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Surface modification of alumina particles by nonionic surfactants: Adsorption of steroids, barbiturates and pilocarpine

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Summary

The sorption isotherms of several drugs (progesterone, testosterone, hydrocortisone, amobarbital, barbital, butobarbital (sodium salt), pilocarpine hydrochloride) on C alumina particles as a function of surfactant concentration (Triton X-100) were constructed. It was found that the adsorption of the drugs is considerably enhanced by the nonionic surfactant above a concentration threshold of the order of 5×10^{-5} mol/l, although Triton X-100 itself is poorly adsorbed on the alumina particles. The maximum increase in drug adsorption due to the surfactant is found to occur close to the critical micelle concentration (CMC); the increase is by a factor of 10 for all compounds studied. Due to the poor adsorption ability of Triton X-100, the drug mole fraction at the particle surface is above 0.8 for all compounds except for pilocarpine. The sorption isotherms were of two types: the more hydrophobic compounds displayed a plateau adsorption above the CMC; for the most hydrophilic compounds and the ionic drugs, the adsorption decreased from its maximum at the CMC to almost zero at higher surfactant concentration. The above phenomena seem to be the consequence of surface particle modifications induced by the surfactant monomers rather than an adsolubilization effect.

Introduction

It has been shown recently that the surface properties of polymeric nanoparticles which have been modified by the adsorption of nonionic surfactants may be used as drug carriers (Harmia et al., 1986; Davis and Illum, 1988; Buckton et al., 1991; Carstensen et al., 1991; Lukowski et al., 1993). In the course of a study on similar chemical systems, it was found interesting to investigate the adsorption of model drugs on a surfactant coated solid mineral. Materials such as alumina or silica dispersions are free from residual impurities, whether polymers or surfactants, the presence of which, in unkown amounts, may complicate the analysis of the uptake of drugs in the case of polymerized nanoparticles (Harmia et al.., 1986).

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It has long been known that surfactants adsorb on solid minerals. Although the adsorption process may vary considerably according to the type of mineral, the charge of the surfactants, the pH of the solution or the presence of salts, a simplified picture has emerged (Levitz, 1991; Cases and Villieras, 1992). Small aggregates (hemimicelles) adsorb at low surfactant concentration. As the concentration is increased, the aggregates grow in size until complete coverage is achieved at a surfactant concentration close to the critical micelle concentration (CMC). Above the CMC, free micelles are usually formed. The adsorption of surfactant reaches a maximum and a plateau is often observed. In some cases, however, adsorption decreases above the CMC (Mukerjee and Anavil, 1975). It has been shown recently using fluorescence decay measurements in the case of a nonionic surfactant, Triton X-100 adsorbed on silica, that the size of the aggregates at concentrations close to the CMC is of the same order of magnitude as that of regular micelles (Levitz et al., 1984; Levitz, 1991). Surfactants may be used for the solubilization of drugs and other compounds mostly above the CMC. In the presence of solid dispersions, adsorbed micellar aggregates could solubilize hydrophobic compounds. This phenomenon has been coined adsolubilization (Harwell et al., 1985). A number of recent publications have dealt with this phenomenon.

Most studies have been concerned with model compounds such as alcohols (Esumi et al., 1990; Lee et al., 1990), dyes (Nunn et al., 1982; Zhu et al., 1988) or organic pollutants (Klumpp et al., 1992). The adsorption of pilocarpine salts on polymeric nanoparticles has also been studied using various nonionic surfactants (Harmia et al., 1986). It was found that nonionic surfactants in the presence of various inorganic salts increased the uptake of the ionic drug by polyacrylate nanoparticles.

In this preliminary report, alumina C was chosen as the substrate, with Triton X-100 (*t*-octylphenol poly(oxyethylene)) with an average of 9.5 ethylene groups as the nonionic surfactant; the drugs were barbiturates, either as acids or salts, pilocarpine hydrochloride and three steroids of different degrees of hydrophobicity. The aim of the present work was to study the adsorption isotherms of these drugs under precise experimental conditions.

