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COMPLEX FORMATION OF CIMETIDINE WITH CAFFEINE IN AQUEOUS SOLUTIONS

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ABSTRACT

The dissolution profiles of cimetidine, a cimetidine-caffeine complex, and a cimetidine-caffeine physical mixture were determined in 0.3% HCl and distilled water at 37°. The cimetidine-caffeine physical mixture had a dissolution rate similar to that of the cimetidine alone while the complex had a slower dissolution rate. Partioning experiments were conducted using either 0.3% HCl or pH 6.7 buffer solution as the polar phase and chloroform as the non-polar phase. The apparent partition coefficient of cimetidine was decreased in the presence of caffeine added either as free caffeine or as a cimetidine-caffeine complex.

INTRODUCTION

A previous report has dealt with the formation and thermal analysis of cimetidine-caffeine complexes in the solid state[1]. It was found that the interaction of cimetidine with caffeine in the solid state resulted in the formation of several complexes having

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different molar ratios. As complex formation may change the physical chemical properties of a drug, studies were conducted on the effect of caffeine on the dissolution and partitioning properties of cimetidine.

EXPERIMENTAL

Materials

The cimetidine was supplied by Smith Kline & French laboratories. The caffeine, methanol and chloroform were obtained from Mallinckrodt.

Spectrophotometric Assay of Cimetidine

Cimetidine, in the absence of caffeine, was assayed at 220 nm. Dilutions were made with 0.3% HCl. Usually, a 1:2000 dilution was required. In the presence of caffeine, dilutions were first made with 0.3% HCl. A 20 ml portion of the diluted sample was transferred to a 125 ml separatory funnel to which was added 20 ml of spectral grade chloroform. The caffeine was extracted into the chloroform by shaking the separatory funnel for 5 minutes. The resulting aqueous solution showed no absorbance at 273 nm, the absorbance maximum for caffeine. Cimetidine was then measured at 220 nm. A 0.3% hydrochloric acid was extracted with chloroform in the same manner to serve as a blank.

Dissolution Studies

The apparent dissolution rates of cimetidine, a cimetidine-caffeine physical mixture, and a cimetidine-caffeine complex, as compressed tablets, were determined using the rotating basket method of the U.S.P. XX[2]. Tablets were compressed on a Carver Laboratory Press at 6000 lb/in^2 using 7/16 inch flat face punches and die. Stirring was performed at a rate of 60 $\pm$ 2 rpm using a synchronous motor. Distilled water or 0.3% hydrochloric acid, 900 ml, previously

equilibrated at 37 ± 0.5^{o}, served as the dissolution medium. Five milliliter samples were taken at appropriate time intervals, filtered through millipore filters, 1.2 μm, and diluted with 0.3% hydrochloric acid. Five milliliters of solvent was added to maintain 900 ml of dissolution medium and the appropriate corrections made in cimetidine concentration. Cimetidine was determined spectrophotometrically and the complex by measuring the tablet weight loss. For the physical mixture and the complex, the tablet was air dried in the basket, removed carefully, and weighed to determine the total amount of cimetidine and caffeine dissolved. The cimetidine-caffeine complex, with a 1:3.25 molar ratio, was obtained from a methanol solution as previously described[1].

Determination of Apparent Partition Coefficients

The apparent partition coefficients of cimetidine, the cimetidine-caffeine complex, and a cimetidine-caffeine physical mixture were determined (at least in duplicate) with chloroform as the organic phase and 0.3% HCl or pH 6.7 solution as the aqueous phase. Equilibration was carried out at room temperature for 24 hours in a 50 ml Bellco glass dome Spinner flask. The cimetidine was assayed in the aqueous phase as previously described

RESULTS AND DISCUSSION

Dissolution rates were determined for cimetidine, a cimetidine-caffeine complex and a cimetidine-caffeine physical mixture from compressed tablets containing an equivalent of 200 mg cimetidine. These experiments were conducted in a relatively large volume of either 0.3% HCl or distilled water to affect "sink" conditions. A 1:3.25 molar ratio of cimetidine to caffeine was employed which corresponded to the previously determined optimum ratio for cimetidine-caffeine complexation in the solid state[1].

