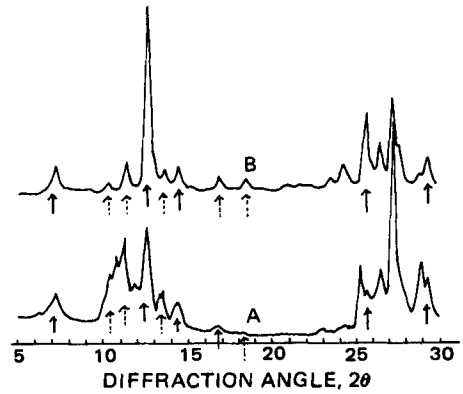

Figure 8—*Changes in X-ray diffraction patterns of the spray-dried products caused by heat-treatment. Key: (A) spray-dried products prepared at 115°, 10,000 rpm; (B) products treated at 110°, 30 min; (→) theophylline; (- - -→) α-aminophylline.*

peak disappeared when the drying temperature was >130°. The weight loss indicated by thermogravimetric curves in Fig. 6B corresponded approximately to the contents of water and ethylenediamine contained in the products as indicated in Fig. 3. The weight loss detected by thermogravimetric analysis decreased with an increase in the drying temperature as shown in Fig. 6B, as predicted from the findings in Fig. 3.

The changes in differential scanning calorimetry and thermogravimetric thermograms, with the rotation speed of the atomizer, are displayed in Fig. 6C. The thermal behaviors of the product prepared with high (low) rotational speed of the atomizer resembled those of the products prepared at high (low) drying temperature. As expected, the weight loss which appeared on the thermogravimetric curve decreased with increasing rotation speed of the atomizer.

Differential scanning calorimetric and thermogravimetric thermograms of the products treated with heating were compared with those of the products prior to the treatment in Fig. 7. After treatment by heating, the endothermic peak at 100° for water releasing disappeared from the thermogram. No weight loss on the thermogravimetric curve at 100° also indicated that the products treated by heating contained no crystalline water. However, an endothermic peak at 127° of the products prepared by spray drying at high temperature or with high rotation speed of the atomizer still remained even after heat treatment at 120°. The products prepared at low drying temperature or at low atomizing speed revealed an endothermic peak at 120° on the thermograph after heat treatment at 110°. The weight loss detected at 127 or 120° by thermogravimetric analysis suggested that some ethylenediamine still remained in the products even after heat treatment.

The X-ray diffraction pattern of the products treated with heating revealed characteristic peaks of theophylline and α-aminophylline at 7.2, 12.5, 14.2, 25.7, 29.3° and 10.2, 11.2, 13.5, 16.7, 18.1°, respectively. The peaks for theophylline strengthened, but no diffraction peaks for aminophylline appeared on the pattern in Fig. 8. These findings proved that the endothermic peak at 116 or 127°, that appeared on the thermogram of the spray-dried products, was caused by the liberation of ethylenediamine contained in a theophylline–ethylenediamine complex.

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Bioavailability of Regular and Controlled-Release Chlorpheniramine Products

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Abstract □ The bioavailability of chlorpheniramine regular-release *versus* controlled-release products was compared using 15 human subjects. The dosage forms evaluated were an 8-mg barrier coated-bead capsule, an 8-mg repeat action tablet, two 4-mg tablets, and 4- and 8-mg syrups. Single doses of each product were administered orally in a 5-way crossover study, plasma samples were collected at specific time intervals, and chlorpheniramine levels assayed by HPLC. Pharmacokinetic analysis was based on a two-compartment open model. The average plasma elimination half-life of chlorpheniramine was calculated to be ~18.3 hr. The controlled-release products gave a higher C_{max} than the 4-mg syrup, but <two 4-mg tablets. The controlled-release products also extended the time necessary to attain peak drug levels compared to the 4- and 8-mg syrups. The area under the curve (*AUC*) data for the controlled-release products was not equivalent to equal amounts of the regular-release products. The study indicated that while the controlled-release chlorpheniramine products were successful in prolonging the time course of absorption, this was at the expense of incomplete bioavailability of the drug.

Keyphrases □ Chlorpheniramine—bioavailability of regular and controlled-release products □ Bioavailability—regular and controlled-release chlorpheniramine products □ Controlled-release products—bioavailability of chlorpheniramine

Chlorpheniramine maleate is commonly used in the treatment of various allergic conditions. The different dosage forms of chlorpheniramine maleate marketed include regular- (or immediate) release and controlled- (or sustained) release products.

