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Coadsorption of the sodium salts of two steroid molecules at a silica/interface as induced by the adsorption of a cationic surfactant

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Abstract

The incorporation of two ionic steroids, namely the sodium salts of hydrocortisone 21-hemisuccinate (HNa) and prednisolone 21-succinate (PNa), at a silica/water interface in the presence of adsorbed cetyltrimethylammonium bromide has been investigated first at a constant pH value. It is shown that this coadsorption effect is qualitatively similar to the adsolubilization effect which is described for neutral molecules. The adsorption of the cationic surfactant induces the coadsorption of the anionic drug molecules although the silica surface is negatively charged. At surfactant equilibrium concentration above the critical micelle concentration the drug molecules are distributed between the adsorbed aggregates and the free micelles. At larger surfactant concentration, the drugs may be completely depleted from the silica/water interface. Based upon Langmuir-type isotherms, the equilibrium constants of the drug molecules with the adsorbed aggregates and the free micelles are calculated. The constants are about three times larger for the former than for the latter aggregates. The signification of such results is discussed. The coadsorption of HNa at low surfactant surface coverage was also investigated in the pH interval between 3 and 9. HNa is strongly coadsorbed at lower pH onto the silica surface. The coadsorption goes through a maximum at a pH value which may be considered as equal to the apparent pK of the drug and decreases to zero at higher pH values. A pK value equal to 4.2 is proposed for HNa. This behaviour is interpreted as the result of the interplay of the drug dissociation and that of the surface silanol groups upon the change of pH.

Keywords: Sodium salts; Adsorption; Molecules

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1. Introduction

Surfactants may adsorb at solid/water interfaces forming various type of aggregates depending upon the characteristics of the solid and of the surfactant, as well as the physicochemical conditions of the chemical system in terms of pH and ionic strength. These surfactant aggregates may incorporate drug molecules which otherwise would not adsorb spontaneously onto the solid/water interface. This phenomenon has been coined cosorption (Rupprecht and Daniels, 1984), coadsorption (Monticone and Treiner, 1995), adsolubilization (Yeskie et al., 1988), this last term being more specifically applied to neutral molecules. A number of investigations have recently shown the main characteristics of this effect which has applications in a variety of practical applications from soil remediation to thin-film formation (Sharma, 1995). In the cases of pharmaceutical interest, many studies have been concerned with silica as the solid substrate as it is used with various dosage forms like suspensions, emulsions and tablets (Rupprecht et al., 1976). Drug molecules such as vitamin E (Golovkova et al., 1995), α-tocopherol (Bidzlilya et al., 1996), acetylsalicylic esters (Daniels and Rupprecht, 1985), genetisic acid (Bernard et al., 1990) or various neutral steroids (Cherkaoui et al., 1998) have been coadsorbed on silica using non ionic or cationic surfactants. Other relevant investigations have been concerned with other solid substrates such as alumina (Clarke et al., 1993), acrylic matrices (Buckton et al., 1991), albumin nanoparticles (Zimmer et al., 1994), cynanoacrylate nanoparticles (Harmia et al., 1986).

The main conclusion which has been derived from these and other studies (Nayyar et al., 1994) is that the adsolubilization phenomenon is analogous to the classical solubilization effect. Using a pseudo-phase model, it may be shown that a partition coefficient may describe the interaction of the drug molecule with the surfactant molecules of the adsorbed layers. It was demonstrated that the coadsorption partition coefficient P_{ads} of neutral molecules is equal to the micellar solubilization constant P_{mic}. However, for solutes which may undergo protonation, P_{ads} is larger than P_{mic} even in a pH region remote by more than 2 U from the pK of that solute (Favoriti et al., 1996).

The case of molecules which may dissociate depending upon the pH of the system has been much less investigated than that of neutral molecules (Nayyar et al., 1994). It concerns the large classes of acids or bases. In order to investigate the coadsorption of ionizable drugs, it was thought of interest to adopt as model compounds, the sodium salts of hydrocortisone 21-hemisuccinate (HNa) and the structurally closely related Prednisolone 21-succinate (PNa). A porous hydrophilic silica dispersion was chosen with a large specific surface area. The isoelectric point of silica being near 2.5, the solid surface is predominantly negatively charged above this pH value. Thus, the charge on the surface is opposite to that of the drug molecules in the pH region above their pK value. Hydrocortisone which had been studied under the same experimental conditions could be used for comparison purposes (Cherkaoui et al., 1998). The cationic surfactant used will be cetyltrimethyammonium bromide (CTAB).

