min	t_{90}[c], min
I	218.0	73.0	94.9	315.5
I–II	145.7	81.6	84.9	282.0
I–III	38.0	4.6	1506.0	5006.0
I–IV	23.3	7.1	970.0	3225.0
I–V	15.3	3.2	6165.0	7196.0
I–VI	21.0	6.6	1050.0	3489.0
I–VII	23.0	8.6	806.0	2681.0
I–VIII	598.0	24.1	287.5	955.5
I–IX (1:6)	353.0	116.0	59.3	197.3
I–II–IX	884.0	—[d]	7.8	26.0
I–III–IX	89.2	36.2	189.0	629.0
I–IV–IX	23.9	8.2	843.0	2805.0
I–V–IX	16.8	2.8	2440.0	8109.0
I–VI–IX	25.7	5.4	1271.0	4225.0
I–VII–IX	35.7	8.5	817.0	2703.0
I–VIII–IX	767.0	—[d]	9.0	30.0

[a] The apparent first-order rate constant of the first segment of the line (up to 60 min). (See Fig. 3.) [b] The apparent first-order rate constant of the second segment of the line (90–150 min). (See Fig. 3.) [c] Values derived from K''. [d] At the end of 60 min, 99% of the drug had gone into solution.

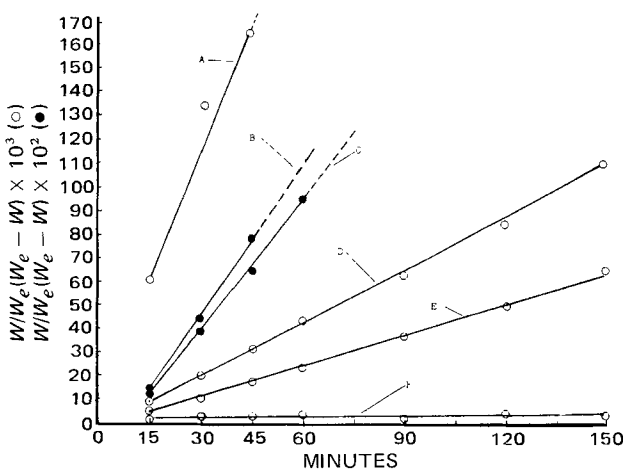

Figure 4—*Dissolution rate of hydrocortisone from selected lipid combinations, with and without lactose, in simulated intestinal fluid at 37° plotted in second-order fashion. Key: A, hydrocortisone–cholesteryl stearate (1:1); B, hydrocortisone–cholesteryl stearate–lactose (1:1:6); C, hydrocortisone–lactose (1:6); D, hydrocortisone; E, hydrocortisone–cholesterol (1:1); and F, hydrocortisone–cholesteryl* n*-decylate (1:1).*

Table V—Dissolution Rate Data for Hydrocortisone–Lipid (1:1) and Hydrocortisone–Lipid–Lactose (1:1:6) Expressed as the Parameters of Apparent Second-Order Kinetics

Sample	K, $\times 10^{-5}$ mg^{-1} min^{-1}	t_{50}, min	t_{90}, min	Initial Dissolution Rate, mg/min
I	68.3	24.3	219.4	2.46
I-II	44.3	37.6	338.0	1.59
I-III	2.9	557.0	5010.0	0.107
I-IV	2.3	705.0	6350.0	0.084
I-V	1.2	1400.0	12600.0	0.042
I-VI	2.0	816.0	7350.0	0.073
I-VII	2.6	645.0	5180.0	0.092
I-VIII	128.6	12.9	117.0	4.63
I-IX (1:6)	250.7	6.6	57.8	9.02
I-II-IX	792.2	2.1	18.9	28.50
I-III-IX	17.1	97.4	877.0	0.61
I-IV-IX	2.6	640.0	5760.0	0.093
I-V-IX	1.3	1300.0	11700.0	0.046
I-VI-IX	2.3	715.0	6430.0	0.083
I-VII-IX	3.5	469.0	4220.0	0.127
I-VIII-IX	1296.9	1.3	11.6	46.40

solution was 2.99% lower than that of an aqueous solution containing only hydrocortisone. Consequently, surface tension lowering is a plausible explanation for the observed rank order in drug dissolution rates for the various drug–lipid combinations.