Little comparative information is currently available

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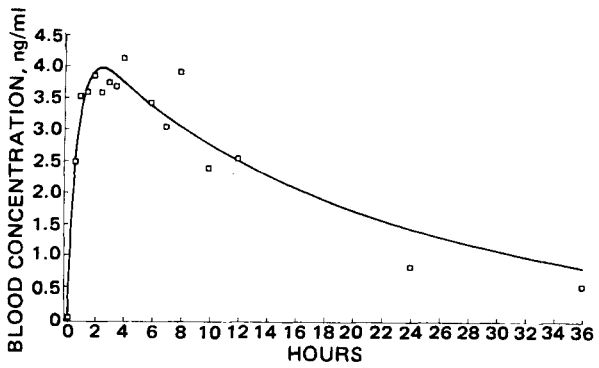

Figure 1—*A comparison of computer predicted (—)* versus *observed (□) chlorpheniramine plasma concentrations* versus *time following administration of the 4-mg syrup.*

concerning the bioavailability of regular-release *versus* controlled-release products or on comparisons among the various controlled-release products themselves. It is generally assumed that the controlled-release products prepared by different methods are bioequivalent. Chlorpheniramine maleate is commercially available as a coated slow-release bead, a repeat-action tablet, a single-dose tablet, and a syrup. *In vivo* comparison of these different dosage forms as well as differently designed products is not currently available.

The present study compares two different controlled-release products of chlorpheniramine maleate to equivalent doses of immediate-release tablets and an equivalent dose and single dose of the drug in solution. In addition, the study provides information regarding the bioequivalency of two sustained-release products formulated by different methods.

EXPERIMENTAL

Subjects—Fifteen healthy male volunteers [18–27 years old (mean 21), 66–80 kg (mean 74), and within ±10% of ideal weight for their height and age (1)] were selected for the study. All subjects were shown by medical examination to be in good physical condition with normal blood and urine chemistry. Informed consent was obtained from all subjects. Each volunteer was instructed to refrain from taking any medication for 1 week prior to and during the study.

The subjects fasted for 8 hr prior to the drug administration. Each subject received 200 ml of water at the time of dosing and at ~1.5 hr postdose. The same low-fat meal was provided for all subjects 3 hr after administration of the dose. A second meal was given to all subjects ~10 hr after initial drug administration. Throughout the study the subjects were ambulatory and proceeded with their normal daily routine. The dose was administered and blood samples (5 ml) were collected immediately before dosing and at 0.3, 0.7, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 7, 8, 10, 12, 24, 36, 48, 72, 96, and 144 hr. Samples were drawn from a forearm vein into heparinized vacuum tubes using indwelling needles from 0 to 4 hr and by venipuncture thereafter. The plasma was separated and frozen until assayed.

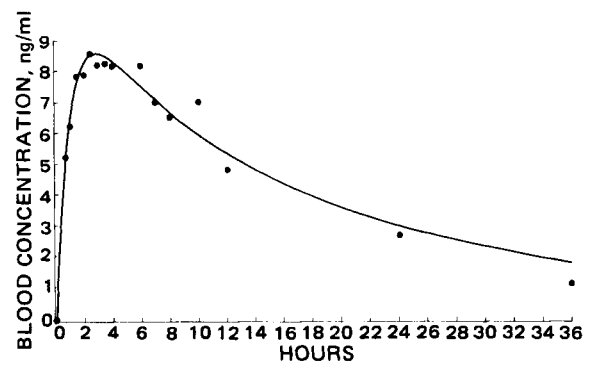

Figure 2—*A comparison of computer predicted (—)* versus *observed (●) chlorpheniramine plasma concentrations* versus *time following administration of the 8-mg syrup.*

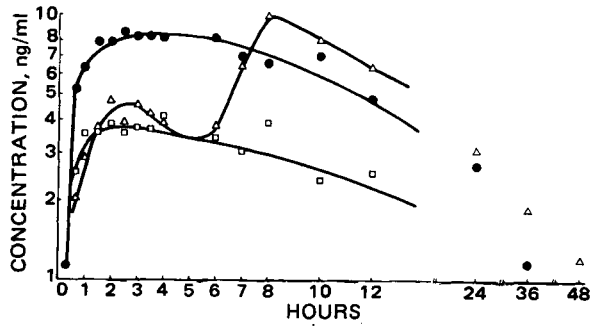

Figure 3—*A comparison of mean plasma concentration–time profiles for the 4- and 8-mg syrups of chlorpheniramine to the 4-mg tablet, administered at 0 and 6 hr. Key: 4-mg syrup (□), 8-mg syrup (●), 4-mg tablet (△).*

Study Design—The drugs as listed in the table below were administered using a five-way crossover design with all subjects receiving each dose.