2. Materials and methods

Hydrocortisone 21-hemisuccinate, sodium salt and Prednisolone 21-succinate sodium salt were both from Sigma. CTAB was also a pure surfactant from Sigma. The critical micelle concentration (cmc) as determined from conductivity measurements was equal to 8.8×10^{-4} mol l^{-1} in agreement with literature values. It was the same surfactant sample as used previously (Cherkaoui et al., 1998). The porous silica used was a pure ($>99.5\%$) sample of Aerosil 200 with a BET surface of 200 ± 25 m^2 g^{-1} (Degussa-France). The added salt was NaCl (Sigma) at a concentration of 0.15 mol l^{-1} except when stated otherwise. Water was purified by Aquatron A4S.

The method used has been described before (Cherkaoui et al., 1998). It is a classical bath-method, 0.2 g of silica was poured into 20 ml vials and kept at 37°C for 24 h with protection from light. The concentration of steroid was constant and equal to 1.0×10^{-3} mol l^{-1}. The pH of the

system was 6.5 except when indicated otherwise. Sodium hydroxide and hydrochloric acids were used when adjusting the pH was necessary. A combined glass electrode was used with a Taccussel (France) potentiometer. After ultracentrifugation at 20 000 rpm for 1 h, the supernatant was analyzed using a spectrophotometer Perkin-Elmer λ5. The wave-length was 248 nm for both compounds and the value of the Beer-Lambert's coefficient ε is 15 390 and 14 070 l mol^{-1} cm^{-1}, respectively, for HNa and PNa.

3. Results and discussion

3.1. Adsorption isotherms at constant pH

Fig. 1 presents the adsorption isotherm of CTAB at the silica/water interface together with the coadsorption of HNa and of PNa as a function of the equilibrium (free) surfactant concentration at pH = 6.5. The adsorption is expressed in mol g^{-1} of solid substance. The surfactant isotherm presents the classical three regions profile. In region 1, isolated surfactant molecules adsorb flat on the solid surface. In region 2, small admicelles are formed which may be viewed as aggregated small bilayers, which grow in number and size until, at the equilibrium cmc (region 3), surface saturation occurs. Micelles start to form

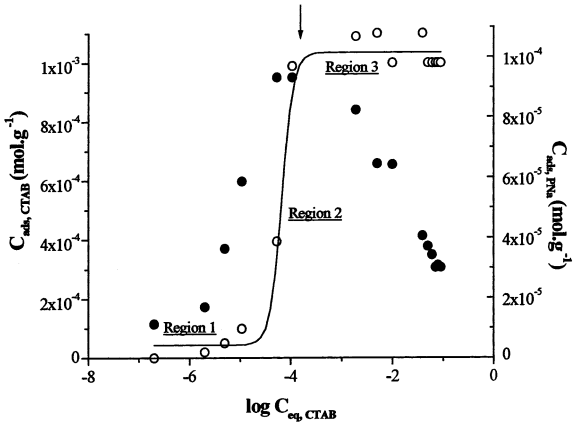

Fig. 1. Adsorption isotherm of CTAB (○) and coadsorption of HNa (●) as a function of surfactant equilibrium concentration. The arrow shows the surfactant cmc.

and the monomer concentration remains constant.

The coadsorption profile is qualitatively (at that pH value) similar to that of neutral steroids. At this pH value (6.5) the drug molecules do not adsorb at the silica surface in absence of surfactant (see below). As CTAB molecules begin to adsorb, HNa as well as PNa are coadsorbed at the silica/water interface. The coadsorption increases up to the CTAB equilibrium cmc. Note that all the drug molecules (1.0×10^{-3} mol l^{-1}) are then coadsorbed at the solid/water interface. As free micelles are formed above the cmc, a decrease of coadsorption is observed. The very sharp increase of the coadsorption curve as the drug is added to the dispersed system suggests that pair wise complexes are formed between the negatively charged drug ion and the cationic surfactant. The complex must indeed be surface active and therefore remains at the silica/water interface. Note that the concentration of drug adsorbed at the maximum is practically equal to the surfactant cmc, a fact which confirms the 1-1 complex formation between the two components at the interface.

The decrease of drug adsorption above the cmc has been noted before with neutral molecules and the same interpretation may be put forward (Favoriti et al., 1996): the drug molecules are distributed between the surfactant aggregates, the free micelles and the aqueous solution. As the steroid concentration is constant, increasing the surfactant concentration above the cmc shifts the solute distribution in favor of the free micelles, hence the decrease of coadsorption.