Apparent First-Order Kinetics—Selected data plotted in first-order fashion are shown in Fig. 3. In Table IV, the hydrocortisone–lipid (1:1) and hydrocortisone–lipid–lactose (1:1:6) preparations are expressed as the parameters of apparent first-order kinetics. The dissolution process followed by these preparations was not simple first order (Fig. 3). From 15 to 60 min, a steeper slope was evident; from 60 to 150 min, the slope changed. Extrapolation of the lines for the bottom three curves to point 2.0 on the ordinate indicates a third slope from 0 to 15 min. Thus, the assumption that the surface area available for dissolution decreases exponentially with time is not true for these drug–lipid delivery systems.

Apparent Second-Order Kinetics—Based on previous studies (8, 9), the *in vitro* dissolution kinetics of the hydrocortisone–lipid and hydrocortisone–lipid–lactose systems could be second order, being functions of the effective surface area and the weight of drug available for dissolution. In Fig. 4, $W/W_e(W_e - W)$ is plotted against time. The parameter W is the weight of drug in solution at time t; W_e is the weight of drug in solution at equilibrium. The slope of each line represents the apparent second-order rate constant, K. The points represent the experimental data, but the lines were drawn from calculated values obtained by regression analysis.

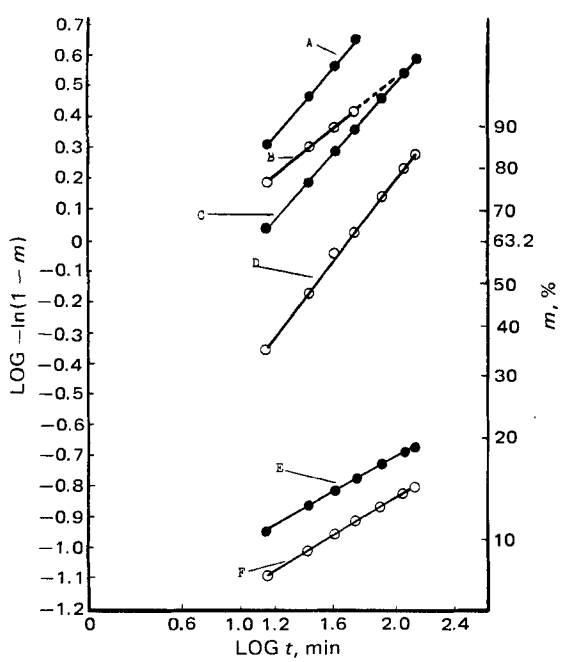

Figure 5—*Dissolution rate of hydrocortisone from selected lipid combinations, with and without lactose, in simulated intestinal fluid at 37° plotted according to the Weibull distribution equation. Key: A, hydrocortisone–cholesteryl stearate–lactose (1:1:6); B, hydrocortisone–cholesteryl stearate (1:1); C, hydrocortisone–lactose (1:6); D, hydrocortisone; E, hydrocortisone–cholesteryl* n*-decylate–lactose (1:1:6); and F, hydrocortisone–cholesteryl* n*-decylate (1:1).*

Table VI—Dissolution Rate Data for Hydrocortisone–Lipid (1:1) and Hydrocortisone–Lipid–Lactose (1:1:6) Expressed as the Parameters of the Weibull Distribution Equation

Sample	Log a[a]	b[b]	T_d[c], min
I	1.10	0.655	47.8
I-II	1.58	0.828	80.7
I-III	1.14	0.351	1.79×10^3
I-IV	1.31	0.346	4.02×10^3
I-V	1.65	0.406	1.16×10^4
I-VI	1.79	0.533	2.31×10^3
I-VII	1.31	0.372	3.36×10^3
I-VIII	0.30	1.100	2.0
I-IX (1:6)	0.51	0.471	12.3
I-II-IX	0.26	0.490	3.1
I-III-IX	1.13	0.529	1.36×10^2
I-IV-IX	1.30	0.371	3.21×10^3
I-V-IX	1.29	0.289	3.00×10^4
I-VI-IX	1.09	0.292	5.63×10^3
I-VII-IX	1.15	0.363	1.52×10^3
I-VIII-IX	0.35	0.577	4.1

[a] The y-intercept of the line, obtained by the least-squares method using a computer. (See Fig. 5.) [b] The slope of the line. [c] The time required to dissolve 63.2% of the hydrocortisone, derived from the Weibull distribution equation (10).

