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THERMAL ANALYSIS OF CIMETIDINE-CAFFEINE COMPLEXES

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ABSTRACT

The preparation and characterization of cimetidine-caffeine complexes in the solid state is described. Ten different molar ratios were considered. Complexes were obtained as shown on their DSC thermograms. The heat of transition of these complexes was calculated and found to be dependent on the molar ratio of cimetidine to caffeine. A phase diagram was constructed for these complexes from which a 1:3.25 molar ratio of cimetidine to caffeine was found to exhibit optimum complexation characteristics. The cimetidine endotherms for physical mixtures of the same molar ratios show no significant changes as compared to that of cimetidine alone.

INTRODUCTION

Cimetidine is a widely used histamine H_2-receptor antagonist. It has been proven useful in the treatment of peptic ulcer and duodenal ulcer disease states by inhibiting basal and meal-

stimulated gastric acid secretion[1]. Absorption of the drug appears to be rapid, with the peak concentration and the time to reach that peak dependent upon the intake of food[2-4]; the bioavailability has been reported to be 60%[4-5].

Of interest in this study is the possible interaction between caffeine and cimetidine. Cimetidine has been advocated as a treatment for coffee-induced gastrointestinal disorders[6] and so it is only natural to investigate the interaction between cimetidine and caffeine.

Complex formation between caffeine and a number of solutes has been reported in the literature[7]. Levy and Reuning investigated the effect of caffeine on the absorption of salicylic acid in rats[8] while Zoglio and co-workers documented an increased absorption of ergotamine in the presence of a caffeine complex[9]. The objective of the present investigation is to study the complex formed by cimetidine free base and caffeine using differential scanning calorimetry and to evaluate the formation and transitions of cimetidine-caffeine complexes in the solid state.

EXPERIMENTAL

Materials

The cimetidine was supplied by Smith Kline & French Laboratories. The caffeine and Methanol A. R. were obtained from Mallinckrodt.

A Perkin-Elmer Model DSC-1 B Differential Scanning Calorimeter was used to make all the quantitative thermal measurements. The scan rate was $10^{o}C\ min^{-1}$ and the sensitivity was 8 mcal sec^{-1} in a nitrogen atmosphere for all experiments. The instrument was calibrated by the use of indium enthalpy of fusion (0.78 Kcal mol^{-1}). The measurement of the area under the peak was taken by the use of a mechanical planimeter (K & E).

Cimetidine-caffeine complexes were prepared by dissolving different molar ratios of cimetidine and caffeine in a sufficient volume of methanol in a porcelin dish. The dish was then transferred to a steam bath with continuous mixing of the contents. After solvent evaporation, the container was immediately transferred to a vacuum desiccator and kept for 24 hours before carrying out the DSC measurements. Physical mixtures of the same molar ratios as used in the complexes were also evaluated by DSC.

RESULTS AND DISCUSSION

Ten different molar ratios of cimetidine to caffeine were considered for the objective of obtaining the optimum ratio for complex formation. The molar ratios were: 1:0.65, 1:1.3, 1:2.6, 1:3.00, 1:3.25, 1:3.575, 1:3.9, 1:5.2, 1:6.5, and 1:7.8. Blank experiments for both cimetidine and caffeine tested in the same manner as the complexes were also carried out.

DSC thermograms of the different cimetidine-caffeine complexes are presented in Figure I. The measurement of the area under the thermogram peak was carried out to provide the direct basis for calculation of transition energies. The following equation was used to convert these area readings to calories:

$$\text{Sample transition (calories)} = \frac{\text{area under the sample transition peak} \times \text{range setting} \times 60}{\text{area of the rectangle} \times 1000 \times 2}$$

where the area of the rectangle is the area on the chart which is one half of the chart in width and equal in length to one minute of run[10].

The results presented in Table I and Figure II show that the values of heat of transition of cimetidine-caffeine complexes differ significantly from those of plain cimetidine or caffeine. It is

