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IN VITRO/IN VIVO EVALUATION OF A LIQUID SUSTAINED RELEASE DOSAGE FORM OF CHLORPHENIRAMINE

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ABSTRACT

Chlorpheniramine-resin complexes were coated with cellulose acetate butyrate to yield microcapsules with a geometric mean diameter of 346 μm. In vitro release rate of chlorpheniramine declined with increasing microcapsule size. Release of chlorpheniramine from the micropcapsules was faster in simulated gastric fluid (pH 1.2) than in simulated intestinal fluid (pH 7.5). A Chlorpheniramine solution administered by rapid intravenous injection to dogs exhibited a two phase decline in plasma drug concentration. A peroral solution resulted in a rapid rise to a peak followed by a sharp decline in plasma chlorpheniramine concentration. Peroral administration of a

microcapsule suspension caused a rapid rise in plasma concentration, but prevented the fast decline.

INTRODUCTION

The most popular route of drug administration at present is the peroral route, which justifies the development of sustained release peroral dosage forms, many of which are solid systems, including tabletted microcapsules (1-3).

The incorporation of sustained release microcapsules into aqueous vehicles often results in substantial loss of the drug core to the suspending media, therefore some investigators have prepared drug-resin complexes before encapsulating with diffusion retarding polymers (4,5). Such complexes effectively prevent the dissolution of the drug into ion-poor suspension media.

In this investigation, the influence of microcapsule size and media pH on the in vitro release of chlorpheniramine from suspended microcapsules of drug-resin complexes was explored and the plasma drug concentration-time profiles following peroral administration of the suspended microcapsules to dogs was compared to that of a peroral solution and a rapid intravenous injection of the drug.

EXPERIMENTAL

Materials

The following materials were used as supplied: chlorpheniramine maleate, brompheniramine maleate, carboxylic acid cation-

exchange resin (Amberlite CG-50^{R} (Aldrich, Milwaukee, WI); methylcellulose 1500 (Fisher Scientific, Fair Lawn, NJ); cellulose acetate butyrate (Scientific Polymer, Ontario, NY); acetone, hexane, liquid paraffin, diethyl ether, magnesium stearate (J.T.Baker, Phillipsburg, NJ); and sorbitan monooleate (Span 80^{R}) (Ruger, Hillside, NJ).

Methods

Carboxylic acid cation-exchange resin particles were dispersed in a concentrated solution of chlorpheniramine and agitated for 24 hours to form complexes. The particles were then separated and washed with deionized water to remove "free" drug and dried at 50°C.

The drug-resin complex particles were coated with cellulose acetate butyrate (polymer:complex ratio 1:1) using an emulsion solvent evaporation method. Briefly, the complexes were disperesed in a 10% polymer solution, which was subsequently emulsified in liquid paraffin containing sorbitan monooleate and magnesium stearate. Following complete evaporation of the solvent the microcapsules were collected, washed with hexane, and dried. Particle size distribution was determined with standard sieves.

The microcapsules were suspended in an aqueous solution of methyl cellulose 1500 to form the suspension dosage form. In vitro release studies were conducted using a modified USP XX paddle method at 100 rpm with simulated gastric fluid (SGF, pH 1.2) or simulated intestinal fluid (SIF,pH 7.5), and a spectrophotometric assay at 260 nm.

After a 12 hour fasting period, each of four dogs recieved 12

mg/70 kg of chlorpheniramine by rapid I.V. injection, a peroral solution, or a peroral microcapsule suspension in a crossover fashion. The oral solution was administered as two 6 mg/70 kg doses 6 hours apart; the suspension contained 12 mg/70 kg of drug released in 24 hours in vitro. The dogs received 100 ml of water at the time of dosing and ad libitum 4 hours post dosing. The same meal was provided each dog 7 hours after dosing.

Due to the limited volume of plasma which could be withdrawn from each dog, blood samples were collected according to different time schedules, depending on the dosage form administered. Samples were drawn from an indwelling catheter situated in the jugular vein into heparinized tubes. The plasma was separated and frozen until assayed.