It is interesting to put these observations on a more quantitative basis. In the case of neutral molecules, the coadsorption of the steroids on the surfactant aggregates could be quantified in terms of a solute partition coefficient using the pseudo-phase model. This approach proved to be inadequate in the case of ionic solutes and also in the present case. A more realistic model was used in terms of Langmuir isotherm.

Thus, one can write:

$$\frac{\theta}{1-\theta} = K_b C_{eq} \quad (1)$$

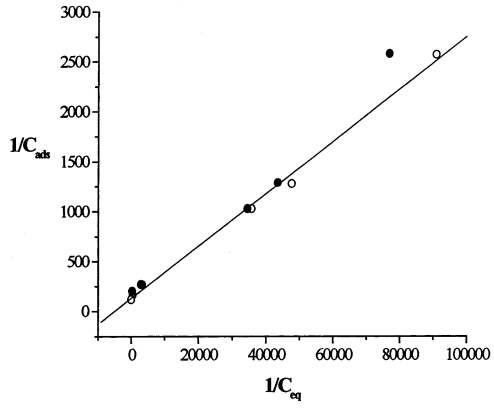

Fig. 2. Representation of Langmuir isotherm by Eq. (2). PNa (●); HNa (○).

where $\theta = C_{ads}/C_{ads,max}$. After the classical rearrangement one obtains the equation:

$$\frac{1}{C_{ads}} = \frac{1}{C_{ads,max}} + \frac{1}{K_b C_{ads,max} \cdot C_{eq}} \quad (2)$$

The variation $1/C_{ads}$ as a function of $1/C_{eq}$ should be a straight-line provided there is no interaction between the solute molecules and that only pair wise interaction occurs between the solute and the adsorption site on the substrate. Fig. 2 and Table 1 presents the results obtained for $C_{ads,max}$, K_b and K_m. The results are undistinguishable for both drugs.

The decrease of drug coadsorption may be described starting with the same Langmuir isotherm as applied to the interaction of the drug molecule with the adsorbed aggregates or with the free micelles.

One obtains, respectively, for the adsorbed species:

$$\frac{\theta_A}{1-\theta_A} = K_b C_{eq} \quad (3)$$

and for the free micelles

$$\frac{\theta_{mic}}{1-\theta_{mic}} = K_{mic} C_{eq} \quad (4)$$

By definition, one has: $C_{tot} = C_{ads} + C_{eq} + C_{mic}$ where the C's refer to the adsorbed, the free (equilibrium) and the micellized solute concentrations.

$$\theta_A = C_{ads}/C_{ads,max}, \quad \text{and} \quad \theta_{mic} = C_{mic}/C_{mic,max}$$

Assuming next that $\theta_A \ll 1$ and $\theta_{mic} \ll 1$, with $C_{mic,max} = pD_{mpic}$ where D_{mic} is the micelle concentration. p represents the number of site per micellized surfactant ($p < 1$). One may admit at a first approximation that p is proportional to the degree of counterion association. For CTAB, one may use the value $\alpha = p = 0.8$ (Favoriti and Treiner, 1998)

One finally obtains the relation:

$$C_{ads} = \frac{C_{tot}}{1 + \dfrac{K_{mic} p (C_{eq}^{surf} - cmc)}{K_b C_{ads,max}^{surf}}} \quad (5)$$

In Eq. (5), the only unknown quantity is $K_m p$, all other quantities being obtained by experiment or calculated from experiment.

Fig. 3 and the Table 1 present the result of the best fitted equation. The fit is indeed acceptable and implies that the model used is essentially correct. The data of the Table show again that K_b is roughly twice as large as K_{mic} as found before for ionizable, but in principle not ionized solutes in the pH domain investigated.

An ad hoc hypothesis may be put forward to interpret this behavior. The surface curvature of micelles is much larger than that of a bilayer adsorbed on a silica surface. In principle, the Laplace pressure effect which was proposed by Mukerjee (1970) to interpret the difference between the solubility of hydrocarbon molecules in the small spherical micelles and in a bulk solvent should not apply in the present case: Laplace

Table 1
Characteristic parameters for the interaction of the anionic drugs with cetyltrimethylammonium bromide at the silica/water interface (K_b) and in solution (K_m) at 25°C

Drug	$C_{ads,max} \times 10^3$ (mol l^{-1})	K_b (l mol^{-1})	K_m p (l mol^{-1})	K_m (l mol^{-1})
PNa or HNa	7.55	5075	2200	2750