	Strength	Dose
Drug 1[1]	4 mg	4 mg (0, 6 hr)
Drug 2[2]	8 mg	8 mg
Drug 3[3]	2 mg/5 ml	4 mg
Drug 4[4]	8 mg	8 mg
Drug 5[3]	2 mg/5 ml	8 mg

The subjects were formed into five groups of three subjects each, such that the total body weights of the five groups were essentially the same. The following scheme was used with 2 weeks between each study period:

	Study Period				
	1	2	3	4	5
Group A (Subjects 1–3)	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5
Group B (Subjects 4–6)	Drug 2	Drug 5	Drug 4	Drug 3	Drug 1
Group C (Subjects 7–9)	Drug 3	Drug 1	Drug 5	Drug 2	Drug 4
Group D (Subjects 10–12)	Drug 4	Drug 3	Drug 1	Drug 5	Drug 2
Group E (Subjects 13–15)	Drug 5	Drug 4	Drug 2	Drug 1	Drug 3

Analysis—The HPLC analyses were performed on a liquid chromatograph[5]. The column contained a packing material consisting of an octadecylsilane material bonded to a microparticulate silica gel[6] (<10 μm) for reversed-phase chromatography. The mobile phase consisted of 1:4 acetonitrile–0.075 *M* monobasic ammonium phosphate whose pH was adjusted to 2.6 with concentrated phosphoric acid. The flow rate was set at 1.0 ml/min, the peaks were monitored at 254 nm, and the recorder sensitivity was set at 0.005 aufs.

Stock solutions of chlorpheniramine base (1.5 μg/ml) and brompheniramine base (2.5 μg/ml) were prepared by dissolving equivalent amounts of chlorpheniramine maleate and brompheniramine maleate in distilled water.

Plasma chlorpheniramine levels were determined by a modification of the HPLC procedure reported previously (2). To 1.5 ml of plasma in a 15-ml centrifuge tube were added 75 μl of brompheniramine (internal standard) and 1 ml of 5% aqueous potassium hydroxide. Ether (3 ml) was then added followed by shaking (15 min) and centrifugation (3000 rpm, 15 min). The aqueous layer was then frozen with the aid of a dry ice–acetone bath and the ether decanted into a clean 15-ml centrifuge tube. To this was added 0.1 ml of 0.5% phosphoric acid, the mixture shaken for 10 min, centrifuged, and refrozen. The ether layer was discarded, and the remaining aqueous portion was placed under a nitrogen stream for 5 min

[1] Chlortrimeton Tablets, Lot #7TW30P56540, Schering Corp., Kenilworth, NJ 07033.

[2] Chlortrimeton Repetabs, Lot #6CC15 and #56411, Schering Corp., Kenilworth, NJ 07033.

[3] Chlortrimeton Syrup, Lot #7ATN501, Schering Corp., Kenilworth, NJ 07033.

[4] Teldrin Spansules, Lot #27S72, Smith, Kline and French Laboratories, Philadelphia, PA 19101.

[5] Waters Associates liquid chromatograph equipped with an M-6000 pump, a U6K injector, and a model 440 UV absorbance detector, Milford, Mass.

[6] μ-Bondapak C_{18}, Waters Associates, Milford, Mass.