An analytical procedure adapted from the literature was used to quantitate the plasma chlorpheniramine concentrations (6). Briefly, plasma samples with added brompheniramine as internal standard were extracted with ether after basifying with potassium hydroxide. The ether layer was re-extracted with a phosphoric acid solution. The extractions were done in duplicate for each sample. A liquid chromatograph with an integrator was used to assay for drug content. Linear regression was applied to the data to obtain a standard curve (ratio of areas = 0.010527 CPM conc + 0.0036064, r = 0.985, n = 22). The precision of the assay was determined at concentrations of 22.5 ng/ml and 45 ng/ml with relative standard deviations of 3.5% and 1.3% (within day) and 13.5% and 8.7% (between days) respectively. The standard curve was then used to obtain estimates of the experimental samples.

RESULTS AND DISCUSSION

In Vitro Drug Release

The size of the microcapsules had a significant impact on the rate of chlorpheniramine release. The times required for 50% of the drug content to be released range from 2.7 hours for 128 um to 6.8 hours for 512 um (see Table 1).

The type of dissolution fluid used, simulated gastric fluid (pH 1.2) or simulated intestinal fluid (pH 7.5), influenced the rate at which chlorpheniramine was released from coated complexes (362 um). The release of chlorpheniramine was faster in simulated gastric fluid than simulated intestinal (see Figure 1).

Release of chlorpheniramine from microencapsulated complexes is by diffusion through the polymer membrane, preceded by an exchange reaction between the adsorbed drug and counter-ions. The

TABLE 1

Effect of Particle Size on Time Required for 25%, 50%, and 75% of Chlorpheniramine to be Released

	TIME IN HOURS FOR % RELEASED		
MICRONS	25%	50%	75%
600/425	3.4±0.00	6.8±0.17	11.5±0.40
425/300	2.0±0.15	5.8±0.25	10.5±0.44
300/212	2.0±0.06	3.9±0.14	6.4±0.20
212/150	1.8±0.05	3.7±0.08	5.9±0.05
150/106	1.2±0.02	2.7±0.02	4.4±0.22

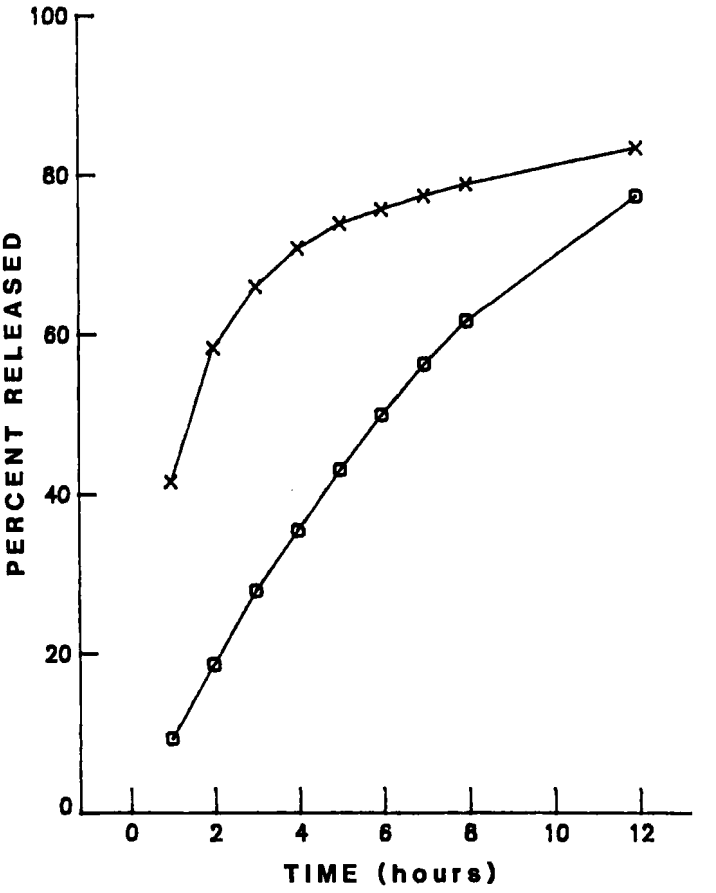

FIGURE 1
Effect of dissolution fluid on the release of chlorpheniramine from microcapsules (362 um). KEY: (X) Simulated gastric fluid and (O) Simulated intestinal fluid.

rate of drug release is, therefore, dependent on the total surface area available for diffusion and polymer membrane thickness (7), which is influenced by the size of the microcapsules. Smaller microcapsules present a larger total surface area to the dissolution fluid when compared to larger microcapsules, with a resulting faster release of chlorpheniramine.