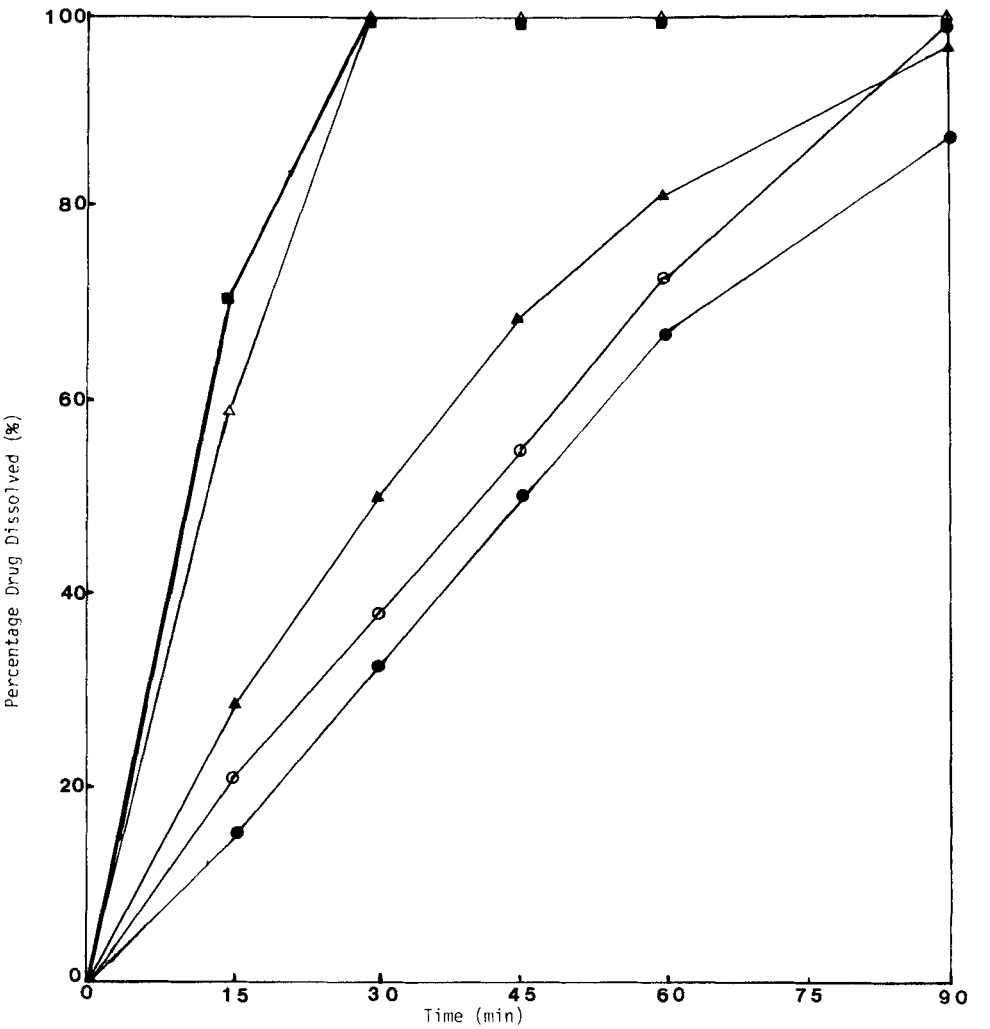

FIGURE 1

Dissolution Rate of Cimetidine, Cimetidine-Caffeine Complex, and Cimetidine-Caffeine Physical Mixture Tablets in Distilled Water and 0.3% Hydrochloric Acid. Key: ○ Cimetidine; ● Cimetidine-Caffeine Complex (in Water); △ Cimetidine; ▲ Cimetidine-Caffeine Complex; ■ Cimetidine-Caffeine Physical Mixture (in 0.3% HCl).

The dissolution profiles are shown in Figure 1. The cimetidine-caffeine complex exhibited slower dissolution as compared to that of the pure cimetidine or the cimetidine-caffeine physical mixture. Both the free cimetidine and the physical mixture dissolved rapidly,

Table 1

Apparent Partition Coefficients of Cimetidine, A Cimetidine-Caffeine Complex and A Cimetidine-Caffeine Physical Mixture

Compound	Composition of Aqueous Phase	Ratio, Organic (chloroform):Aqueous Phase	Apparent Chloroform/water Partition Coefficient
Cimetidine	0.3% HCl	1:1	0.061
Cimetidine-Caffeine Physical Mixture	0.3% HCl	1:1	0.010
Cimetidine-Caffeine Complex	0.3% HCl	1:1	0.014
Cimetidine	pH 6.7 solution	1:1	0.097
Cimetidine-Caffeine Physical Mixture	pH 6.7 solution	1:1	0.040
Cimetidiene-Caffeine Complex	pH 6.7 solution	1:1	0.052

being 100% dissolved in 30 minutes. This is certainly to be expected as cimetidine, a weak base with a pK_a of 7.09[3], is very soluble in 0.3% HCl. The complex is obviously less soluble and had a $t_{90\%}$ of 90 minutes. Slower dissolution rates were obtained in distilled water for the free cimetidine and the complex with both forms having similar dissolution profiles.

The apparent chloroform/water partition coefficients for cimetidine, the physical mixture, and the complex are shown in Table 1. They are listed as apparent partition coefficients as the aqueous phase contained both ionized and nonionized cimetidine. The low values of the partition coefficient reflect the large ionic concentration of cimetidine. It is apparent that the presence of caffeine causes a marked change in the partitioning of cimetidine. This was true for both the cimetidine-caffeine complex and the cimetidine-caffeine physical mixture which supports the concept of a cimetidine-caffeine complex occurring in aqueous solution.

These studies suggest that there exists the potential for caffeine to affect the absorption rate of orally administered cimetidine. Further in vivo studies would obviously be required to substantiate this observation.

REFERENCES

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