Table I—Average Plasma Concentrations[a] at each Sampling Time of Chlorpheniramine (ng/ml) from Five Different Administrations

Time, hr	Syrup, 8 mg	Drug 2, 8 mg	Drug 4, 8 mg	Tablet, 4 mg	Syrup, 4 mg
0.7	5.2 ± 4.3	1.6 ± 2.4	0.6 ± 1.1	2.0 ± 2.2	2.5 ± 2.1
1	6.3 ± 3.8	2.1 ± 2.0	0.7 ± 0.7	2.9 ± 2.5	3.5 ± 2.0
1.5	7.8 ± 3.4	2.6 ± 1.5	1.2 ± 1.3	3.8 ± 2.9	3.6 ± 1.6
2	7.9 ± 2.5	3.2 ± 2.0	1.7 ± 1.6	4.8 ± 2.4	3.9 ± 1.8
2.5	8.6 ± 3.1	2.7 ± 1.0	2.4 ± 2.4	3.9 ± 3.2	3.6 ± 1.1
3	8.2 ± 1.8	3.3 ± 1.1	2.8 ± 2.0	4.6 ± 2.4	3.8 ± 1.3
3.5	8.3 ± 2.2	3.2 ± 1.7	4.2 ± 1.9	4.3 ± 2.6	3.7 ± 2.5
4	8.2 ± 3.2	3.9 ± 1.7	4.6 ± 2.4	3.9 ± 2.4	4.1 ± 1.8
6	8.2 ± 3.3	6.1 ± 2.8	6.1 ± 2.6	3.8 ± 2.3	3.4 ± 1.0
7	7.0 ± 1.9	6.5 ± 1.8	5.2 ± 2.0	6.4 ± 4.1	3.1 ± 0.9
8	6.5 ± 1.4	7.3 ± 4.1	6.4 ± 3.3	10.0 ± 4.9	3.9 ± 1.8
10	7.0 ± 3.5	6.1 ± 4.1	5.1 ± 2.7	8.1 ± 3.2	2.4 ± 1.0
12	4.8 ± 2.9	4.9 ± 2.0	4.0 ± 2.5	6.4 ± 2.4	2.5 ± 1.0
24	2.7 ± 1.7	2.1 ± 0.9	1.8 ± 1.0	3.1 ± 2.0	0.8 ± 0.6
36	1.2 ± 1.0	1.0 ± 0.9	1.4 ± 1.0	1.9 ± 1.2	0.5 ± 0.5

[a] Mean of 15 values ± *SD*.

Table II—Mean Pharmacokinetic Parameters[a] Across Individual Subjects for Chlorpheniramine Maleate Dosage Forms

Parameter	Syrup, 8 mg	Drug 2, 8 mg	Drug 4, 8 mg	Tablet[c], 4 mg	Syrup, 4 mg
$t_{1/2}$, hr	17.3 ± 4.4	17.6 ± 4.4	21.2 ± 7.4	20.8 ± 4.4	14.6 ± 3.4
FD/V_c, ng/ml[b]	6.3 ± 2.4	4.9 ± 1.7	3.8 ± 1.7	5.4 ± 2.0	3.1 ± 1.0
Time of peak concentration, hr	3.8 ± 2.7	7.6 ± 2.3	6.1 ± 1.3	6.1 ± 2.3	3.4 ± 2.5
Peak concentration, ng/ml	11.3 ± 2.9	9.7 ± 3.9	7.5 ± 3.2	11.0 ± 4.1	5.9 ± 2.3
$AUC_{0\to\infty}$[d]	156.3 ± 60.7	119.2 ± 33.7	113.0 ± 46.2	169.6 ± 85.6	65.4 ± 21.8

[a] Mean of 15 values ± *SD*. [b] Fraction of the dose absorbed expressed as concentration in its distribution volume in the body calculated from $FD/V_c\beta = AUC_{0\to\infty}$. [c] Administered twice as single 4-mg doses at 0- and 6- hr intervals. [d] Obtained by trapezoidal rule technique. The last measured plasma concentration was divided by the least squares slope value for the β phase, indicating log–trapezoidal extrapolation to zero concentration (*i.e.*, $AUC_{0\to\infty}$).

to rid of residual ether. A 60- to 80-μl portion of the aqueous phase was then injected into the liquid chromatograph.

Calibration curves were constructed by adding 3.5-, 5.0-, 10-, and 20-μl quantities of the chlorpheniramine stock solution into individual 15-ml centrifuge tubes containing 1.5 ml of blank human plasma to give the equivalent of 3.5, 5.0, 10.0, and 20.0 ng of chlorpheniramine/ml. To each tube was then added 75 μl of brompheniramine stock solution (internal standard) and each tube assayed according to the procedure described above.

