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In vitro adsorption-desorption of famotidine on microcrystalline cellulose

Sandra L. Rivera, Samir Ghodbane *

Merck Manufacturing Division, WP38-3, West Point, PA 19486, USA

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Abstract

The adsorption of famotidine onto microcrystalline cellulose PH-101 (MCC) was studied in buffered systems and in water/alcohol mixtures. Aqueous and alcohol systems were fitted using the Freundlich and Langmuir equations, respectively. In buffered systems where ion-pairing appeared to be the predominant mechanism of interaction, adsorption can be minimized by either increasing the ionic strength or decreasing the pH. In the hydroalcoholic mixtures, the non-electrostatic interactions (such as hydrogen bonding) are dominant and famotidine adsorption is markedly decreased. Adsorption also decreases with increasing alcohol content. The free energies of adsorption were calculated in the case of alcohol/water mixtures in the range of temperature investigated (15–45°C). They showed that the adsorption process is exothermic. Finally, it was shown that the adsorbed famotidine molecules were completely desorbed at pH 2.

Key words: Famotidine; Microcrystalline cellulose; Surface adsorption interaction; Adsorption; Desorption; Langmuir isotherm; Freundlich isotherm

1. Introduction

The two major excipients found in PEPCID are microcrystalline cellulose (MCC) and pregelatinized starch. They are employed in almost a 1:1 ratio and make up roughly 85% of the tablet weight. The high excipient/drug ratio could potentially lead to drug-excipient interactions. Increased drug-excipient interactions may also result from the suspension and/or dissolution (El-Samaligy et al., 1986; Qtaitat et al., 1988) of famotidine in the granulating fluid (alcohol-water-MCC-pregelatinized starch mixture). The adsorption properties of the cellulose derivatives are well known and have been studied extensively in the textile and paper industry (Franz et al., 1982). The adsorption of some drugs onto various adsorbents has also been established (Nyqvist et al., 1978; Franz et al., 1982; El-Samaligy et al., 1986; Ghannam et al., 1992). This fact implies a decrease in the actual amount of drug available to be delivered to the blood stream in the organism. Famotidine (Mol. Wt = 337.43 g/mol) is an H_2-receptor antagonist (Fig. 1A) that is a highly

* Corresponding author (present address): Warner-Chilcott Laboratories, 182 Tabor Road, Morris Plains, NJ 07950, U.S.A.

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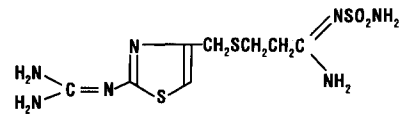
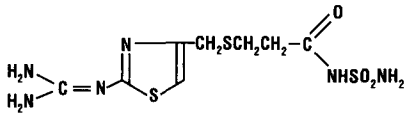


a. Famotidine



b. A_1 Degradate

Fig. 1. Chemical structure of famotidine and A_1 degradate.

potent inhibitor of gastric acid secretion in humans. It is known to exhibit two polymorphic modifications (Hegedus et al., 1989). The polymorph which melts at approx. 163°C was selected as the active component in the 20 and 40 mg PEPCID formulations prepared by wet granulation. In this study, only the adsorption of famotidine onto MCC has been investigated. The issue of famotidine-pregelatinized starch interactions will be addressed at a later date. MCC is an excipient widely used in tabletting because of its attractive compression and disintegration properties (Nyqvist et al., 1978). The influence of several parameters (temperature, pH, ionic strength and water/alcohol ratio) on famotidine-MCC interactions was investigated. These parameters were chosen because they are critical in the granulating (during product formulation) and extraction steps (upon analysis of the tablets). This study was also designed to determine those conditions that would lead to minimum adsorption and to further our understanding of the mechanism of drug-excipient interactions. The reversibility of the adsorption process, which is essential to ensure the complete bioavailability of famotidine, was also demonstrated.