In Vivo Studies

The plasma drug concentration versus time profile for chlorpheniramine following a rapid I.V. injection exhibited a rapid decrease in drug concentration followed by a more moderate decline after approximately one hour (see Figure 2). A semi-logarithmic plot of the plasma concentration-time data revealed two linear portions of the curve, a distribution phase and an elimination phase (see Figure 3).

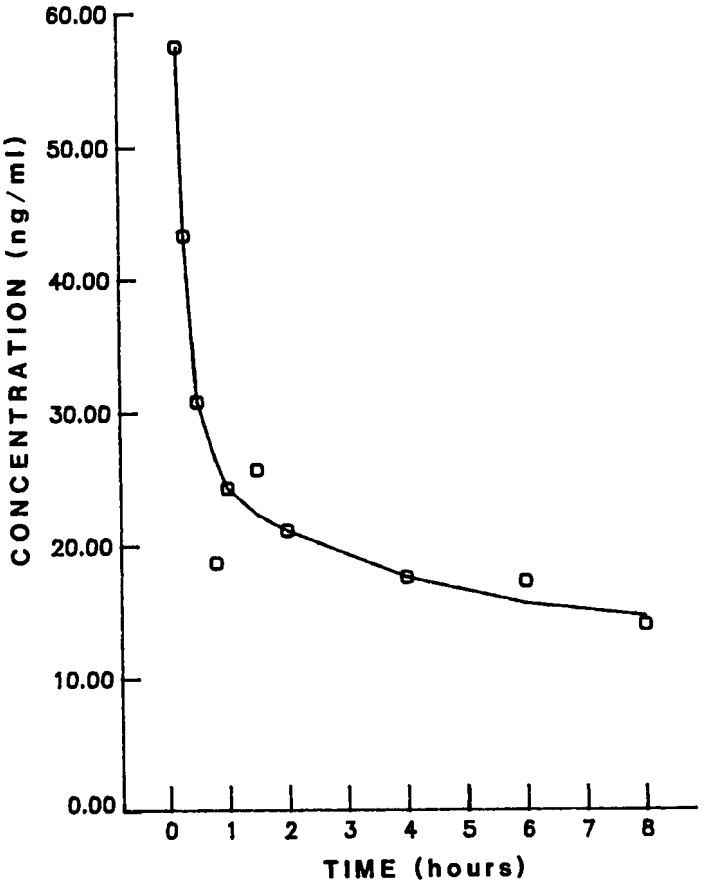

FIGURE 2
Plasma drug concentration versus time profile following a rapid I.V. injection of chlorpheniramine.