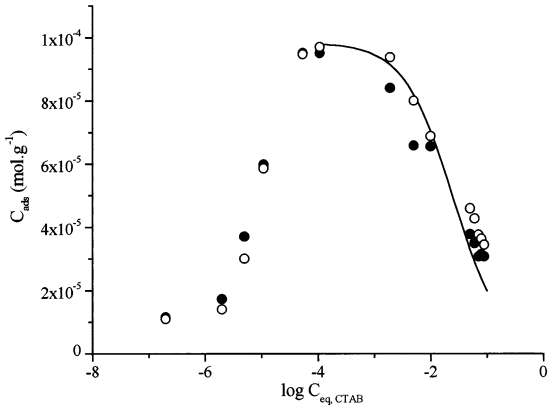

Fig. 3. Coadsorption of PNa (●) and HNa (○) as a function of CTAB equilibrium concentration. The full line represents the fitted Eq. (5).

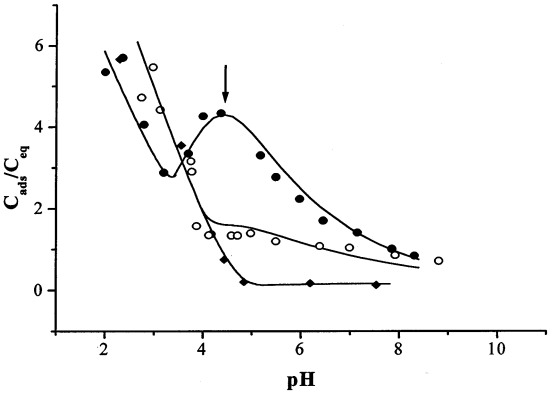

Fig. 4. Variation of the ratio of adsorbed to free drug molecule (total concentration $C = 4.4 \times 10^{-4}$ mol l^{-1}) as a function of pH at constant CTAB concentration: ($C = 6.0 \times 10^{-4}$ mol l^{-1}): (◆) no surfactant NaCl: ($C = 1.0 \times 10^{-2}$ mol l^{-1}). (●) CTAB + NaCl ($C = 1.0 \times 10^{-2}$ mol l^{-1}); (○) CTAB + NaCl ($C = 1.0 \times 10^{-1}$ mol l^{-1}). The arrow points out the pK of succinic acid.

pressure should be nil for the essentially flat bilayer which is formed by the cationic surfactant onto the silica surface. However hydrocarbons are suppose to penetrate the interior of the hydrocarbon-like micelle, an effect which may partially be opposed by the Laplace pressure; the steroid molecules seem too large to be considered as solubilized within the surfactant aggregates, whether free micelles or adsorbed bilayers.

3.2. Drug adsorption at a function of pH

The conclusion reported above is valid at the pH of the experiments, i.e. pH = 6.5 where both the silica surface and the drug molecules are strongly ionized. It was of interest to investigate the effect of pH on the drug coadsorption in the whole pH region above the silica isoelectric point. It is clear that below this pH value, the CTAB molecules should desorb from the silica surface. It was decided to screen the pH effect by conducting series of experiments at (relatively) constant surfactant concentration. This would be difficult to perform rigorously because surfactant adsorption varies with the pH of the system as the result of the ionization of the solid surface. However, it has been recently shown that this effect, although real, has not a great influence on the solute coadsorption provided one remains in the dilute surfactant concentration range, i.e. in the region where only isolated CTAB molecules are present onto the silica surface, i.e. region 1 of the isotherm depicted on Fig. 1 (Favoriti and Treiner, 1998).

The experimental procedure was exactly the same as before. Fig. 4 presents three different curves as a function of pH. (i) The adsorption of HNa in the absence of surfactant; (ii) the coadsorption of HNa ($C = 4.0 \times 10^{-4}$ mol l^{-1}) in the presence of CTAB at a concentration of 6.0×10^{-4} mol l^{-1} and a concentration of added salt of 1.0×10^{-2} mol l^{-1}; and (iii) the same isotherm as before with a concentration of added salt of 1.0×10^{-1} mol l^{-1}. As it was shown above that PNa and HNa behave in a very similar manner, only HNa coadsorption was studied as a function of pH. In all three cases, it was verified that HNa in solution does not precipitate in the pH region of interest between 3 and 9.

