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In Vitro Adsorption Studies of Cimetidine

F. GANJIAN, A. J. CUTIE, and T. JOCHSBERGER ˣ

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Abstract □ The adsorption of cimetidine on selected pharmaceuticals including kaolin, activated charcoal, talc, and nonsystemic antacids was determined at pH 5.0 and 25°. The Langmuir and Freundlich adsorption isotherms showed that cimetidine adsorption was significant with activated charcoal, kaolin, talc, and magnesium trisilicate and was virtually nonexistent with magnesium hydroxide and aluminum hydroxide. Equations expressing the Freundlich and Langmuir adsorption isotherms were evaluated for each adsorbent. The approximate amounts of cimetidine adsorbed per gram of adsorbent were 25.6, 0.402, 0.291, and 0.343 mg for charcoal, kaolin, talc, and magnesium trisilicate, respectively. These *in vitro* studies indicate that some cimetidine may be lost when it is administered concomitantly with pharmaceutical adsorbents.

Keyphrases □ Cimetidine—adsorption onto various pharmaceutical adsorbents, *in vitro* □ Adsorption—cimetidine, various pharmaceutical adsorbents, *in vitro* □ Interactions—adsorption of cimetidine onto various pharmaceutical adsorbents

Numerous pharmaceuticals contain substances that are capable of adsorbing various drugs and other compounds (1–8). These substances include clays such as kaolin and talc and silicates found in some antacid–antiflatulent preparations. The purpose of this study was to determine if any adsorption interaction occurred with some commonly employed pharmaceutical ingredients including kaolin, talc, magnesium trisilicate, aluminum hydroxide, magnesium hydroxide, activated charcoal, and the H_2-receptor antagonist cimetidine used for the treatment of duodenal ulcers and gastric hypersecretion. Since antacids are recommended commonly for concurrent therapy with cimetidine, it was of interest to determine if any *in vitro* interaction was evident. To evaluate the efficiency of the adsorption, activated charcoal was employed as a standard.

EXPERIMENTAL

Reagents—Activated charcoal[1], kaolin[1], talc[2], aluminum hydroxide[1], magnesium hydroxide[1], and magnesium trisilicate[3] were reagent grade. Cimetidine[4] was compendial grade and was used without further purification. Methanol was certified ACS spectroanalyzed grade[1].

Procedure—All potential adsorbents (aluminum hydroxide, charcoal, kaolin, magnesium hydroxide, magnesium trisilicate, and talc) employed were washed repeatedly with distilled water followed by spectroanalytical grade methanol until the wash solution exhibited no absorbance at 226 nm (the wavelength of maximum cimetidine absorption). The adsorbents were passed through a 20-mesh sieve[1] while still moist and permitted to dry in an oven at approximately 45°. The dried materials then were passed through a 100-mesh sieve to ensure that the particle sizes of all of the adsorbents were 100 mesh or smaller. One gram of adsorbent was used in all cases, except for charcoal where only 50 mg was utilized.

Adsorbate mixtures were prepared by diluting aqueous cimetidine solutions (~12 mg/liter) with appropriate amounts of distilled water. The final pH of the solutions was 5.0[1]. The solutions then were agitated vigorously[5] for 10 min at 25° and allowed to stand for 20 min. Twenty-five-milliliter aliquots of the supernate were drawn from each solution, centrifuged[6] for 20 min, and assayed spectrophotometrically[7] at 226 nm. The reference solutions were prepared in an identical manner as the sample, with the cimetidine solution replaced by distilled water.

RESULTS AND DISCUSSION

The results of the *in vitro* adsorption of cimetidine onto various substances are given in Tables I–III and Figs. 1 and 2. The data are presented as both Freundlich constants (Eq. 1) and Langmuir constants (Eq. 2) as well as in terms of the adsorption rate:

$$\frac{x}{m} = kC^n \qquad \text{(Eq. 1)}$$

$$\frac{x}{m} = \frac{\alpha C}{1 + \beta C} \qquad \text{(Eq. 2)}$$

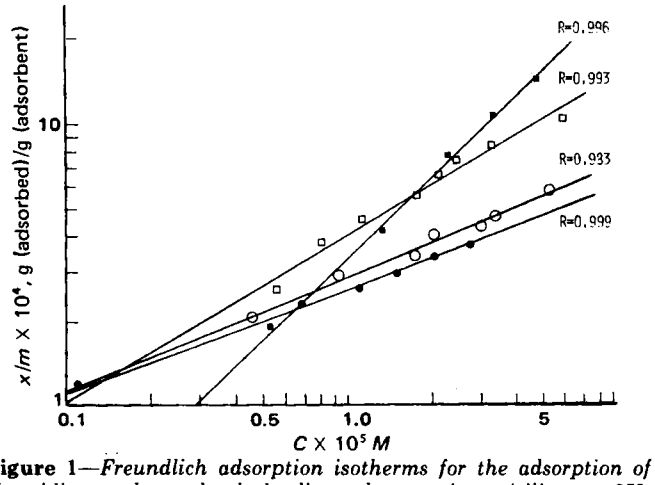

Figure 1—*Freundlich adsorption isotherms for the adsorption of cimetidine on charcoal, talc, kaolin, and magnesium trisilicate at 25°. Key:* ■, *magnesium trisilicate;* □, *kaolin;* ○, *talc; and* ●, *charcoal (values* × 10^2*).*

[1] Fisher Scientific Co., Fair Lawn, N.J.
[2] Matheson, Coleman and Bell, Norwood, Ohio.
[3] Mallinckrodt, St. Louis, Mo.
[4] Smith Kline and French Laboratories, Philadelphia, Pa.
[5] Shaker bath 6250, Eberbach Corp., Ann Arbor, Mich.
[6] Dynac centrifuge, Clay-Adams Co., New York, N.Y.
[7] Spectronic 200, Bausch & Lomb.