2. Materials and methods

2.1. Materials

MCC PH-101 was obtained from FMC Corp., Holmer City, PA, U.S.A. Famotidine and its degradate A_1 were used as received from Yamanouchi Pharmaceutical Co., Balladyne, Ireland. The purities of famotidine and A_1 were determined by high-performance liquid chromatography to be in excess of 99.9%. The stability of famotidine in aqueous solutions (pK_a = 6.45) is pH dependent, with maximum stability at near neutral pH and decreases with either increasing or decreasing solution pH (Suleiman et al., 1989; Najib, et al., 1990). Anhydrous SD3A alcohol (95%) was supplied by Quantam (Quebec, Canada). Acetonitrile (HPLC grade), potassium phosphate, sodium phosphate monobasic, potassium chloride and sodium acetate were all ACS reagent grade (Fisher scientific, Malvern, PA, U.S.A.). The reagents were used without further purification.

2.2. Instrumentation

The apparatus consisted of a model 590 HPLC pump equipped with a model M-490 variable-wavelength absorbance detector, a model 710B WISP sample processor and a model 840 data module computer (all from Waters Instruments, Milford, MA). Chromatographic separation was achieved with a C-18 μBondapak column (30 cm × 3.9 mm), with 10 μm particle size. The column temperature was 40°C. The mobile phase consisted of 0.1 M sodium acetate (pH 6.0)/acetonitrile (93:7 v/v). The final pH was adjusted with glacial acetic acid. The flow rate was 1.5 ml/min, and detection was performed at 270 nm.

2.3. Adsorption isotherm

Control solutions, ranging in concentrations (C_o) from 0 to 600 μg/ml, were prepared from 400 or 700 μg/ml stock solutions of famotidine. The solvent used to prepare the control solution was as noted in the text. A series of famotidine-MCC systems were prepared by suspending known weights of Avicel PH-101 (MCC) in 3 ml of famotidine control solution in borosilicate glass tubes (13 × 100 mm). The tubes were then placed in crushed dry ice to lower the vapor pressure of the solution and sealed. The suspensions were

equilibrated at the selected experimental temperature for 150 min by means of a Chemap Vibromixer in a Lauda refrigerating circulating water bath. The solid was allowed to settle for 60 min at constant temperature. The glass tube was broken open, and the supernatant was filtered through a 0.45 μm membrane (Gelman 4477). The amount of famotidine adsorbed, Q in μg of drug/g of MCC, was then determined according to the following expression (Franz et al., 1982):

$$Q(\mu g/g) = (C_o - C) \cdot V/m \quad (1)$$

where C and C_o are the equilibrium and initial solution concentrations of famotidine (in μg of drug/ml solution), respectively, m denotes the weight of adsorbent (in g), and $V = 3$ ml is the volume of the famotidine-MCC solution.

2.4. Standard

A calibration curve was prepared using four standards for famotidine and the A_1 degradate (Fig. 1B). C was calculated from the calibration curve. At low pH (less than 4), famotidine partially hydrolysed to yield the A_1 degradate in a 1:1 molar ratio (Najib et al., 1989). As a result, an additional calibration curve was determined for A_1 at low pH and the amount of famotidine present in solution back calculated.

2.5. Effect of pH and ionic strength (I)

The effect of pH on the adsorption of famotidine on MCC was studied in 0.01 M phosphate buffer at pH 2.1, 4.5, and 7.0 keeping the ionic strength constant (at 0.5, or 0.2, or 0.025 M) at 25°C. The buffer solutions were prepared from a dilution of 0.1 M phosphate solution adjusted to pH 2.1, 4.5, and 7.0, respectively, with 0.1 M NaOH. The ionic strength of the 0.01 M buffers was controlled using a 2.0 M potassium chloride solution. The 0.1 M phosphate buffer (pH 7) was prepared by dissolving potassium hydrogen phosphate (6.85 g, 0.0538 mol) and sodium phosphate dibasic (7.18 g, 0.0506 mol) in deionized water. The pH was adjusted to 7.0 with 0.1 M sodium hydroxide and brought to 1.0 l with deionized water. The 0.1 M phosphate buffer (pH 4.5) was prepared by dissolving potassium hydrogen phosphate (13.65 g, 0.1003 mol) in 1.0 l deionized water. The 0.1 M phosphate buffer (pH 2) was prepared by an initial dilution of 7.6 ml of concentrated phosphoric acid (14.7 M, 85% w/w) into 800 ml of deionized water. After pH adjustment by addition of NaOH (25% w/w), the solution was brought to 1.0 l volume with deionized water.