The negatively charged steroid does not adsorb on silica above a pH value of about 5 in the absence of surfactant. In the presence of surfactant and added salt at low concentration (1.0×10^{-2} mol l^{-1} of NaCl) HNa is incorporated to the silica/water interface as the consequence of the coadsorption effect described above. However, a maximum is observed around pH = 5. The same behavior has been recently described in the case of weak acids coadsorbed on silica or weak bases coadsorbed on alumina in the presence of a

cationic surfactant in the former case and of an anionic surfactant in the latter (Monticone et al., in press). The maximum was systematically observed around the pK of the solutes. The interpretation which was proposed of this observation is the following: At high pH values, the silica surface is completely ionized so that the favorable interaction between the negatively charged molecule and the cationic surfactant is outbalanced by the repulsion between the anionic molecule and the completely ionized silica surface. As the pH of the system draws nearer to the pK of the solute, the coulombic interaction between the solute (say, anionic) and the cationic surfactant increases as there are less anionic sites on the silica surface and therefore less repulsion to the approach of the dissociated molecule. Below the pK, the decreased coadsorption is as a result of the smaller interaction between the neutral acid molecules and the adsorbed surfactant aggregates. To summarize, increasing the pH from below the pK increases the coadsorption because of the ionization of the solute and above the pK, the coadsorption decreases as a result of the silica surface repulsion induced by the increasing ionization of that surface.

To the best of our knowledge, the pK of these drugs has not been determined before. However, the pK of succinic acid is equal to 4.16. Therefore it may be considered, by analogy with the previously studied acids, that the maximum observed on Fig. 4 is closely related to the pK of HNa (or PNa), i.e. $pK = 4.2$. The comparison between these two numbers suggests that the pK value assumed above for HNa is most certainly correct.

The specific behavior encountered in the present situation is the increase of coadsorption at very low pH values. This is as a result of the fact that HNa is strongly adsorbed on silica even in the absence of surfactant as shown on Fig. 4. This was not the case with the previously studied acids.

The effect of salt concentration is worth noticing. At higher added salt concentration (1.0×10^{-1} mol l^{-1} of NaCl) the coadsorption decreases dramatically around $pH = 4$ and the maximum disappears. This is most certainly as a result of a charge screening effect. The ionized form of the drug molecules which was coadsorbed as the result of the strong coulombic interaction with the cationic surfactant at the silica/water interface is partially screened by the added salt, an effect which decreases the interaction with the CTAB molecules. Addition of inorganic salt at a constant pH value classically increases the adsorption of the surfactant. This in turn would increase the coadsorption of the drug molecules. However, the present experiments were performed at constant CTAB adsorbed concentration, hence the decrease of solute coadsorption as compared to the values at lower ionic strength. At lower pH values, HNa coadsorption increases again as with the other two situations because of the favorable interaction of the neutral form of the acid molecule with the silica surface.

In the cases of the acids and of the bases investigated previously (Monticone et al., 2000) it could be demonstrated that the maximum coincides with the pK of these solutes and a chemical model was proposed to interpret this observation. This model could not be applied in the present case, as pointed out above, because of the strong adsorption of the drug neutral form onto the silica surface at low pH values which prevents the determination of the partition coefficient of HNa (nor PNa) in its neutral form. This quantity was necessary in order to use the proposed model (Monticone et al., 2000).

Finally it may be pointed out that adsorption maximum for ionizable solutes at solid/water interfaces may occur for a variety of certainly related reasons. Noteworthy is the classical case of benzoic acid adsorbed on kaolinite in the absence of surfactant (Clarke and Armstrong, 1972). If the point of zero charge of kaolin plays an important role, the fact that both positive and negative charges are present on the solid dispersion complicates somewhat the interpretation of such a maximum.

4. Conclusions

The adsorption of a cationic surfactant such as CTAB on silica may induce the coadsorption of anionic drug molecules. At constant pH, above the surfactant equilibrium cmc, HNa or PNa are

distributed between the adsorbed surfactant aggregates, the free micelles and the solution. It is shown that the drug coadsorption partition coefficient is about three times larger than the corresponding micellar constant. The difference in the aggregates surface curvatures may be partly responsible for this behavior. Variation of the system pH between 3 and 9 shows that the coadsorption of HNa goes through a maximum at a pH value close to the pK of the corresponding acid. The maximum is interpreted as the result of an increased silica surface ionization at higher pH values which is unfavorable to the interaction with the cationic surfactant and an unfavorable interaction with the same components at low pH values because of the formation of a neutral drug species. Around the pK of the drug molecule, both of these effects are at a minimized, hence the adsorption maximum.

