Pharmaceutical Research, Vol. 5, No. 3, 1988

Report

Phenobarbital Adsorption from Simulated Intestinal Fluid, U.S.P., and Simulated Gastric Fluid, U.S.P., by Two Activated Charcoals

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Received July 13, 1987; accepted October 2, 1987

Adsorption of phenobarbital from simulated intestinal and gastric fluids by two activated charcoals was studied. Adsorption isotherm data were analyzed by the linearized Langmuir equation and by nonlinear least-squares regression employing both Langmuir and Freundlich models. These analyses indicated differences in the capacities of the two charcoals for phenobarbital which could not be completely explained by surface-area considerations.

KEY WORDS: phenobarbital; adsorption; activated charcoal; Langmuir; Freundlich.

INTRODUCTION

The administration of activated charcoal has been shown to be effective in increasing phenobarbital clearance (1). A new activated charcoal (SuperChar, Gulf Bio-Systems, Inc., Dallas, Tex.) has a surface area of approximately 3000 m^2/g, resulting from a large number of pores which, on average, are much smaller in radius than those of a typical activated charcoal. Access to such pores by phenobarbital would be questionable since its structure is not compact. Phenobarbital adsorption on SuperChar was therefore compared using two adsorption models to phenobarbital adsorption on a typical activated charcoal (Darco KB-B, American Norit, Jacksonville, Fla.).

EXPERIMENTAL

Simulated intestinal fluid, U.S.P. (without pancreatin; SIF), and simulated gastric fluid, U.S.P. (without pepsin; SGF), were prepared according to the *United States Pharmacopeia, Volume XXI.*

Approximately 456 and 228 mg of phenobarbital (J. T. Baker Chemical Co., Phillipsburg, N.J.), free acid, were dissolved in 250 ml of SIF and SGF, respectively. Eight differing aliquots of the appropriate stock solution were diluted to 100 ml using the same batch of SIF or SGF as was used to prepare the phenobarbital stock solution. Five-milliliter aliquots were removed from each of these dilutions. A 1.0-ml portion was taken and ultrafiltered by centrifugation through a 30,000 MW exclusion disposable filter cartridge (Amicon, Danvers, Mass.). These filtered samples were used to construct a standard curve for phenobarbital.

All charcoals were vacuum dried (100°C, 25-μ pressure) for 24 hr prior to use. Eight samples of the appropriate charcoal (25.0 ± 0.2 mg each) were individually weighed, then placed in separate glass bottles, and the appropriate phenobarbital stock solution was added. The bottles were rotated at 37.0 ± 0.1°C in a Vanderkamp sustained-release apparatus (Van-Kel Industries, Inc., Edison, N.J.) at 15 rpm for 20 min. A 1.0-ml sample was removed from each bottle for ultrafiltration and subsequent analysis.

The sample concentration was determined using a Hewlett Packard 8450A spectrophotometer (Hewlett Packard, Scientific Instruments Division, Palo Alto, Calif.) operating at the 254-nm absorbance maximum of ionized phenobarbital. Samples in SIF were prepared for analysis by diluting a 150-μl aliquot of the filtrate to 5.0 ml with 0.1 *N* NaOH, while 250-μl aliquots and 0.2 *N* NaOH were used when the studies were in SGF. The amount of phenobarbital adsorbed was determined by mass balance.

The surface areas of the activated charcoals were determined by multipoint BET analysis (Quantasorb, Jr., Quantachrome Corp., Syosset, N.Y.) employing nitrogen as the adsorbate.

RESULTS AND DISCUSSION

The ultraviolet assay for phenobarbital yielded Beer's Law plots with excellent linearity (correlation coefficients >0.999 in all cases) and reproducibility.

All isotherms had the basic shape of a Type I isotherm as classified by Brunauer (2) and the data were therefore analyzed according to the Langmuir treatment (Figs. 1 and 2). The Langmuir treatment is summarized by the equation

$$\frac{x}{m} = \frac{k_1 k_2 C_{eq}}{1 + k_1 C_{eq}} \quad (1)$$

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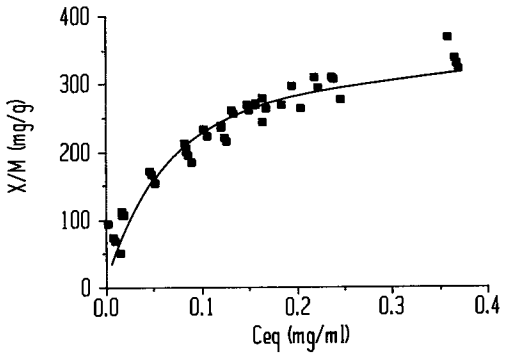

Fig. 1. Adsorption of phenobarbital from SGF by Darco KB-B. The curve was fit to the data according to the Langmuir model.

where x is the amount of solute adsorbed, m is the mass of adsorbent, C_{eq} is the concentration of unadsorbed solute at equilibrium, k_1 is an affinity constant, and k_2 is a constant indicating the capacity of an adsorbent for a given material. The linearized form of this equation indicates that a plot of $C_{eq}/(x/m)$ versus C_{eq} should have a slope of $1/k_2$ and an intercept of $1/(k_1k_2)$. Adsorption data were analyzed by both linear and nonlinear (3) least-squares regression, with the data from each group of three runs being simultaneously fit (Table I).