Ratios of chlorpheniramine peak heights to those of the internal standard (*D/IS*) were calculated for each chromatogram. Regression analysis of these data at the various concentrations of chlorpheniramine gave typical results: slope, 0.0403; intercept, 0.0212; and correlation coefficient, 0.9967 (n = 16). The standard error of estimate of $Y(D/IS)$ on X (chlorpheniramine concentration) was ±0.0122. The minimum detectable quantity of chlorpheniramine that can be measured using the procedure is 1 ng/ml (S/N = 2). The slope and intercept data from regression analysis for chlorpheniramine were then used to solve for drug concentration in the human plasma samples: D/IS = (slope X concentration) + intercept.

Interassay reproducibility of chlorpheniramine determined by the assay of spiked plasma samples containing 3.5, 5.0, 10.0, and 20.0 ng/ml gave percent relative standard deviations (*RSD*) of 9.7, 7.9, 5.4, and 5.0%, respectively (n = 10). Interassay reproducibility of the drug at the 2.5-ng/ml level was 15% (n = 10). Linearity of the calibration curve <2.5 ng/ml was assumed using the linear regression calculation for the standard curve data. Interassay accuracy data at the 3.5-, 5.0-, 10.0-, and 20.0-ng/ml levels gave the following typical results (n = 3): 6.6, 4.4, 0.7, and 0.15%, respectively.

Pharmacokinetic Analysis—Individual curves following administration of syrup dosage forms, that is, immediately available drug not having to undergo disintegration or dissolution, were graphed and the data analyzed *via* NLIN[7] or SAS[8]. Both one- and two-compartment open models with first-order absorption and elimination were examined. Although both models are indistinguishable if one only looks at the residual sum of squares of the model fit, the two-compartment model gives better results (Figs. 1 and 2).

All pharmacokinetic parameters reported here are the results of using the above computer program and the two-compartment model. For a particular dosage form, plasma half-lives for each subject were calculated from least-square fits of the terminal slope of the log plasma chlorpheniramine concentration *versus* time curve. The individual subject half-life data was then used to calculate the mean plasma half-life for the particular dosage form. The *AUC* data were calculated by computer using the trapezoidal rule technique. The last measured plasma concentration

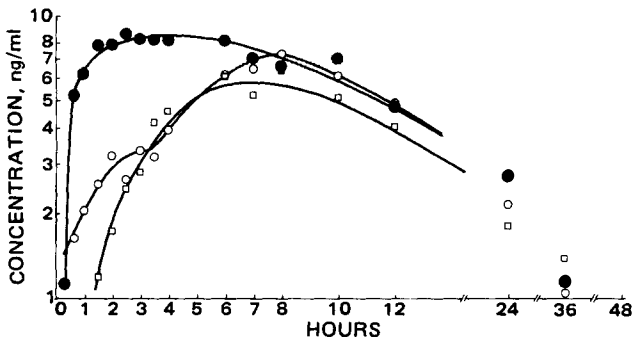

Figure 4—*A comparison of mean plasma concentration–time profiles for the 8-mg chlorpheniramine dosage forms studied (i.e., the immediately available syrup, the repeat action formulation, and the coated slow-release bead). Key: 8-mg syrup (●), Drug 2 (○), Drug 4 (□).*

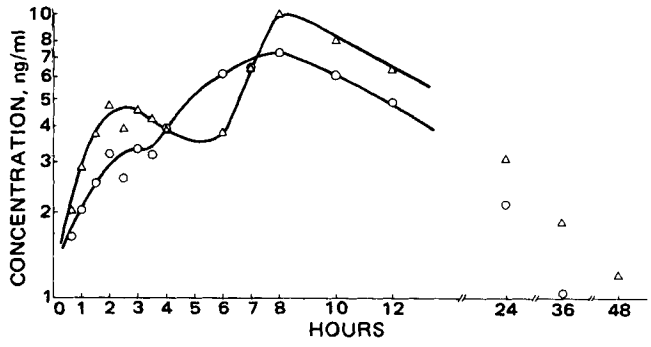

Figure 5—*A comparison of mean plasma concentration–time profiles for the repeat action chlorpheniramine formulation to two single 4-mg tablets, administered at 0 and 6 hr. Key: 4-mg tablet (△), Drug 2 (○).*

[7] A modified Gauss-Newton method for fitting nonlinear regression function by least squares. See Ref. 3 for details.

[8] Statistical Analysis System, SAS Institute, Inc., 1979 Users Guide.

