damage in the rectal mucosa of rats. However, the administrations of DC-Na with polyacrylic acid gel and Witepsol H-15 gave no histological alteration of the rectal mucosa in rats (Fig. 8). These results suggest that the polyacrylic acid gel counteracts the local damage to the rectal mucosa by DC. Furthermore, polyacrylic acid gel has been shown effective in the treatment of colonic ulcer (9).

In conclusion, DC-Na preparations using polyacrylic acid gel base may be favorable as a micro-enema with a high bioavailability and reduced irritation of mucosal membranes. Furthermore, the DC-Na gel preparation containing oleic acid (10% v/v) may be useful as a micro-enema with prolonged action.

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Adsorption and Chemical Stability of a Cationic Aggregating Ester – Propantheline Bromide – on Silica Surfaces in Aqueous Dispersions

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Abstract: The adsorption behavior of cationic aggregating substances such as antimicrobial quats or phenothiazine derivatives on silica surfaces in aqueous media has been extensively investigated. However, the chemical stability of adsorbates in such systems was unknown. Propantheline bromide (PPBr) was selected as a model to investigate the stability of hydrolyzable substances in silica-containing aqueous dispersions or in adsorbates on silica carriers used for solid drugs. The quaternary ester PPBr showed an appreciable adsorption on the silica surface, the extent of which was increased by raising the pH of the aqueous phase or by the addition of neutral salts such as $NaNO_3$. In parallel to the adsorption process, hydrolysis of PPBr occurs in these aqueous silica dispersions to yield xanthene carbonic acid and a quaternary alcohol component. Adsorption and hydrolysis were found to be mutually influencing reactions. Because of the adsorption of PPBr, the rate of ester decomposition was enhanced in these silica dispersions when compared to aqueous solutions of PPBr at the same pH. Simultaneously, an increase in PPBr adsorption is observed, as well as adsorption of the decomposition product xanthene carbonic acid. This result can be attributed to ion-pair adsorption of the latter with PPBr. The rate constants of PPBr decomposition were found to depend directly on the silica content of the dispersion, although at higher concentrations a decreased catalytic effect was observed. These phenomena are discussed on the basis of the adsorbate structure and exchange processes.

Cationic aggregating and non-aggregating organic substances are known to be adsorbed onto silica surfaces from aqueous solution (1), the intensity of adsorption depending both on ion-exchange with the weakly acidic silanol groups and on v. d. Waal interactions of the non-polar organic moieties, as well as water structure effects. Electrostatic interactions in the electrical double layer at the silica/water interface determine the binding of ionic aggregating substances such as surfactants or phenothiazine derivatives (2, 3).

Aqueous drug preparations containing silica and cations can be influenced by these adsorption phenomena in different ways; for example, the bioavailability of active ingredients, the viscosity of the liquid phase, suspension stability and flocculation processes have all been found to be controlled by these interactions (4, 5, 6). While there is a voluminous literature dealing with the chemical stability of hydrolyzable substances in drug preparations (7, 8, 9), only a few cases have been reported in which the chemical stability of drugs physically adsorbed on carriers of the silica type was determined (10, 11, 12).

The main purpose of the present paper was to determine the stability of an ester that is adsorbed onto the silica surface from aqueous solution as a function of its adsorption behavior. Propantheline bromide was selected as a model: this drug molecule has an ester linkage and a quarternary ammonium group, thereby exhibiting the character of a strong cationic electrolyte. The silica used as adsorbent was obtained from

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hydrolytic polycondensation of polyethoxysiloxane, which yields amorphous, porous particles with a well defined pore structure and high chemical purity. The mean pore diameter was controlled to 14 nm, a size which has been proven to not significantly influence the rate of ad- or desorption in comparison to nonporous colloidal silicas (6). The specific surface area as measured by N_2 adsorption and calculated according to the BET-theory, was 510 $m^2 \cdot g^{-1}$.

Materials and Methods

Materials. All chemicals were either official or reagent grade. Propantheline bromide (PPBr) was obtained from Searle Pharmaceuticals Northumberland, GB. Porous silica was prepared by hydrolytic polycondensation from polyethoxysiloxane; specific surface area 510 m^2/g, mean pore diameter 14 nm (26).

Adsorption of propantheline. Aliquots of 500 mg silica were weighed into 100 ml stoppered flasks, and 50.0 ml of a propantheline bromide solution ranging from 1 to 20 mmol/l was added. The sealed flasks were shaken at 21 ± 1°C for 30 min. Aliquots of the supernatant liquid were taken for analysis of the propantheline equilibrium concentration by UV light absorption.

Kinetic studies of propantheline degradation. Appropriate aliquots of porous silica and 20.0 ml of propantheline bromide solutions were mixed in 25 ml stoppered flasks. The flasks were then shaken in a water bath at selected temperatures (± 0.5K) and the content of propantheline and its degradation product xanthene carbonic acid monitored at intervals by HPLC analysis.