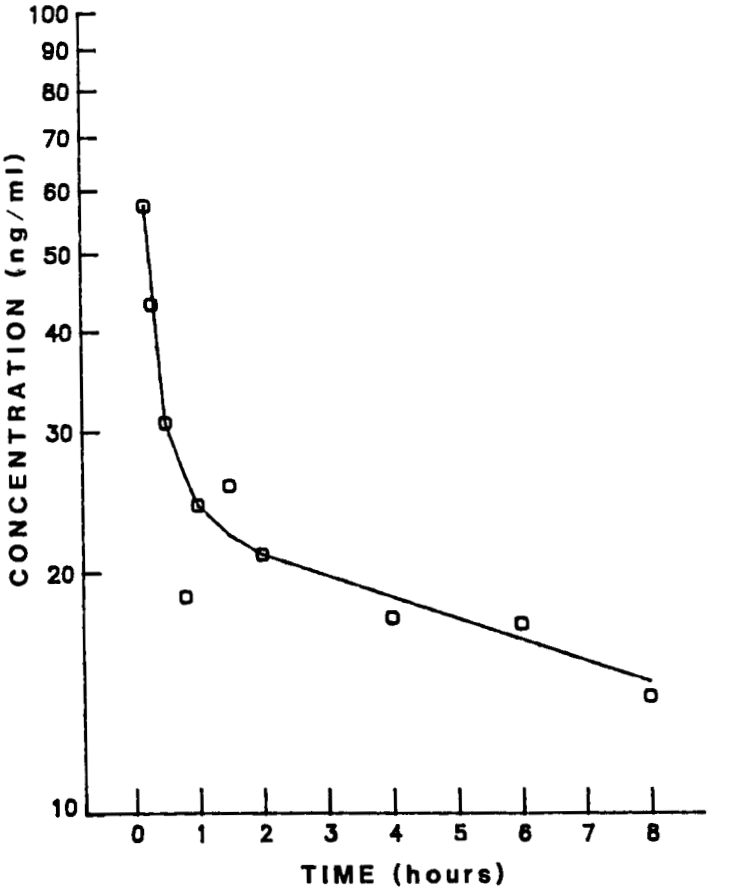

FIGURE 3
Log plasma drug concentration versus time profile following a rapid I.V. injection of chlorpheniramine.

Using the method of residuals and the plasma drug concentration versus time data following a rapid I.V. injection, the intercepts A and B were calculated as 57.07 ng/ml and 23.39 ng/ml respectively. The elimination half life was calculated from the slope of the terminal β phase elimination as 11.5 hours. The distribution half life, calculated from the residual line of the α phase, was 0.2 hours.

Administration of a peroral solution of chlorpheniramine maleate resulted in a rapid rise to a peak (18.08 ng/ml and 26.13 ng/ml) in one hour, followed by an equally sharp decline in plasma concentration (see Figure 4). The microcapsule suspension caused a similar rapid rise in plasma concentration (14.6 ng/ml), but the decline in drug concentration was much slower (see Figure 5).

If the plasma drug concentration versus time profiles of the peroral solution and the microcapsule suspension are contrasted, the advantage of the sustained release product is apparent: the peaks and troughs in plasma concentrations are eliminated.

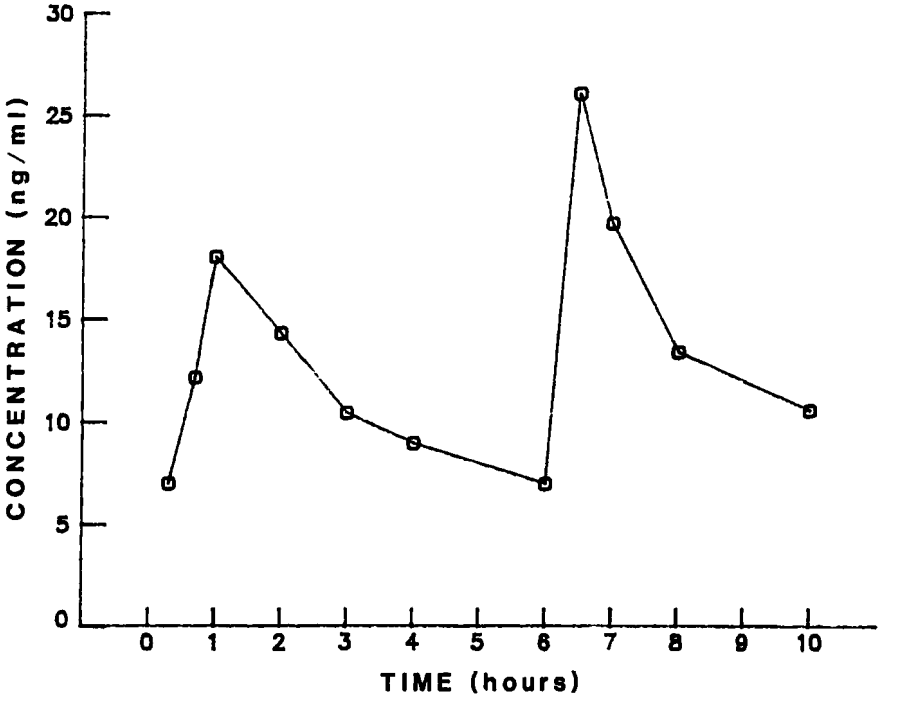

FIGURE 4
Plasma drug concentration versus time profile following a peroral administration of a chlorpheniramine solution.