2.6. Solubility of famotidine

The saturated solubility of famotidine in different solvents was studied to determine the range of concentration to be used in the adsorption experiments. The solubility of famotidine was evaluated by placing 200 mg of famotidine into a borosilicate glass tube (13 × 100 mm) with 3 ml of the solvent to form a saturated solution. The tubes were sealed, and the saturated solutions were equilibrated for 24 h at 25°C as described previously for the adsorption experiments. Experiments which lasted 80 h showed that equilibration had been reached within 24 h. The supernatant was analyzed by HPLC to determine the amount of famotidine in solution.

2.7. Desorption experiments

The adsorption complexes were prepared by addition of 50 ml of control famotidine solution in 25% SD3A to a 100 ml flask containing 2 g of MCC. This slurry was equilibrated for 24 h at 25°C. The amount of drug adsorbed on the MCC was calculated according to Eq. 1. This adsorbed amount was considered to be 100% of the possible drug that could be desorbed during the elution procedure. The slurry was filtered, and the MCC-famotidine complex was dried at 70°C under vacuum. 1 g of the dried complex was then placed into a 50 ml centrifuge tube and 25 ml of 0.1 M phosphate buffer (pH 2) were added. The suspension was shaken for a designated period of time at 25°C, centrifuged and the supernatant analyzed for famotidine. The overall elution procedure consisted of four steps which required the same volume of buffer (25 ml) but different shaking periods (5, 10, 15, and 75 min, respectively).

The supernatants were in all cases analyzed by HPLC.

3. Results and discussion

The accepted method for describing adsorption at a given temperature is to plot Q (μg/g) as a function of the equilibrium concentration C (μg/ml). Several isotherm shapes can be observed and can be differentiated according to the shape of the initial part of the curve (Adamson, 1982). The Langmuir isotherm is the simplest theoretical model to explain monolayer adsorption of dilute solutions (Adamson, 1982). The basic assumptions with this model are that: (i) molecules are adsorbed on fixed number of localized sites; (ii) each site can only hold one adsorbate molecule; (iii) all sites are energetically equivalent; (iv) there are no adsorbate-adsorbate interactions.

The Langmuir adsorption isotherm is given by the following equation:

$$Q(\mu g/g) = \frac{Q_{sat} \cdot b \cdot C}{(1 + b \cdot C)} \quad (2)$$

where C is the concentration of unadsorbed solute at equilibrium in (μg/ml), b represents the affinity constant and is related to the force of interaction between the adsorbent and the bound molecules. Q_{sat} is the maximum adsorbent capacity (or monolayer capacity). The linear expression of the Langmuir isotherm, which is used to determine Q_{sat} and b, is listed below:

$$C/Q = 1/(b \cdot Q_{sat}) + C/Q_{sat} \quad (3)$$

The Freundlich isotherm, although purely empirical, has nevertheless proven to be a useful tool in the evaluation of drug adsorption onto tablet excipients. It can be expressed as follows:

$$Q = K \cdot C^p \quad (4)$$

In this case again, the linear form of the equation is used to determine the Freundlich parameters:

$$\log Q = \log K + p \log C \quad (5)$$

The constant K gives a rough measure of the relative adsorbent capacity for a given drug while p (also a constant) estimates the affinity of the adsorbate for the adsorbent (Adamson, 1982). Comparison of the Freundlich and Langmuir constants is not meaningful because the former are empirical in nature whereas the latter are parameters of a theoretical model.

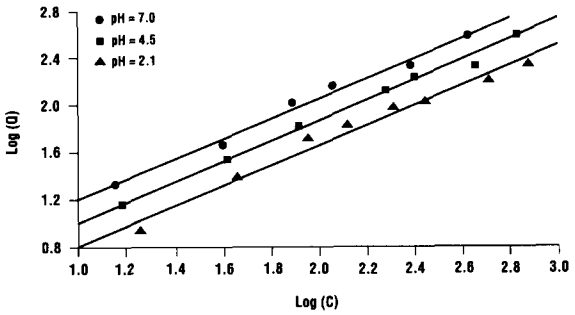


Fig. 2. Linear Freundlich plots in buffers ($I = 0.2$ M) at different pH values and $T = 25$°C.

The experimental data were plotted using the Langmuir and Freundlich isotherms. Data generated in water-alcohol mixtures were fitted using the Langmuir isotherm. In purely aqueous systems, the Freundlich isotherm yielded a much better fit and was used for analysis.