Table V gives the values for K, t_{50}, t_{90}, and the initial dissolution rate for the 1:1 hydrocortisone–lipid and 1:1:6 hydrocortisone–lipid–lactose preparations. The initial dissolution rates, when both t and $W = 0$, are calculated from:

$$\frac{dW}{dt} = kW_e^2 \qquad \text{(Eq. 1)}$$

The most rapid dissolution rate for hydrocortisone was exhibited by the hydrocortisone–cholesteryl stearate–lactose (1:1:6) preparation. The slowest release of the drug occurred from hydrocortisone–cholesteryl n-decylate (1:1).

On the basis of the regression analyses of the dissolution rate data, the assumption of a particular kinetic model is valid if the correlation coefficient, r, approaches unity. Fitting of the experimental data to the second-order kinetic model yielded an average value of $r = 0.955$ for the hydrocortisone–lipid (1:1) preparations. The average value of r for the hydrocortisone–lipid–lactose (1:1:6) preparations was 0.967. Thus, with deviations of only 3.3 and 4.5% from unity, the second-order kinetic model appears to be valid.

Weibull Cumulative Distribution Preparation—Langenbucher (10) reported that a more general function, which might be applied to linearize common types of dissolution curves, is the Weibull distribution equation:

$$\log [-\ln(1 - m)] = b \log (t - T_i) - \log a \qquad \text{(Eq. 2)}$$

where m expresses the accumulated fraction of drug in solution at time t; b is the shape parameter, obtained from the slope of the line; a is the scale parameter estimated from the y-intercept; and T_i is the location parameter, representing the time lag before the onset of dissolution (in this instance $T_i = 0$).

Figure 5 is a log–log plot of $-\ln(1 - m)$ *versus* t for selected 1:1 hydrocortisone–lipid combinations with and without lactose. Table VI lists the log a, b, and T_d values for all 1:1 hydrocortisone–lipid combinations with and without lactose. The T_d value represents the time required to dissolve 63.2% of the drug. The versatility of the log–log plot is evident in Fig. 5; it is possible to calculate the time required for any percentage of the drug to be dissolved by use of the auxiliary ordinate scale shown on the right-hand side. All points on Fig. 5 are experimental; the lines are drawn from the predicted values obtained from the least-squares method using a computer.

The log–log plots (Fig. 5) exhibit the closest fit to the experimental data as compared with the lines generated in Figs. 3 (first order) and 4 (second order). Thus, in Table I, it is apparent that 90.8% of the hydrocortisone had dissolved from the 1:1 hydrocortisone–cholesteryl stearate preparation after 45 min. The t_{90} values from the first-order, second-order, and Weibull distribution curves were 955, 117, and 41 min, respectively. With hydrocortisone–cholesteryl stearate–lactose (1:1:6), 85.2% of the drug

had dissolved after 15 min. The t_{90} values for the first-order, second-order, and Weibull distribution curves were 30, 11.6, and 19 min, respectively. These results support the utility of the Weibull cumulative distribution equation in the linearization of experimental data.

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ACKNOWLEDGMENTS AND ADDRESSES

Received July 21, 1976, from the *Department of Allied Health and Industrial Sciences, College of Pharmacy and Allied Health Professions, St. John's University, Jamaica, NY 11439.*

Accepted for publication January 24, 1977.

[x] To whom inquiries should be directed.