References

Bernard, R., Fuchs, E., Strnadova, M., Sigg, J., Vitzhum, J., Rupprecht, H., 1990. The mediated adsorption (cosorption) of anionic drugs by cationic surfactants onto silica. Progr. Coll. Polym. Sci. 83, 110–117.

Bidzlilya, V.A., Golovkova, L.P., Vlasova, N.N., Bogomaz, V.I., 1996. Adsorption of α-tocopherol and its analogs on the surface oh highly dispersed silica from aqueous micellar solutions of noniongenic surfactants. Russ. J. Phys. Chem. 70, 275–277.

Buckton, G., Efentakis, M., Al-Hamoud, H., Rajan, Z., 1991. The influence of surfactants on drug release from acrylic matrices. Int. J. Pharm. 74, 169–174.

Clarke, C.D., Armstrong, N.A., 1972, Influence of pH on the adsorption of benzoic acid by kaolin. Pharm. J. 44–45.

Cherkaoui, I., Monticone, V., Vaution, C., Treiner, C., 1998. Surface modifications of silica particles by a cationic surfactant: adsolubilization of steroids from aqueous solutions. Int. J. Pharm. 176, 111–120.

Clarke, J.G., Wicks, S.R., Farr, 1993. Surfactant mediated effects in pressurized metered dose inhalers formulated as suspensions. I. Drug/surfactant interactions in a model propellant system. Int. J. Pharm. 93, 221–231.

Daniels, R., Rupprecht, H., 1985. Adsorption and chemical stability of a cationic aggregating ester-propantheline bromide- on silica surfaces in aqueous dispersions. Pharm. Res. 185, 170–176.

Favoriti, P., Treiner, C., 1998. Binding of aromatic anions to cetylpyridinium aggregates either adsorbed at silica/water, alumina/water, titanium dioxide interfaces and in solution. Langmuir 14, 7493–7502.

Favoriti, P., Mannebach, M.H., Treiner, C., 1996. Surface interactions on silica particles between a cationic surfactant and sodium salicylate. Langmuir 12, 4691–4696.

Golovkova, L.P., Bidzilya, V.A., Vlasova, N.N., Bogomaz, 1995. Solubilization and adsorption of a short-chain analog of vitamin E in the presence of a noniogen surfactant. Russ. J. Phys. Chem. 69, 961–964.

Harmia, T., Speiser, P., Kreuter, 1986. Optimization of pilocarpine loading onto nanoparticles by sorption procedures. Int. J. Pharm. 33, 45–54.

Monticone, V., Treiner, C., 1995. Effect of pH and ionic strength on the adsorption of cetylpyridinium chloride and the coadsorption of phenoxypropanol at a silica/water interface. Coll. Surf. 104, 285–293.

Monticone, V., Favoriti, P., Lemordant, D., Treiner, C., 2000. Effect of pH on the coadsorption of weak acids to silica/water and weak bases to alumina/water interfaces as induced by ionic surfactants. Langmuir 16, 258–264.

Mukerjee, P., 1970. Odd-even alternation in the chain length variation of micellar properties. Kolloid Z.Z. Polym. 236, 76–79.

Nayyar, P.S., Sabatini, D.A., Harwell, J.H., 1994. Surfactant adsolubilization and modified admicellar sorption of nonpolar, polar and ionizable organic contaminants. Environ. Sci. Technol. 28, 1874–1881.

Rupprecht, H., Daniels, R., 1984. Coasorption von p-hydroxybenoesaureestern (parabene) mit nonylphenol-polyglykolen an porosen SiO_2 aus wasser. Prog. Coll. Polym. Sci. 69, 159–166.

Rupprecht, H., Biersack, M.J., Kindl, G., Liebl, H., 1976. Drug reactions on silica. Pharm. Ind. 38, 1009–1012.

Sharma, R. (Ed.), 1995. Surfactant Adsorption and Surface Solubilization. ACS Symposium Series, Wahington, DC, p. 615.

Yeskie, M.A., Harwell, J.H., O'Rear, E.A., 1988. On the structure of aggregates of adsorbed surfactants: The surface charge density of the hemimicelle/admicelle transition. J. Phys. Chem. 92, 2346–2352.

Zimmer, A.K., Maincent, P., Thevenot, P., Kreuter, J., 1994. Hydrocortisone delivery to healthy and inflamed eyes using a micellar polysorbate 80 solution or albumin nanoparticles. Int. J. Pharm. 110, 211–222.