Materials and Methods

Materials

Hydrocortisone, testosterone and progesterone were obtained from Sigma, barbital and amobarbital from Expandia (France), butobarbital (sodium salt) from Coopération Pharmaceutique Française and pilocarpine hydrochloride from EGA-Chemie. Triton X-100 (TX- 100) (Packard) was used as received. Its CMC was measured using surface tension measurements at 25°C employing a tensiometer (Kruss K 10 T). The CMC in pure water was 3.4×10^{-4} mol/l. In the presence of 0.15 mol/l of NaCl, the CMC value decreased to 1.8×10^{-4} mol/l. In the presence of 10 wt% of ethanol and 0.15 mol/l of NaCl, the CMC was equal to 2.5×10^{-4} mol/l (Fig. 1). Sodium chloride was from Merck. Alumina C (a gift from Degussa) had a specific B.E.T. area of 100 ± 15 m^2/g (as indicated by the manufacturer). Doubly distilled water was used in all experiments.

Table 1 presents the chosen maximum UV absorption wavelengths for the drugs and for the surfactant. Experiments were conducted in duplicate so that the blank was constituted by silica + surfactant at the same surfactant concentration

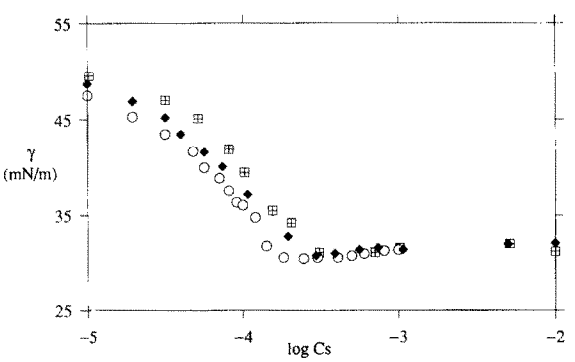

Fig. 1. Surface tension as a function of surfactant concentration at 25°C: (⊞) pure water; (○) 0.15 mol/l NaCl; (◆) 0.15 mol/l NaCl + 10% ethanol.

as the drug + alumina + surfactant system of interest. Blue or red chemical shifts were noted in the presence of the surfactant for the maximum wavelength (λ) of some of the drugs. Thus, the maximum value of λ was taken as the reference for each surfactant concentration. The chemical shift was independent of surfactant concentration. The spectrophotometer (Perkin-Elmer Lambda 5) was equipped with a thermostated jacket. The barbiturates were analyzed at pH 13.

Sorption isotherms

Several solid-to-solution ratios were investigated. It was found that the optimum experimental conditions were obtained for a ratio of 0.1 g of alumina for 10 ml of solution. The solutions were equilibrated for 4 days in screw-top tubes which were placed in a thermostated bath at 35 ± 1°C. The pH was adjusted to 4.5 for all systems. After ultracentrifugation at 30000 rpm for 30 min at the same equilibrium temperature it was found that the supernatant still contained some alumina particles. Thus, the solutions were filtrated using 0.1 μm filters (Millipore). Longer centrifugation times did not improve the separation. The final pH of the solutions, as measured using a combination glass electrode, were equal to 6.8 in all cases. The steroid solutions were protected from light during the equilibration process.

TABLE 1

Maximum UV wavelength of the compounds used in the presence and absence of surfactant (pH 6.8)

Compounds	λ (max) [a] (nm)	λ (max) [b] (nm)
TX-100	276.5	–
Testosterone	248.9	246.8
Hydrocortisone	247.5	246.0
Progesterone	247.0	246.0
Pilocarpine	210.0	212.5
Barbital	238.0	–
Butobarbital	236.0	–
Amobarbital	238.0	–

[a] In the absence of surfactant.

[b] In the presence of TX-100 (λ is independent of surfactant concentration).

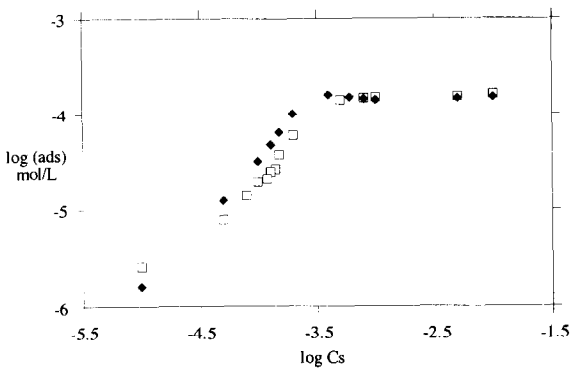

Fig. 2. Adsorption of Triton X-100 with equilibrium surfactant concentration at 35°C: (◆) pure water; (□) in the presence of 10% ethanol.