Influence of Metoclopramide and Propantheline on GI Absorption of Griseofulvin in Rats

F. JAMALI and J. E. AXELSON [x]

Abstract □ The effect of metoclopramide and propantheline preadministration on the plasma levels of orally administered griseofulvin was studied. Griseofulvin was administered as an aqueous suspension in 0.5% polysorbate 80 or as a 100% polyethylene glycol 600 solution. Metoclopramide preadministration increased the gastric emptying rate, but propantheline retarded it. The effect on griseofulvin absorption induced by metoclopramide and propantheline was sharply dependent upon the dosage form of griseofulvin administered. When griseofulvin was administered as a suspension dosage form following metoclopramide administration, the griseofulvin peak plasma concentration was reduced by 59% while a concurrent 50% reduction in relative bioavailability was observed. Pretreatment with metoclopramide resulted in a shift of the time required for attainment of the peak plasma griseofulvin concentration. In contrast, metoclopramide administration prior to a dose of griseofulvin dissolved in 100% polyethylene glycol 600 sharply increased both the relative bioavailability and the maximum plasma level of griseofulvin by 234 and 145%, respectively. Propantheline administration prior to a single dose of griseofulvin suspension decreased the maximum plasma level by 30% and delayed the time of its attainment from 5.78 to 19.00 hr with a 50% increase in relative availability. When griseofulvin was administered as a 100% polyethylene glycol solution dosage form, propantheline preadministration reduced both the maximum plasma level and the area under the plasma concentration–time curve by 64 and 44%, respectively.

Keyphrases □ Griseofulvin—GI absorption, effect of metoclopramide and propantheline preadministration, rats □ Metoclopramide—effect of preadministration on GI absorption of griseofulvin, rats □ Propantheline—effect of preadministration on GI absorption of griseofulvin, rats □ Absorption, GI—griseofulvin, effect of metoclopramide and propantheline preadministration, rats □ GI absorption—griseofulvin, effect of metoclopramide and propantheline preadministration, rats □ Antifungal agents—griseofulvin, GI absorption, effect of metoclopramide and propantheline preadministration, rats □ Antiemetics—metoclopramide, effect of preadministration on GI absorption of griseofulvin, rats □ Anticholinergic agents—propantheline, effect of preadministration on GI absorption of griseofulvin, rats

Griseofulvin, a chemically neutral systemic antifungal antibiotic, is commonly used in the treatment of dermatophyte infections in humans (1–4) and domestic animals (5). As a result of inherently poor aqueous solubility (approximately 15 mg/liter at 37°), the drug is slowly, erratically, and incompletely absorbed from the human GI tract (6). However, it is an exceptionally effective antifungal agent after oral administration.

Because griseofulvin is poorly absorbed, it has been used as an investigational model to examine various parameters affecting drug absorption. Its slow and erratic absorption characteristics are the direct result of unusually slow dissolution after oral administration as a solid dosage form. Early experimentation with griseofulvin led to classical observations about the effect of particle-size reduction (7), surfactants (8), and dietary lipids (9) on the absorption of a drug with low solubility and poor availability.

The effects of particle-size reduction (7), micellar solubilization (10), molecular dispersion (11), and emulsification (12) on improving the absorption of poorly absorbed drugs are well recognized. However, far less is known about the effect of GI motility on the absorption of poorly absorbed drugs (13–15). Since griseofulvin is a very poorly soluble drug and its absorption takes place largely in the intestine (16), it was desirable to study the effect of gastric emptying and GI motility on its absorption. Metoclopramide (13) and propantheline (13–15) were used successfully as investigational probes in similar absorption studies to increase or decrease GI motility, respectively.

The purpose of this work is to demonstrate the effect of changes in GI motility on the relative availability of griseofulvin after preadministration of motility-modifying agents.

EXPERIMENTAL

Dosage Forms—Micronized griseofulvin[1] (specific surface area of 1.32 m^2/g) was used in the preparation of two dosage forms. The first preparation was an aqueous suspension containing 25 mg of micronized griseofulvin/ml in 0.5% polysorbate 80 in water. The second preparation was a solution of griseofulvin prepared by dissolving 12.5 mg of drug in

[1] Supplied by Dr. Milo Gibaldi, State University of New York at Buffalo, Buffalo, N.Y.