3.1. Effect of pH and ionic strength

Fig. 2 corresponds to the linear Freundlich plot of famotidine adsorption onto MCC as a function of pH at a constant ionic strength of 0.2 M. Linear least-squares analysis (LLSA) of the data yielded the Freundlich parameters p and K. These parameters were determined as a function of pH and ionic strength (Table 1). The correla-

Table 1
Values of Freundlich constants for the adsorption of famotidine on MCC at constant ionic strength

Ionic strength	pH	p	K	R^2
0.025 M	7.0	0.759	6.310	0.996
	4.5	0.809	3.177	0.991
	2.1	1.097	0.337	0.997
0.2 M	7.0	0.890	1.968	0.995
	4.5	0.917	1.130	0.991
	2.1	0.880	1.117	0.977

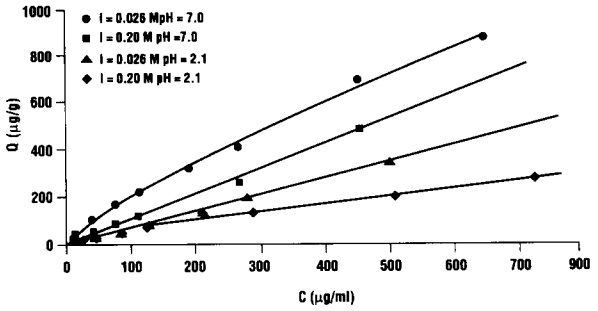


Fig. 3. Effect of pH and I on adsorption in buffered systems (T = 25°C).

tion coefficients (R^2) indicate good linearity. The experimental data points were fitted by means of the Freundlich parameters listed in Table 1. The influence of both pH and ionic strength on drug adsorption is illustrated in Fig. 3. In general, adsorption decreased with: (i) decreasing pH at constant ionic strength; (ii) increasing ionic strength at constant pH.

The influence of pH on the drug adsorption at a constant ionic strength of 0.026 M is shown in Fig. 4. The crossover between the Freundlich isotherms corresponding to a pH of 4.5 or 7 could, at first, seem unusual. Each plotted set of equilibrium values (C,Q) was determined by averaging the data generated by the analysis of three independently prepared samples (n = 3). The experimental error on Q is illustrated by the size of the error bars which correspond to twice the standard deviation. This analysis (see error bars on graph) indicated that famotidine adsorption

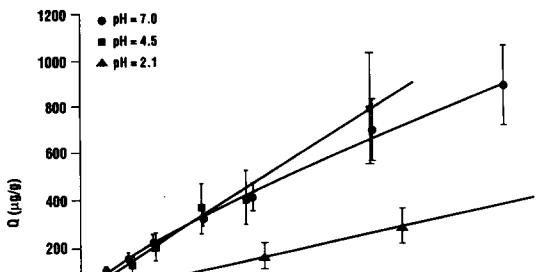


Fig. 4. Freundlich adsorption isotherms (T = 25°C) in buffers (I = 0.026 M).

was, within experimental errors, the same at these two pH values (4.5 and 7). In this instance, the experimental conditions at pH 7 (50% drug ionized and a fully ionized MCC surface) are completely reversed at pH 4.5 (fully ionized drug and 50% ionized MCC surface). Since the ionic strength is low (0.026 M), buffer ion competition is minimal. The results, which are a reflection of drug-MCC interactions, suggest that, at an ionic strength of 0.026 M, adsorption of the drug on MCC is similar at pH 7 and pH 4.5. At pH 2.1, both the adsorbent surface and the drug are fully protonated. As a result, ion-pair interactions are basically non-existent and drug adsorption is dramatically reduced. Under such conditions, the effect of ionic strength becomes minimal as shown in Fig. 4. Adsorption appears to be slightly greater at higher concentration which could be due to some residual Van Der Waals and/or hydrogen bonding interactions.