All experiments were performed at constant equilibrium solute concentration in the presence of 0.15 mol/l NaCl in order to increase the degree of adsorption of the surfactant on alumina. The initial solutions for the steroids were equal to 0.001 mol/l; 10 wt% of ethanol had been added for solubility reasons. For the other solutes, the experiments were performed in the aqueous salt solution at an equilibrium concentration of 0.01 mol/l. At these very low solute concentrations, it is generally agreed upon that the adsorption of surfactant is not modified by solute addition (Zhu et al., 1988). Note finally that the effect of temperature on the CMC of surfactants around room temperature is small enough that the results at 25°C may safely be applied to the sorption experiments which were performed at 35°C.

Results and Discussion

Triton X-100 isotherm

Fig. 2 presents the variation of nonionic surfactant adsorbed vs equilibrium concentration in the presence and absence of 10 wt% ethanol on a log/log scale. A classical isotherm is obtained with the plateau value starting at an equilibrium concentration close to the CMC. In the presence of ethanol, adsorption of the surfactant is slightly decreased below the CMC, but the plateau value was found to remain unchanged by the presence

of ethanol. It is noteworthy that in the case of a cationic surfactant, dodecyltrimethylammonium bromide adsorbed on a polystyrene latex (Connor and Ottewill, 1971), not only that portion of the curve below the CMC but also the whole curve was shifted towards lower equilibrium concentrations upon addition of the same quantity of ethanol. The main feature of the TX-100 isotherm is the very poor adsorption of surfactant even in the presence of added NaCl. The adsorption density can be calculated from the relationship:

$$\Gamma = \Delta CV/ma \qquad (1)$$

with

$$A = 1/N\Gamma \qquad (2)$$

where ΔC is the concentration of adsorbed material (in mol/l), V denotes the volume of liquid (in l), m is the amount of solid (in g), a represents the surface (m^2) per g of alumina, N is Avogadro's number and A the surface area occupied per monomer. In the present case, one finds, at the plateau value: $A_{s/l} = 1050$ Å^2. The Gibbs equation was applied to the surface tension measurements on the TX-100 solutions, which enabled the calculation of the surfactant surface area at the liquid/vapor interface. The value obtained is: $A_{l/v} = 53$ Å^2. Incidentally, this figure hardly varies with the addition of the 10% of ethanol or the 0.15 mol/l of salt (see the parallel slopes of Fig. 1 just below the CMC). Thus, it is clear that at the adsorption plateau, the alumina particles are far from complete coverage, the latter situation being the most common one observed (Levitz et al., 1984).

Adsorption of the drugs

Barbiturates The drugs chosen represent a variety of chemical compounds. Butobarbital and pilocarpine are respectively negatively and positively charged ions. Amobarbital and barbital differ in their hydrophobicity as do the three steroids. Figs 3–6 present the results obtained. The ordinate is defined by:

$$\Delta = (C^s_{ads} - C^o_{ads})/(C_t - C^o_{ads}) \qquad (3)$$

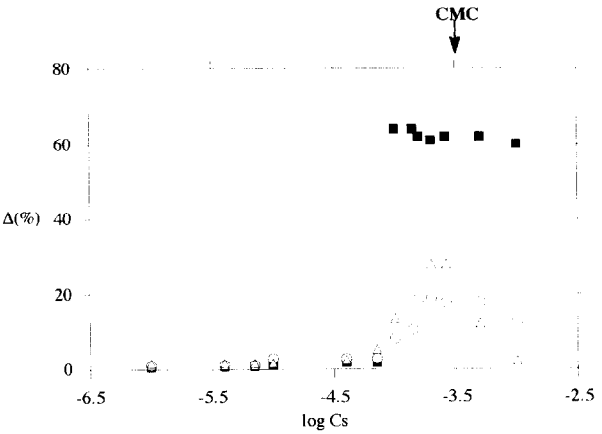

Fig. 3. Adsorption of barbiturates as a function of surfactant concentration: (■) amobarbital; (○) barbital; (△) butobarbital.

where C^s_{ads} and C^o_{ads} are the concentrations in mol/l of drug adsorbed in the presence and in absence of surfactant, respectively, and C_t the total drug concentration. Eqn 3 therefore describes the increase in drug adsorption (relative to the initial drug concentration) due to the adsorbed surfactant.