Table III—Duncan's Multiple Range Tests of Pharmacokinetic Parameters

Dosage Form	Mean	Grouping[a]			F	$PR > F$
Peak Concentration (C_{max})						
8-mg Syrup	11.3 ng	A			8.70	0.0001
2 × 4-mg Tablets	11.0 ng	A				
Drug 2	9.7 ng	A				
Drug 4	7.5 ng		B			
4-mg Syrup	5.9 ng		B			
Time to Peak (t_{pk})						
Drug 2	7.6 hr	A			9.22	0.0001
2 × 4-mg Tablets	6.1 hr	A				
Drug 4	6.1 hr	A				
8-mg Syrup	3.9 hr		B			
4-mg Syrup	3.4 hr		B			
$t_{1/2}$						
Drug 4	21.2 hr	A			4.48	0.0033
2 × 4-mg Tablets	20.8 hr	A				
Drug 2	17.6 hr	A	B			
8-mg Syrup	17.3 hr	A	B			
4-mg Syrup	14.6 hr		B			
$AUC_{0\to\infty}$						
2 × 4-mg Tablets	169.6	A			11.89	0.0001
8-mg Syrup	156.3	A				
Drug 2	119.2		B			
Drug 4	113.0		B			
4-mg Syrup	65.4			C		
FD/V_c						
8-mg Syrup	6.34	A			11.42	0.0001
2 × 4-mg Tablets	5.42	A	B			
Drug 2	4.92		B			
Drug 4	3.83			C		
4-mg Syrup	3.14			C		

[a] Members of the same group are statistically similar at the $\alpha = 0.05$ level of significance.

was divided by the least-squares slope value for the β-phase, indicating log-trapezoidal extrapolation to zero concentration (*i.e.*, $AUC_{0\to\infty}$). Other bioavailability parameters were calculated following the usual methods (4).

RESULTS AND DISCUSSION

In examining controlled-release dosage forms, consideration of drug plasma levels is integral to ensuring that such dosage forms adhere to the release characteristics claimed. The barrier-coated bead product (Drug 4) is designed such that, "a therapeutic dose of antihistamine is released promptly and the remaining medication, released gradually, sustains the effect for a prolonged period" (5). The chlorpheniramine repeat action tablet (Drug 2) contains 8 mg of drug such that the "dosage is divided equally between an outer layer for rapid absorption and an inner core protected by special timed barrier for release 3–6 hr after ingestion" (6). In this study, three additional doses were administered: the 4- and 8-mg syrups to provide a comparison of plasma levels (if these quantities of drug were immediately released from an oral dose) and 4-mg tablet given at 0 and 6 hr to provide comparative repeat action plasma concentrations of two single doses.

The equation for an open two-compartment model with first-order absorption is (7):

$$C = Le^{-\alpha t} + Me^{-\beta t} + Ne^{-k_a t} \qquad \text{(Eq. 1)}$$

Using this equation, parameters fitting the model were derived for 4- and 8-mg syrups:

4-mg Syrup: $C = 2.8e^{-0.61t} + 4.4e^{-0.047t} - 7.2e^{-1.03t}$ residual sums of square = 1.87;

8-mg Syrup: $C = 4.0e^{-0.13t} + 7.3e^{-0.040t} - 11.3e^{-0.98t}$ residual sums of square = 2.66.

Only the data from the 4- and 8-mg syrups have been applied to the model since the other dosage forms or administrations were of a controlled form and, thus, not theoretically able to be fit to such a model. It should be noted that the one-compartment model was also examined. The criteria for choosing the two-compartment model to describe the data include lower sum of square, more valid plasma elimination half-life [considering recent literature information of 20–30 hr (8–11)], and curvature of the blood level–time curve data after C_{max}.

Figures 1 and 2 show plots of mean plasma chlorpheniramine levels *versus* time following oral administration of 4- and 8-mg syrups, respectively. The smooth curve in each figure is a computer prediction using the mathematical models derived for the respective syrups. Both figures show that a reasonable prediction of the data results when using the two-compartment model.

Table I shows the average plasma chlorpheniramine levels and standard deviation for each of the five different doses (dosage forms) as a function of time. Due to drug already in solution, the plasma levels for the two syrup treatments were detectable at 0.7 hr. The remaining dosage forms could only be detected 1 hr after administration. None of the five different doses were analytically detectable at 0.3 hr or >36 hr in plasma.