Examination of the famotidine interaction with the functional groups on MCC should shed some light on the adsorption mechanism. One proposed mechanism for adsorption is hydrogen bonding between the glucose hydroxyl groups and the amine and imidamide groups of famotidine (Sorby et al., 1966). Another proposed mechanism involves ion pairing whereby the ionization equilibrium of the carboxyl groups on the surface of MCC shifts as the pH increases from 2 to 7. The carboxyl groups are products of the hydroxyl groups' oxidation in the anhydroglucose units (pK_a = 4) (Franz et al., 1982). As a result, the MCC surface should be fully protonated at pH 2.1 and fully ionized at pH 7. At pH 4.5, the MCC carboxyl groups are expected to be approx. 50% ionized. The pK_a of famotidine is 6.45 which suggests that it may exist in a fully protonated form at pH 4.5 and pH 2.1. At pH 7, approx. 50% of famotidine should be protonated. Accordingly, it is likely that adsorption may occur via ion pairing interactions.

MCC adsorption capacity increases with pH and is highest at pH > 6 (2 pH units higher than the pK_a) because the carboxyl groups become fully ionized. At pH 7 and an ionic strength of 0.025 M, only some of the adsorption sites are occupied by the buffer ions. It should be pointed

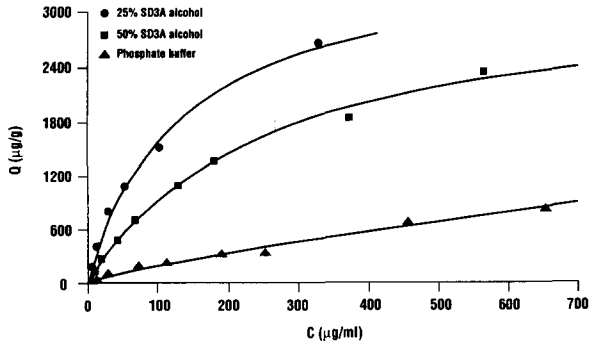


Fig. 5. Adsorption isotherms ($T = 25$°C) of famotidine in hydroalcoholic mixtures and in a pH 7 phosphate buffer.

out, however, that additional adsorption of the unionized form of famotidine to the surface via hydrogen bonding can also occur (El-Gamal et al., 1986). When the ionic strength is raised to 0.2 M, the buffer ions compete with the drug for the available sites and drug adsorption decreases accordingly. At pH 4.5 or less, adsorption occurs mainly through ion pairing because famotidine is expected to be fully protonated. Increasing ionic strength at pH 4.5 leads to decreased drug adsorption due to added competition of buffer ions for the adsorption sites.

3.2. Effect of solvent composition

The adsorption of famotidine in SD3A/water mixtures and in pH 7 phosphate buffer ($I = 0.025$ M) was determined (Fig. 5). The data indicate that an increase in the alcohol content from 25 to 50% depresses drug adsorption onto MCC. The level of adsorption can be related to the solubility of famotidine in the alcohol mixtures. Since the solubility of famotidine increases from 3.02 mg/ml in 25% SD3A alcohol to 5.8 mg/ml in 50% SD3A alcohol, it may be speculated that the more soluble the drug in an hydroalcoholic system, the weaker its interaction with the adsorbent surface. It is interesting to note that famotidine exhibits a solubility maximum at 60%w/w SD3A in SD3A/water mixtures (Table 2). The adsorption of famotidine onto the MCC surface is even lower in buffered systems. This lower adsorption may be related to the cationic species present in the buffer. The potassium and sodium ions may be ion-pairing with the negatively charged adsorption sites present on the MCC surface, thus reducing the number of adsorption sites. Ion-pairing is basically non-existent in alcoholic mixtures because of the absence of ions in solution. In alcohol/water mixtures, adsorption occurs mainly through hydrogen bonding interaction of famotidine with the surface.

Table 2
Solubility of famotidine in different solvents at 25°C

Solvent	Solubility (mg/ml)
Deionized water	1.02
20% (w/w) SD3A alcohol	2.00
25% (w/w) SD3A alcohol	3.02
40% (w/w) SD3A alcohol	4.93
50% (w/w) SD3A alcohol	5.80
60% (w/w) SD3A alcohol	6.68
80% (w/w) SD3A alcohol	4.71
SD3A alcohol	0.95
Phosphate buffer (pH 7, $I = 0.025$ M)	1.83

3.3. Effect of temperature

The adsorption of famotidine was studied at various temperatures in SD3A alcohol/water mixtures. The linear form of the Langmuir isotherm was used to extract the Langmuir parameters (Table 3) at four different temperatures in the case of 25% SD3A/water mixtures. The