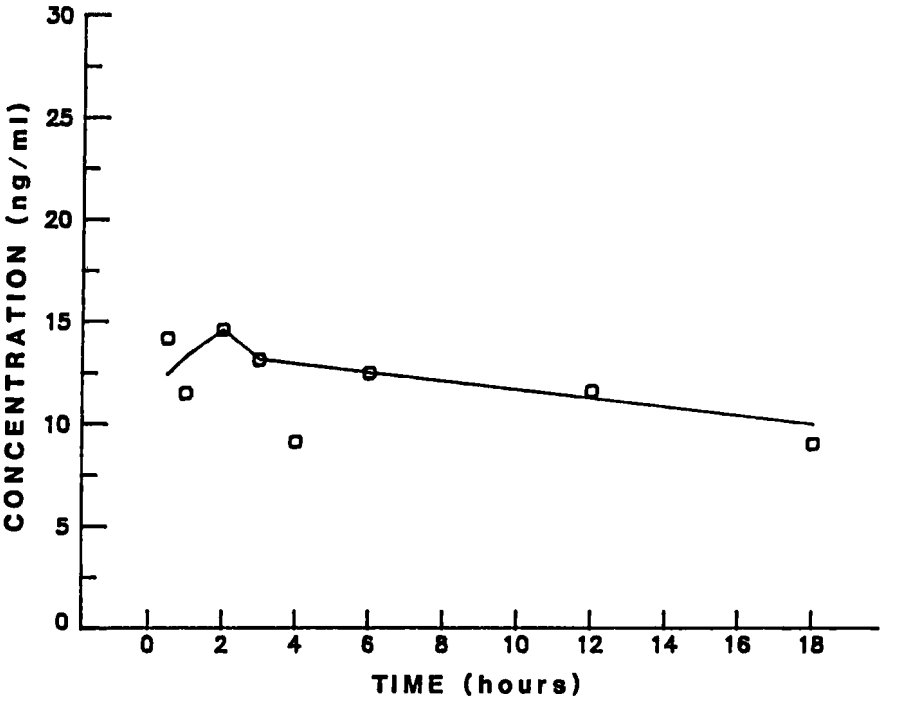

FIGURE 5
Plasma drug concentration versus time profile following a peroral administration of a microcapsule suspension.

A comparison of the area under the curves (AUC) from the peroral solution and the microcapsule suspension dosage form with the rapid I.V. injection AUC showed that the solution was 91% bioavailable, whereas the suspension had an 83% absolute bioavailability. If the AUCs of the peroral solution and the suspension are compared, the relative bioavailability of the suspension is calculated at 98% (see Table 2).

Some scatter of the I.V. data was observed near the lower plasma concentration values, which may be due to the variability in detection of the drug in plasma near the sensitivity limits of

TABLE 2

Comparison of Area Under the Curve and Bioavailability for Three dosage Forms of Chlorpheniramine

DOSAGE FORM	AUC	% ABSOLUTE BIOAVAILABILITY	% RELATIVE BIOAVAILABILITY
I.V.	399.19	100.0	---
ORAL SOLUTION	367.48	92.1	---
ORAL MICROCAPSULE SUSPENSION	332.49	83.3	90.5

the assay. Even though the scatter of the data points make the bioavailability results inconclusive, the suspended microcapsules did maintain the plasma drug levels fairly constant up to 12 hours.

SUMMARY

1. Smaller microcapsule size resulted in faster drug release.
2. Chlorpheniramine was released faster in simulated gastric fluid than in stimulated intestinal fluid.
3. After peroral administration, the microcapsule suspension maintained the chlorpheniramine plasma concentration approximately constant, whereas the peroral solution showed a rapid rise and decline in plasma levels.
4. The microcapsule suspension had an absolute bioavailability of approximately 83%.

Footnotes:

1. Waters Associates Liquid Chromatography, M-6000 pump, U6K injector, Model 440 UV absorbance detector, Micro Bondapak, Waters Associates, Milford, Massachusetts.
2. Hewlett-Packard 3390A, Avondale, PA.

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