Figure 3 illustrates a plasma level–time profile for the 4- and 8-mg syrups and the 4-mg tablet (administered at 0 and 6 hr). The similarity of the blood levels of drug for the two 4-mg doses can be seen up to the 7-hr sample when the second 4-mg tablet, administered at 6 hr, began to show an increased chlorpheniramine concentration.

Plasma level profiles for the 8-mg syrup, Drug 4, and Drug 2 are shown in Fig. 4. It can be seen that Drug 4 and Drug 2 produce plasma levels which are essentially equivalent, while the peak level of the 8-mg syrup is definitely higher than the other two dosage forms. The similarity in plasma level profiles of Drug 2 and the two single administered 4-mg tablets is illustrated in Fig. 5.

The mean pharmacokinetic parameters for the various dosage forms of chlorpheniramine are shown in Table II. The average plasma elimination half-life ranges from 14.6 hr for the 4-mg syrup to 21.2 hr for Drug 4. An ANOVA of the $t_{1/2}$ of the five dosage forms of drug in each of the 15 subjects produced a calculated F value of 4.48 which, when compared to the $F_{0.99}$ (4, 56) of 3.65, indicates a significant difference in the half-life. The plasma elimination $t_{1/2}$ of the 4-mg syrup was significantly lower than Drug 4 and two 4-mg dosage forms as measured by the Duncan's Multiple Range Test (12). It is believed that the difference is attributable to the intersubject variability and the relatively low terminal phase levels of the 4-mg syrup which approached the limits of the assay sensitivity. The ~18.3-hr average half-life for all dosage forms studied is longer than that found previously (2), but is comparable to the reported 20–30 hr data (8–11).

The mean fraction of dose absorbed expressed as concentration in the distribution volume of the body (FD/V_c) ranged from 3.1 ng/ml after the 4-mg syrup to 6.3 ng/ml following the 8-mg syrup (Table II). As can be seen in Table III, three different categories of degrees of absorption are present with respect to the 8-mg syrup as the reference standard. The two 4-mg tablets are grouped with the 8-mg syrup, while the repeat action tablets and the two 4-mg tablets are members of both the reference standard and the second group. The coated slow-release beads and the 4-mg syrup dosage forms formed the last groups demonstrating significantly less absorption than the reference 8-mg syrup dosage form.

The peak concentration (C_{max}) of chlorpheniramine varied widely among the five different doses. However, the level of peak concentration increased as expected in the order of the 4-mg syrup, Drug 4, Drug 2, tablets, and 8-mg syrup. The calculated F value of 8.70, when compared to the $F_{0.99}$ (4, 56) of 3.65, showed that there is a significant difference between the highest plasma concentrations reached for each dose. In Table III, a Duncan's Multiple Range Test of these data indicates that the peak concentration produced by the 8-mg syrup is different from those peak concentrations found for Drug 4 and the 4-mg syrup in all 15 subjects. This shows that the controlled-release Drug 4 dosage form was apparently not releasing a large quantity of its dose immediately.

An ANOVA of the time to peak concentration produced a calculated F of 9.22, which is significantly different when compared to $F_{.99}$ (4, 56) of 3.65. Tables II and III show that the average t_{pk} of the 4- and 8-mg syrups are statistically similar. The t_{pk} of Drug 4 (6.1 hr) is not significantly different from Drug 2 (7.6 hr), even though the release mechanisms are not the same. Dissolution studies of these two dosage forms, currently underway in these laboratories, should provide additional drug release information.

An examination of the plasma half-life multiple range data reveals that Drug 2 and the 8-mg syrup displayed half-lives which could be considered in either the high or low groups (Table III). However, Drug 4 clearly had a statistically longer plasma half-life when compared to that of the 4- and 8-mg syrups. Of the four pharmacokinetic parameters evaluated, the plasma half-life measures displayed the lowest F value among the five dosage forms. It follows that the plasma half-life was the single parameter which displayed overlap between the dosage form groups. Thus, the sustained-release dosage forms have the least impact on the plasma half-lives of the chlorpheniramine blood levels when compared to their impact on peak time, peak height, and AUC.