Fig. 3 presents the results for the three barbiturates where Δ is expressed in mol%. In all cases, the extent of drug adsorption on alumina particles is very small at low surfactant concentration until an adsorption threshold is observed at an average surfactant concentration of $C_{th} = 5 \times 10^{-5}$ mol/l (Table 2), i.e., below the CMC. After an increase in adsorption a plateau value is reached for the two barbituric acids, just below the CMC, while for butobarbital, maximum adsorption is observed exactly at the CMC, followed by a rapid decrease at higher surfactant concentration.

The striking features of these results is the considerable amount of drug adsorbed relative to the small quantity of TX-100 on the particle surface as noted above. One may quantify this result by calculating the maximum mole fraction of adsorbed drug x_{max} at the particle interface (Table 2). Even if the amount of drug adsorbed in the absence of surfactant is subtracted from the total amount, the mole fraction of drug would be still above $x = 0.8$ in most cases. The maximum

TABLE 2

Some characteristics for the adsorption of various drugs onto alumina surfaces in the presence of Triton X-100 at 35°C (plateau value: $C_t = 0.00016$ mol / l)

Solute	x_{max}	C_{ads}^{max} [a]	C_{ads}^{o} [b]	C_{th} [c]	C_{eq}	A [d] (Å^2)
Testosterone	0.79	0.0005	0.00025	2×10^{-6}	0.001	330
Progesterone	0.85	0.0008	0.000009	2×10^{-6}	0.001	210
Hydrocortisone	0.84	0.0008	0	6×10^{-5}	0.001	210
Barbital	0.95	0.0020	0.00015	5×10^{-5}	0.010	85
Butobarbital	0.95	0.0030	0.00027	5×10^{-5}	0.010	55
Amobarbital	0.97	0.0064	0.00046	4×10^{-5}	0.010	25
Pilocarpine	0.15	0.00029	0.000028	7×10^{-5}	0.010	570

[a] Maximum drug adsorption in mol/l in the presence of surfactant under the present experimental conditions.
[b] Drug adsorption on alumina in 0.15 mol/l NaCl aqueous solutions, in the absence of surfactant.
[c] Surfactant concentration threshold for drug adsorption.
[d] Surface area per molecule according to Eqns 1 and 2 at maximum drug adsorption.

drug uptake is about 60% of the total amobarbital concentration. It is lower for the less hydrophobic barbital, as expected. The extremely rapid increase in adsorption of amobarbital above C_{th} is surprising as it resembles that described for a cooperative process of lateral interactions between adsorbed molecules such as in the case of surfactants. The very steep slope is not tractable in terms of idealized models such as Langmuir or Freudlich isotherms. However, as noted in Table 2, the maximum adsorption increase due to the surfactant is almost identical for the three barbiturates, by a factor of 10.

An estimate of the surface area occupied by the barbiturates may be performed in order to test the validity of the present results on physical grounds. Applying Eqns 1 and 2 to the maximum uptake of the drugs leads to the results in the last column of Table 2. Although the A value for amobarbital is somewhat low, the surfaces obtained are reasonable assuming that the molecules sit essentially perpendicular to the particle surface as do surfactants at the vapor/liquid interface. These results imply furthermore complete coverage of the alumina surface.

The curious behavior of butobarbital deserves some specific comments. As the drug is completely ionized, one would not expect a high degree of adsorption in the nonionic admicelles. Micellar solubilization of salicylic acid in nonionic micelles as a function of pH shows that the drug solubility in its ionized form hardly increases with surfactant concentration (Collett and Withington, 1971). However, the alumina surface at pH 6.8 is positively charged. Thus, attraction of the negative barbiturate ions could occur through coulombic forces. This question will be addressed further below.