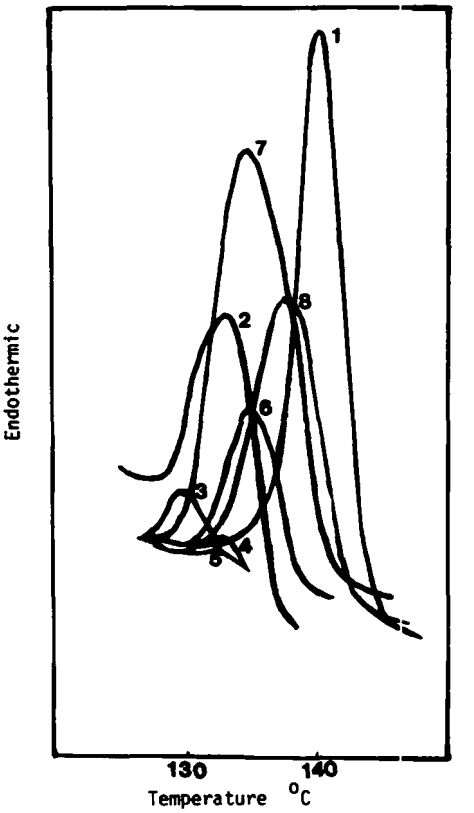

FIGURE 1

Thermograms of Cimetidine Caffeine Complexes. Caffeine Mole Fraction 1-0, 2-0.394, 3-0.565, 4-0.722, 5-0.750, 6-0.781, 7-0.796, 8-0.839. There was no cimetidine peak observed for caffeine mole fractions of 0.765, 0.855, and 0.886.

also clear that these values depend to a great extent on cimetidine-caffeine molar ratios. These values range from 8.9668 Kcal mol^{-1} for pure cimetidine and 1:3.9 ratio to zero Kcal mol^{-1} for the 1:3.25, 1:6.5 and 1:7.8 molar ratios of cimetidine to caffeine.

It is apparent that no free cimetidine is present at molar ratios of 1:3.25, 1:6.5 and 1:7.8. The molar ratios themselves indicate

TABLE I

Thermodynamic Parameters for the Complex Formation

Between Cimetidine and Caffeine at 140°C

Cimetidine:Caffeine Molar Ratio (mole/mole)	Caffeine Mole Fraction	Cimet. Sample Transition ΔH		Peak Temp. °C	
		Cal g^{-1}	Kcal mol^{-1}	Cimet.	Caff.
1 : 0.000	0.000	35.533	8.9668	140.0	N.P.*
1 : 0.650	0.394	18.067	4.5592	132.5	N.P.
1 : 1.300	0.565	05.700	1.4383	131.5	N.P.
1 : 2.600	0.722	01.133	0.2859	133.0	218
1 : 3.000	0.750	00.300	0.0757	131.5	220
1 : 3.250	0.765	00.000	0.0000	N.P.	227
1 : 3.575	0.781	09.100	2.2964	131.5	220
1 : 3.900	0.796	35.533	8.9668	134.0	219
1 : 5.200	0.839	24.167	6.0986	136.0	230
1 : 6.500	0.855	00.000	0.0000	N.P.	230
1 : 7.800	0.886	00.000	0.0000	N.P.	230.5
0 : 1.000	1.000	00.000	0.0000	N.P.	238.5

*N.P. = No endotherm was obtained and therefore no peak temperature was observed.

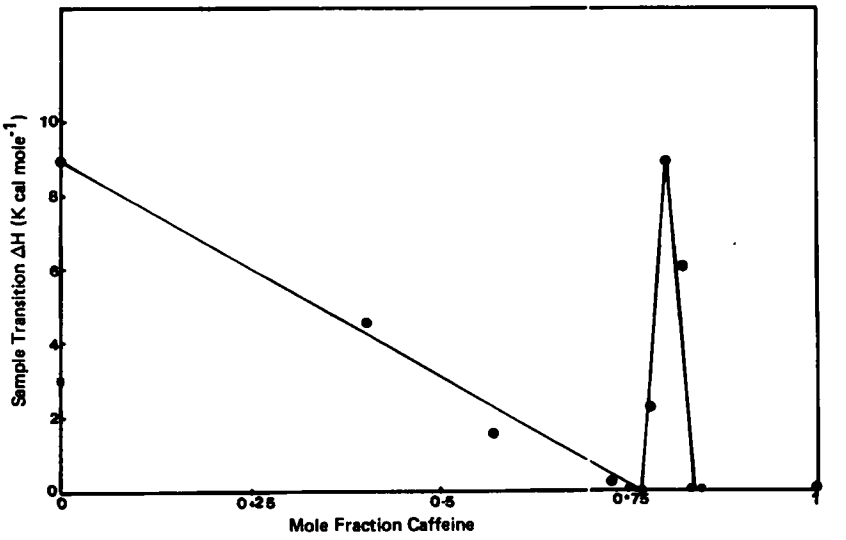

FIGURE 2

Phase Diagram of Cimetidine-Caffeine Complexes at 140°C.

the formation of a unique complex with a 4:13 complex corresponding to the 1:3.25 ratio and a 2:13 complex corresponding to the 1:6.5 ratio. The 1:7.8 ratio is difficult to understand as it is not a multiple of the first two but, indeed, is a multiple of the 1:3.9 ratio which indicates all the cimetidine is free with no complex formation.