The derivation of the Langmuir equation is dependent upon four assumptions (4): all of the sites for adsorption are equivalent (i.e., the heat of adsorption is independent of surface coverage), the adsorbed phase is confined to a monolayer, lateral interactions between adsorbate molecules do not occur, and adsorbed molecules are localized. These are strenuous assumptions and the first assumption is especially problematic when dealing with activated charcoal. Depending on the activation process, the charcoal surface has been shown to have hydroxyl, carbonyl, and lactone groups (5) and various metallic impurities, especially zinc (6). Physical irregularities in the surface may also result in a varying heat of adsorption with surface coverage (7,8).

Since the Freundlich equation has been found to be useful in describing drug adsorption by tablet excipients and by activated charcoal (9,10), this model was also employed

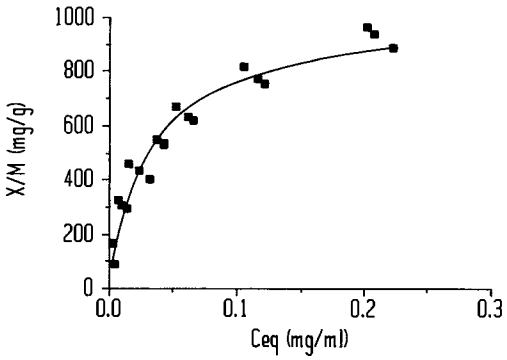

Fig. 2. Adsorption of phenobarbital from SGF by SuperChar. The curve was fit to the data according to the Langmuir model.

(Figs. 3 and 4) and a Type I isotherm was no longer assumed. The Freundlich equation is

$$\frac{x}{m} = KC_{eq}^{P} \qquad (2)$$

where K is a constant related to the capacity of the adsorbent for the adsorbate and P is a constant related to the affinity of the adsorbent for the adsorbate. Equation (2) was fit to the data as before (Table I). K represents the amount of adsorbate bound by the adsorbent when in equilibrium with a solution of adsorbate having unit concentration. In this study, that would mean a solution having a concentration of 1 mg/ml. Based on an approximate solubility of phenobarbital of 1 g/liter in SGF (11) and ~2 g/liter in SIF, this is a physically realistic system even though the experimental values of C_{eq} did not go that high. Therefore, K will be used as a capacity.

The Freundlich equation was first employed in a purely empirical manner (12). It can, however, be derived with the assumption that variation in the amount adsorbed with change in surface coverage is entirely due to change in the heat of adsorption (4). This continual change in the heat of adsorption seems applicable to the activated-charcoal case since it is unlikely that the different sites have exactly the same heats of adsorption or that they are so different that a stepped isotherm results. The Freundlich model unfortunately predicts both infinite adsorption at infinite concentration and infinite heat of adsorption at zero coverage. Various patches have been employed to deal with these problems (4,13) and it may be that these patches are no more restrictive in understanding drug adsorption onto charcoal than are the assumptions implicit in the Langmuir model.

The correlation coefficients obtained from the linearized Langmuir treatment are appreciably better than the correlation coefficients obtained from the nonlinear regression analysis in every case (Table I). This is to be expected when one or more plotted terms are common to each axis and is likely artificial. Both charcoals exhibited only minor differences in adsorption capacity between SGF and SIF when the Langmuir model was employed. Substantial differences in affinity constants were seen for each charcoal between the two media. This is an expected result since the solubility of phenobarbital is roughly twice as great in SIF as in SGF. Application of the Freundlich model to the data resulted in differences in the estimates for both K and P with a change in medium. Interestingly, this model yielded results consistent with the Langmuir model for SuperChar but opposite to the Langmuir model for Darco KB-B. The exact physical importance of these results is not clear at this time.

As published recently (10), the Freundlich model was found to yield higher correlation coefficients than did the Langmuir model and comparison of Figs. 1 and 2 with Figs. 3 and 4 is instructive. The most appropriate model for the adsorption process should never be selected solely on the basis of statistical comparisons, however, the Freundlich model also seems to have more appropriate heat-of-adsorption assumptions. Resolution of this issue must await further studies on surface composition and heats of adsorption.