It is interesting to note that pilocarpine being positively charged is poorly adsorbed on alumina particles at the pH of operation (Fig. 4). Also, the very large value obtained for the surface area of this ion is in agreement with this result. This observation supports the hypothesis that coulombic forces dominate the surface adsorption of the ionic drugs. The reverse situation has been described (Harma et al., 1986) for this same drug which is adsorbed on polyacrylic nanoparticles. Here, it was assumed that the presence of an excess of sulfate ions induced a negative charge on the particles, and hence an increase in pilocarpine adsorption below the CMC of nonionic surfactants. However, it must be stressed that neither butobarbital with alumina, nor pilocarpine with polyacrylic nanoparticles is adsorbed above the nonionic surfactants' CMC. This is an interesting observation as the nonionic surfactants are of very different structures: *t*-octylphenol ethoxylate for the former drug, Tween,

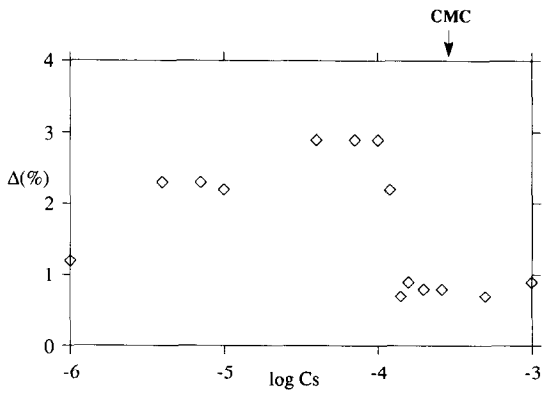

Fig. 4. Adsorption of pilocarpine hydrochloride as a function of surfactant concentration.

Brij, Myrj, Pluronic for the latter. Moreover, in the case of the nanoparticles, surfactants are used in the preparation process which could alter some of the particles' surface properties. This complication evidently does not occur with alumina. Thus, a common cause should be found for the non-adsorption of the ionic drugs above the CMC.

Steroids The situation appears even more complex with the three steroids. Their hydrophobicity, as measured by the log P value on the octanol/water scale, where P is the drug partition coefficient between the two phases, is equal to 1.55, 3.29 and 3.87, respectively, for hydrocortisone, testosterone and progesterone (Yalkowsky et al., 1980). Progesterone and testosterone display a similar pattern with a plateau value attained somewhat below the CMC as noted before with the barbiturates (Fig. 5). Note, however, the continuous increase in adsorption for progesterone from the very dilute surfactant concentrations upwards. The adsorption of this steroid is increased by a factor of 100, due to the presence of TX-100. Moreover, as with the case of the barbiturates, the striking feature of these results is the tremendous increase in adsorption at such low surfactant coverage. Note that the presence of ethanol in the experiments with the steroids does not change the order of magnitude of the observed effects: up to 90% of the 0.001 mol/l of steroid is adsorbed for progesterone and the corresponding mole fraction of the steroid with respect to surfactant is above 0.95. The case of hydrocortisone appears somewhat different (Fig. 6). The maximum adsorption increase is almost the same as that of progesterone and very high indeed as almost all of the drug is then adsorbed. However, above the CMC of TX-100, a rapid decrease in adsorption occurs. This behavior seems similar to that noted for butobarbital, sodium salt. It is by far the most water soluble of the three steroids.

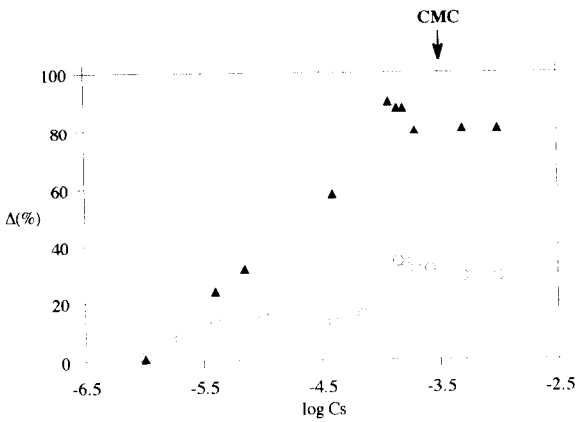

Fig. 5. Adsorption of steroids as a function of surfactant concentration in 10% ethanol solutions: (▲) progesterone; (○) testosterone.

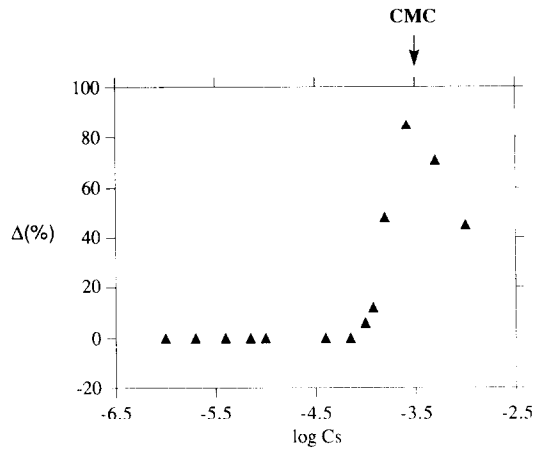

Fig. 6. Adsorption of hydrocortisone as a function of surfactant concentration in 10% ethanol solutions.