The phase diagram shown in Figure III also indicates the presence of a cimetidine-caffeine interaction. The physical mixture of cimetidine and caffeine shows an increase in the cimetidine peak temperature at a 1:3.25 molar ratio (there is a discontinuity at the 1:3.25 molar ratio for the complex as well as at the 1.65 molar ratio). There is also an increase in caffeine peak temperature for the complex and the 1:3.25 molar ratio. There appears to be a

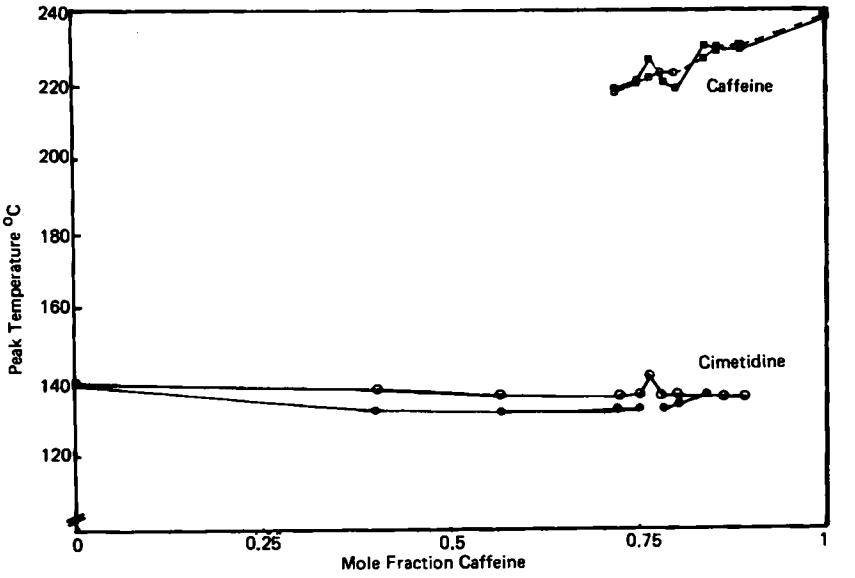

FIGURE 3

Peak Temperature of Cimetidine-Caffeine Complexes and Physical Mixtures. Cimetidine Peak, ● Cimetidine-Caffeine Complex, ○ Cimetidine-Caffeine Physical Mixture; Caffeine Peak, ■ Cimetidine-Caffeine Complex, □ Cimetidine-Caffeine Physical Mixture.

small change in the caffeine peak temperature for both the complex and the physical mixture at a 1:6.5 molar ratio, but it is difficult to be certain.

Table II gives the values of the heat of transition of cimetidine-caffeine physical mixtures of the same molar ratios considered for the complexes. No significant differences were observed between the heat of transition values for cimetidine and those for the physical mixtures. This also indicates that the changes observed for the complexes are mainly due to cimetidine-caffeine complex formation and not to the presence of caffeine per se.

TABLE II

Thermodynamic Parameters for the Complex Formation Between Cimetidine and Caffeine Physical Mixtures

Cimetidine:Caffeine Molar Ratio (mole/mole)	Caffeine Mole Fraction	Cimet. Sample Transition ΔH		Peak Temp. °C	
		Cal g^{-1}	Kcal mol^{-1}	Cimet.	Caff.
1 : 0.000	0.000	35.533	8.9668	140.0	N.P.*
1 : 0.650	0.394	35.533	8.9668	138.0	N.P.
1 : 1.300	0.565	29.867	7.5370	136.0	N.P.
1 : 2.600	0.722	35.533	8.9668	136.0	218
1 : 3.000	0.750	35.533	8.9668	136.5	220
1 : 3.250	0.765	35.533	8.9668	140.0	222
1 : 3.575	0.781	31.2667	7.8902	136.0	223
1 : 3.900	0.796	31.2667	7.8902	135.5	223
1 : 5.200	0.839	35.5330	8.9668	135.5	227
1 : 6.500	0.855	31.2667	7.8902	135.5	230
1 : 7.800	0.886	31.2667	7.8902	135.0	230
0 : 1.000	1.000	00.0000	0.0000	—	238

*N.P. = No endotherm was obtained and therefore no peak temperature was observed.

It is difficult to speculate on the effect of this complex formation on cimetidine absorption as the cimetidine free base has been used rather than the salt which would exist in the stomach. Further studies are under way to evaluate complexation of the salt form; in addition, the dissolution and partitioning behavior of the complex is being studied.

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