Table 3
Values of Langmuir constants for the adsorption of famotidine on MCC at constant solvent composition

Solvent	Temperature (°C)	Q_{sat} (μg/μg)	b (ml/μg)	$-\Delta G$ (kcal/mol)	R^2
25% SD3A	15.0	3625	0.0123	1.190	0.991
	25.0	3527	0.0088	1.181	0.990
	37.0	2544	0.00771	1.209	0.990
	45.0	2512	0.00517	1.177	0.975
50% SD3A	15.0	2785	0.00823	1.133	0.976
	25.0	2825	0.00526	1.106	0.994
	37.0	2465	0.00314	1.071	0.994
	45.0	2421	0.00242	1.058	0.993

parameters were then used to plot the adsorption isotherms (Fig. 6). For the sake of brevity, the data corresponding to 50% SD3A/water mixtures are not shown. At constant alcohol content, famotidine adsorption onto the MCC surface diminishes with increasing temperature. The tendency of the values of Q_{sat} to decrease as the temperature increases means that the adsorption process is exothermic (Okada et al., 1987). The affinity constant, b, which gives an indication of the force of interaction between the adsorbent and the adsorbate, also decreases as the temperature increases. The data generated can be used to calculate the free energy of adsorption at infinite solution ($\Delta G°$). The free energy can be calculated from the Langmuir isotherm. When the surface is covered with an amount of drug equal to one-half its monolayer adsorption capacity, the equilibrium concentration of the drug in the liquid phase ($C_{\frac{1}{2}}$) is equal to $1/b$ (from the Langmuir equation, $C = 1/b$ when $Q = Q_{sat}/2$). The constant $1/b$ (in mol/l) is defined as:

$$1/b = (55.5 \exp(\Delta G°/RT)) \quad (6)$$

where T and R are the temperature and the gas constant (in cal/mol per K), respectively (Rosen, 1989). $\Delta G°$ was calculated for SD3A alcohol (25 and 50%) at different temperatures (Table 3). $\Delta G°$ does not change significantly in the temperature range used. The data show that the adsorption process is exothermic with values of -1.2 and -1.1 kcal/mol for 25 and 50% SD3A, respectively.

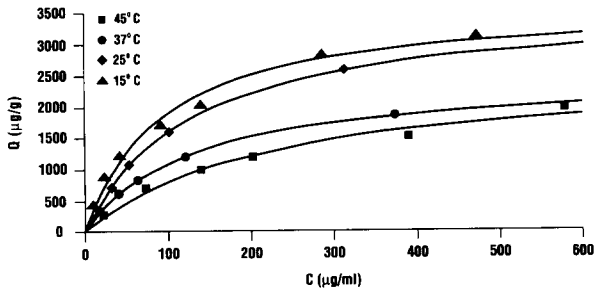


Fig. 6. Langmuir adsorption isotherms at various temperatures in 25% SD3A alcohol.

Table 4
Desorption data for famotidine

Elution no.	Time (min)	Cumulative % desorbed
1	5	86.5
2	10	97.8
3	15	99.6
4	75	101.9

3.4. Desorption experiment

The desorption data (Table 4) showed that famotidine is completely eluted in phosphate buffer solution (pH 2.0) after 15 min. The results of this desorption experiment indicated that the adsorption of famotidine onto MCC would be completely reversed at a pH of 2.

4. Conclusion

The predominant mechanism of famotidine interaction with the adsorbent surface appears to be ion-pairing in buffered systems whereas hydrogen bonding is prevalent in alcohol/water systems. In the buffered systems (used to extract famotidine from the tablets), adsorption can be minimized by either increasing the ionic strength or decreasing the pH. In the hydroalcoholic mixtures (used in granulation), the non-electrostatic interactions (such as hydrogen bonding) are dominant and famotidine adsorption is markedly decreased. Adsorption also decreases with increasing alcohol content from 25 to 50%. The free energies of adsorption were calculated in the case of alcohol/water mixtures in the range of temperature investigated (15–45°C). They showed that the adsorption process is exothermic. Finally, it was shown that the adsorbed famotidine molecules were completely desorbed at pH 2. The adsorption process was shown to be exothermic and completely reversible at gastric pH and ionic strengths.

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