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Table I—Freundlich Constants for Adsorption of Cimetidine onto Various Adsorbents

Adsorbent	$k \times 10^4$, g (adsorbed)/g (adsorbent)	n
Kaolin	4.02	0.621
Magnesium trisilicate	3.43	0.943
Talc	2.91	0.384
Charcoal	256	0.347

Table II—Langmuir Constants for Adsorption of Cimetidine onto Various Adsorbents

Adsorbent	$\alpha \times 10^{-1}$, g (adsorbed)/mg (adsorbent)	$\beta \times 10^{-4}\ M^{-1}$
Kaolin	5.68	3.72
Talc	4.63	6.57
Magnesium trisilicate	3.83	0.475
Charcoal	877	21.6

where x/m is the grams of drug adsorbed per gram of adsorbent, C is the equilibrium concentration of the unbound drug, and k, n, α, and β are constants.

The data indicate that activated charcoal is about two orders of magnitude more efficient in the adsorption of cimetidine than are kaolin, talc, and magnesium trisilicate. Magnesium hydroxide and aluminum hydroxide did not adsorb cimetidine to any significant extent. This lack of adsorption is reflected in the adsorption rate as well as in the Freundlich constant k and the Langmuir constants α and β. These latter constants

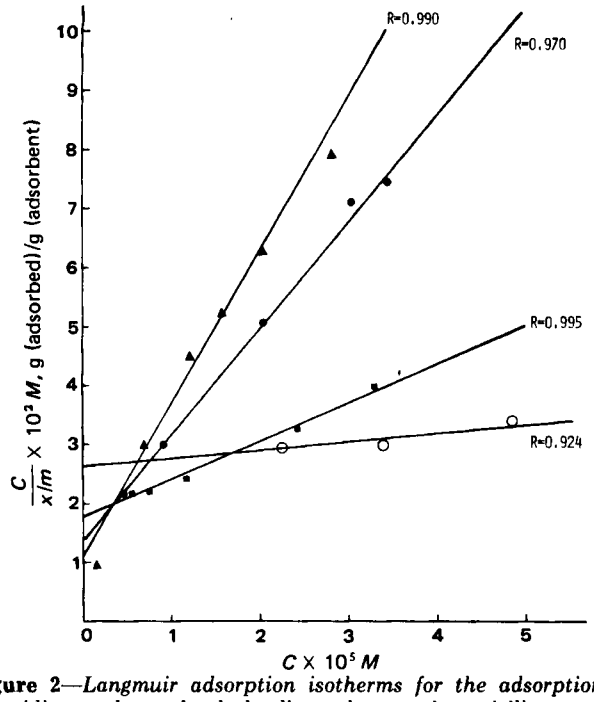

Figure 2—*Langmuir adsorption isotherms for the adsorption of cimetidine on charcoal, talc, kaolin, and magnesium trisilicate at 25°. Key: ▲, charcoal (values × 10⁴); ●, talc; ■, kaolin; and ○, magnesium trisilicate.*

Table III—Adsorption Rate of Cimetidine [a] with Different Adsorbents

Adsorbent	$(x/m)^b \times 10^4$, g (adsorbed)/ g (adsorbent)	Adsorption Rate $\times 10^3$, g (adsorbed)/ g(adsorbent) hr
Charcoal	118	35.4
Kaolin	4.69	1.41
Magnesium trisilicate	4.23	1.27
Talc	3.33	1.00
Magnesium hydroxide	0.00	0.00
Aluminum hydroxide	0.00	0.00

[a] The initial concentration was $3.20 \times 10^{-5}\ M$. [b] At equilibrium.

are directly related to the adsorption rate and inversely to the desorption rate. Therefore, the larger their values, the more efficient is the adsorbent. The Freundlich constant k represents the drug amount adsorbed per unit weight of adsorbent at a unit drug concentration (Eq. 1).

The Freundlich constant n is always less than unity (9) and represents the drug amount adsorbed for a given concentration change. Larger n values reflect a greater fraction of adsorbed drug to unbound drug. This value, in turn, reflects the ratio of the rate of adsorption to desorption and the relative strength of the bond between the drug and the binding site. The n value is largest for magnesium trisilicate, which appears to indicate that while the number of sites available on this adsorbent are somewhat less than for charcoal, as reflected in a lower per gram adsorption, the interaction of the magnesium trisilicate with cimetidine is stronger. This interaction could be the result of an electrostatic interaction between anionic silicate and the positive charge on the cimetidine molecules. The pKa of cimetidine (10) is 6.8; at pH 5.0, the drug exists almost entirely in the cationic form. Khalil (11) showed that adsorption of materials on magnesium trisilicate diminishes its uptake of hydrochloric acid, which could be significant in the use of antacids utilizing magnesium trisilicate concomitantly with cimetidine.

The results of aluminum hydroxide and magnesium hydroxide, although negative, are interesting. Bodemar *et al.* (12) showed that blood cimetidine levels are reduced in the presence of both compounds. The present work indicates that the source of this reduction is not due to the cimetidine adsorption.

The *in vitro* results with kaolin and talc indicate possible interference with cimetidine therapy by these substances. However, the clinical significance of this interaction has not been demonstrated.

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