It was believed that SuperChar would adsorb more phenobarbital as a result of its greater surface area but that the

Table I. Model Parameters for the Various Adsorption Systems Studied

System	Langmuir equation		Freundlich equation, nonlinear regression
	Linear regression	Nonlinear regression	
KB-B, SGF (N^a = 5)			
k_1 (ml/mg)	16.1	15.6	P = 0.374
k_2 (mg/g)	373	372	K (mg/g) = 506
r	0.981	0.957	0.975
$s_{y\cdot x}$[b]	5.4 × 10^{-5}[c]	23	18
KB-B, SIF (N = 3)			
k_1 (ml/mg)	6.5	6.6	P = 0.403
k_2 (mg/g)	418	414	K (mg/g) = 421
r	0.983	0.968	0.977
$s_{y\cdot x}$	9.8 × 10^{-5}[d]	22	19
SuperChar, SGF (N = 3)			
k_1 (ml/mg)	33.1	33.2	P = 0.359
k_2 (mg/g)	1023	1002	K (mg/g) = 1659
r	0.985	0.960	0.974
$s_{y\cdot x}$	1.2 × 10^{-5}[e]	75	60
SuperChar, SIF (N = 3)			
k_1 (ml/mg)	17.0	22.1	P = 0.268
k_2 (mg/g)	1064	996	K (mg/g) = 1156
r	0.991	0.946	0.981
$s_{y\cdot x}$	2.8 × 10^{-5}[f]	76	46

[a] N refers to the number of runs (eight points each) that were simultaneously fit.
[b] $s_{y\cdot x}$ = (residual mean square)$^{0.5}$.
[c] $1/k_1 = 6.19 \times 10^{-2}$; $1/k_2 = 2.68 \times 10^{-3}$.
[d] $1/k_1 = 1.54 \times 10^{-1}$; $1/k_2 = 2.39 \times 10^{-3}$.
[e] $1/k_1 = 3.02 \times 10^{-2}$; $1/k_2 = 9.77 \times 10^{-4}$.
[f] $1/k_1 = 5.89 \times 10^{-2}$; $1/k_2 = 9.40 \times 10^{-4}$.

increase in amount adsorbed would not be as great as the increase in surface area, a direct consequence of the pores being too small for complete drug accessibility. The latter assumption was incorrect. Darco KB-B was found to have a surface area of 1511 m^2/g, while SuperChar was found to have a surface area of 2773 m^2/g. Although SuperChar has a surface area approximately 1.8 times that of Darco KB-B, it can adsorb 2.6 (Langmuir) to 3.1 (Freundlich) times as much phenobarbital. Apparently, either multilayer adsorption was occurring on SuperChar, unlikely for solutes this dilute, or the adsorption site spacing on Darco KB-B was not effective in maximally packing phenobarbital molecules. The projected area that a single phenobarbital molecule should occupy on the adsorbent surface, obtained from group contributions, is 100–120 $Å^2$/molecule (14,15). This value assumes orientation parallel to the surface with neither overlap of functional groups nor open spaces. The apparent areas occupied by a phenobarbital molecule on the charcoal surface, using the Langmuir model since k_2 has a more exact physical meaning than K in the Freundlich model, are presented in Table II. The apparent areas obtained from the SuperChar results are seen to agree more closely with the estimated area and it is concluded that the active adsorption site spacing on Darco KB-B is probably not optimal for phenobarbital.

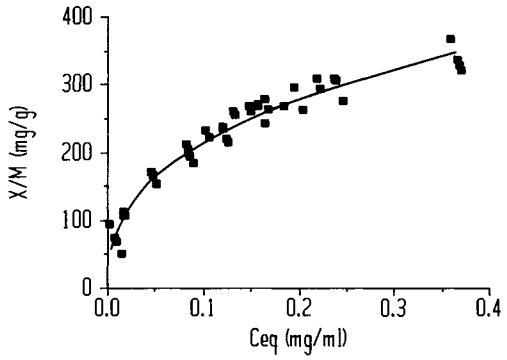

Fig. 3. Adsorption of phenobarbital from SGF by Darco KB-B. The curve was fit to the data according to the Freundlich model.

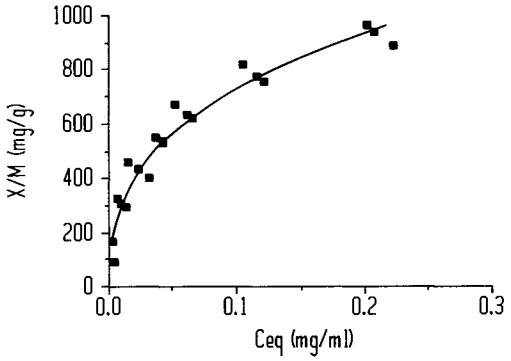

Fig. 4. Adsorption of phenobarbital from SGF by SuperChar. The curve was fit to the data according to the Freundlich model.

Table II. Apparent Area Occupied by a Phenobarbital Molecule on the Charcoal Surface

System	Area (Å²; Langmuir equation)	
	Linear regression	Nonlinear regression
KB-B, SGF	156	157
KB-B, SIF	139	141
SuperChar, SGF	104	107
SuperChar, SIF	100	107

ACKNOWLEDGMENT

This work was supported by National Institute on Drug Abuse Grant DA04083.

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