There is a strong relationship between the type of chlorpheniramine dosage form and the AUC data from 0 hr to infinity. The AUC parameter

Table IV—*AUC* and *AUC* Ratios for Chlorpheniramine Dosage Forms

Subject	$AUC_{0-\infty}$ hr, μg hr/ml					*AUC* Ratios			
	A 4-mg Syrup	B 8-mg Syrup	C 2 × 4-mg Tablet	D Drug 4	E Drug 2	A/B	C/B	D/B	E/B
1	73.6	49.8	36.5	80.1	84.7	1.48	0.73	1.61	1.70
2	43.8	178.7	102.8	92.4	89.9	0.25	0.58	0.52	0.50
3	52.2	147.9	78.8	92.4	143.9	0.35	0.53	0.62	0.97
4	90.5	187.2	194.8	115.4	134.0	0.48	1.04	0.62	0.72
5	85.2	138.7	147.8	108.4	82.2	0.61	1.07	0.78	0.59
6	70.8	158.6	152.2	100.6	106.1	0.45	0.96	0.63	0.67
7	57.9	267.2	312.1	91.2	179.4	0.22	1.17	0.34	0.67
8	71.5	256.4	350.6	142.9	148.8	0.28	1.37	0.56	0.58
9	58.7	143.3	214.7	127.2	111.7	0.41	1.50	0.89	0.78
10	64.7	135.2	223.9	199.5	98.4	0.54	1.66	1.48	0.73
11	61.7	119.5	129.4	61.9	103.6	0.52	1.08	0.52	0.87
12	23.8	237.6	72.5	36.5	61.4	0.10	0.31	0.15	0.26
13	117.9	130.1	200.6	190.4	153.9	0.91	1.54	1.46	1.18
14	50.3	97.8	146.9	84.9	129.9	0.51	1.50	0.87	1.33
15	59.5	96.9	179.6	171.5	159.3	0.61	1.85	1.77	1.64
Mean	65.5	156.3	169.6	113.0	119.2	0.51[a]	1.13	0.85	0.88
CV, %	33	39	50	41	28	65	40	58	47
Percent of *AUC* ratios within limit of 0.75–1.25[b]			—	—	—	47%	33%	20%	27%

[a] 75/75 test for A/B would be 0.38–0.63 based on the 0.75–1.25 range. [b] See Ref. 13.

was the only pharmacokinetic measure which was separated into three distinct subgroups without any overlap. As expected, the 4-mg syrup delivered the least amount of drug over the duration of the blood sampling. This is because the amount of actual drug present is one-half the amount in all other administrations, and with the small dose administered, the blood levels of drug at early and late sampling times could not be determined by the analytical method. The *AUC* computed for a 4-mg tablet (by using the data from 0 to 6 hr and extrapolating to infinity) compared well with recent published data (11). The sustained dosage forms of Drugs 4 and 2 were not able to deliver the quantity of drug delivered by two of the 4-mg tablets or the single dose of 8-mg syrup. The sustained dosage forms comprised the intermediate Group B (Table III).

Table IV presents individual *AUC* data along with ratios of the individual *AUC* data per 8-mg syrup *AUC*. The mean *AUC* ratios for each dose and dosage form were approximately that of the predicted values. On an individual basis, however, the results show considerable deviation from the mean. Using these data, only a few individuals would pass the 75/75 test (13) because of the large intra- and intersubject variation.

Are the controlled-release dosage forms of chlorpheniramine successful? The most successful controlled-release dosage form should increase to the same peak concentration and at the same rate, when compared to the immediate release (noncontrolled) drug product. The dosage form should also increase the time the drug remains at the peak concentration and, in addition, have about twice the area under the blood level–time curve (assuming that the controlled-release dosage form contains twice the amount of drug contained in a normal, single oral dose). With these criteria, examination of Figs. 3–5 and Tables I–III would indicate that neither the coated slow-release bead product nor the tablet within a tablet product meet all of these conditions. Both of the controlled-release dosage forms give a higher peak concentration than the single 4-mg syrup, but both provided less drug concentration at the C_{max} than two 4-mg tablets. As expected, the time the peak levels occurred was extended over the immediately available syrups and was about the same time as the two 4-mg tablets. The *AUC* of the controlled-release formulations was not equivalent to the same amounts of noncontrolled release products, nor were they equal to two times the *AUC* of the 4-mg syrup (realizing the difficulties involved in obtaining an exact *AUC* for this small dose). Neither the coated bead nor tablet within a tablet was completely successful; however, more valid conclusions can be made following data reduction of a recently completed multiple-dose study of these same dosage forms.

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