The above phenomena are intriguing, not so much because of the order of magnitude of the increased adsorption (large increases in adsolubilization have been noted before, for example, with alkanols on alumina in the presence of sodium dodecyl sulfate (Lee et al., 1990)), but because of the very small amount of adsorbed nonionic surfactant. It may be pointed out that in the case of alcohols, hydrogen bonding between the protic molecules may favor the adsorption process. Such a possibility must be rejected with the molecules studied here.

It may be noted, however, that in contrast to the case of the alkanols, the adsorption of several of the drugs on alumina in the absence of surfactant is not negligible (see Table 2). Thus, it appears that the small number of adsorbed surfactant molecules per particle is enough to modify

the surface so that it becomes even more favorable to drug adsorption.

An estimation of the surface area occupied by the various steroids was carried out using Eqns 1 and 2 and the data of Table 2. The results should evidently be considered as approximate values. Using a standard method of calculation of surface areas (Bondi, 1964) one finds for testosterone, progesterone and hydrocortisone, respectively, the following values: 163, 180 and 191 $Å^2$. Comparison of experimental and calculated values shows that the results are reasonable and compatible with a model of complete coverage of the alumina particles by the steroids (except for testosterone which is clearly less adsorbed than the other two compounds), the molecules lying flat on the solid surface.

Whether this situation can still be described by the so-called adsolubilization phenomenon is not certain. As noted before, TX-100 is poorly adsorbed on alumina. Even if hemimicelles are formed, they should be of a small size; a model of adsolubilization in the case of such large molecules as the steroids needs either large or continuous surfactant structures. Neither seems to be possible in the present situation. Thus, it appears that the adsorption of the drugs is more closely related to the change in the properties of the alumina surface induced by the surfactants than to a solubilization phenomenon, the occurrence of which implies the participation of a large number of molecules or ions forming a pseudophase.

Finally, one may speculate as to why the ionic drugs need some surfactant molecules to be adsorbed at the particle surface if coulombic forces are playing the dominant role. The following mechanism may be put forward involving three interrelated phenomena: (a) The experiments are performed in the presence of a relatively high concentration of NaCl. In the absence of surfactant, the excess of chloride ions concentrate in the particle electrical double-layer, preventing the negatively charged barbiturate ion from approaching the mineral surface. (b) As the surfactant concentration threshold is reached, small micelles are formed on the mineral surface (Cases and Villieras, 1992), displacing some chloride ions and allowing the drug ion to approach the particle surface. (c) As a result of the favorable coulombic interaction between barbiturate ions and alumina particles, desorption of surfactant monomers occurs. As the CMC is then reached, surfactant monomers may participate in the formation of regular free micelles; chloride ions adsorb again on the particles, hence the decrease in adsorption of this barbiturate. The same reasoning with the reversed electric charges should apply for pilocarpine hydrochloride which adsorbs in the presence of surfactants on polyacrylate nanoparticles only below the CMC of a variety of nonionic surfactants (Harmia et al., 1986). In the case of alumina, repulsive coulombic forces prevent any adsorption of the positively charged pilocarpine ion.

In conclusion, drug molecules may be adsorbed to a large extent on alumina surfaces at a pH of 6.8 with added salt, in the presence of very small quantities of the nonionic surfactant TX-100. The various types of isotherms observed suggest different adsorption mechanism for the various drugs studied. For the barbituric acids and the steroids alike (except for the most hydrophilic, hydrocortisone), the more hydrophobic the molecule the greater the adsorption. Up to 90% of progesterone present can thus be adsorbed. For both types of drugs, the adsorption starts above a surfactant concentration threshold, and a plateau value is reached somewhat below the CMC and is maintained above this surfactant concentration. For more ionic drugs, coulombic forces play a dominant role as expected; as a consequence, at the pH of the experiments, butobarbital is adsorbed at the CMC, while hydrochloride pilocarpine is not adsorbed to a great extent. For most compounds studied, the minimum surface area occupied per molecule is compatible with close to complete coverage of the alumina particles.

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