UV Analysis. Propantheline was analyzed with a spectrophotometer (DMR 10 Zeiss, Oberkochen, FRG) at 281 nm, absorbing layer thickness 1 cm.

HPLC Analysis. Samples were diluted with 0.1 mol/l KH_2PO_4 solution at concentrations of 0.5 to 2×10^{-3} mol/l. They were analyzed by employing a chromatographic system consisting of a sample injector (Rheodyne 7010 with 10 µl loop), a constant flow pump (Series 2 liquid chromatography, Perkin Elmer), a reversed-phase column (RP-8; 5 µm; length 25 cm), a variable wave length detector (Perkin Elmer) operated at 281 nm, and a digital integrator (Chromatographic Data Station Sigma 10 Perkin Elmer). Mobile phase composition: 3.00 heptane sulfonic acid, 12.00 acetic acid (99 %), bidistilled water 300, methanol 400; flow rate 0.3 ml/min.

Results and Discussion

Adsorption

Influence of pH. The adsorption of propantheline cations onto the silica surface from aqueous solution is similar to that seen with phenothiazine binding e. g. with acranil (4) (Fig. 1). The adsorption isotherm of propantheline is of a Langmuir type and shows no sudden increase in the adsorbed amount of drug at higher concentrations, as is shown by the aggregating surfactant cations of dodecylpyridinium chloride (4). During the establishment of adsorption equilibria at higher adsorption values the pH of the aqueous phase was found to decrease from 4.2 for the pure aqueous dispersion of the silica to 3.6, indicating ion-exchange at the silanol groups according to:

$$-\underset{|}{\overset{|}{\mathrm{Si}}}-\mathrm{OH} + \mathrm{Propantheline}^{+} \rightleftharpoons -\underset{|}{\overset{|}{\mathrm{Si}}}-\mathrm{O}-\mathrm{Propantheline} + \mathrm{H}^{+}$$

Note that the aqueous propantheline bromide stock solution has a pH of 6.5. In this pH range the cation exchange occurs onto only 5 % of the total number of the silanol groups present at the silica surface (13) because of the weakly acidic character of the silanol groups.

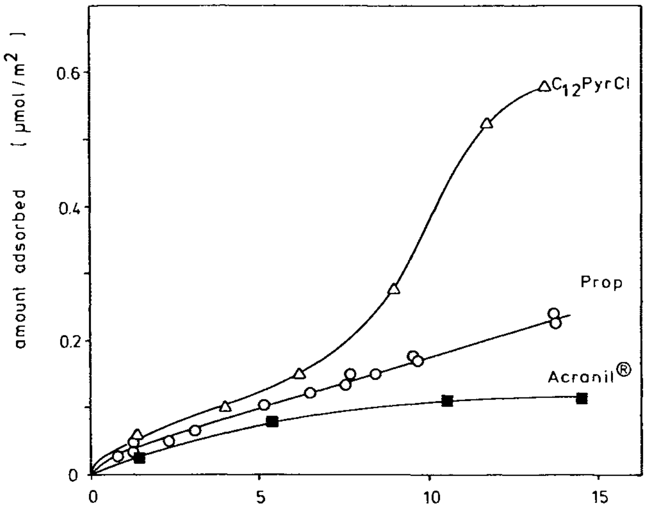

Fig. 1 Adsorption of cationic aggregating drugs onto 1 % silica from aqueous solution at 21° C.

The adsorption of propantheline onto the silica surface is strongly influenced by the addition of phosphate buffer (Fig. 2); shifting the pH from the acidic (pH 3.6) to the weakly alkaline range (pH 7.6) by the addition of buffer markedly increased the adsorption of propantheline, an effect that can be assigned to the increased number of dissociated silanol groups in this pH-range. These then act as additional adsorption sites at the silica surface according to the following equations:

$$-\underset{|}{\overset{|}{\mathrm{Si}}}-\mathrm{OH} + \mathrm{OH}^{-} \rightleftharpoons -\underset{|}{\overset{|}{\mathrm{Si}}}-\mathrm{O}^{-} + \mathrm{H_2O}$$

$$-\underset{|}{\overset{|}{\mathrm{Si}}}-\mathrm{O}^{-} + \mathrm{Propantheline}^{+} \rightleftharpoons -\underset{|}{\overset{|}{\mathrm{Si}}}-\mathrm{O}-\mathrm{Propantheline}$$

As demonstrated by Bolt (14) the number of negatively charged surface sites on silica is dependent on the pH, the ionic strength of alkaline additives, the number of silanol groups per unit surface area and the dissociation behavior of the silanol groups. The effects of these parameters on the amounts of adsorbed propantheline are evaluated in Table I by the ratio, Q, of drug adsorption over the number of active silica adsorption sites. The conditions for the adsorption equilibrium were 5 mmol/l propantheline cations and 50 mmol/l phosphate buffer, with adjustment to the required pH value.

The ratio of adsorbed propantheline over the negatively charged adsorption sites available is slightly increased with increasing pH, as has also been reported by Allen and Matijevič for the exchange of sodium ions (15). Because of the strongly basic character of propantheline the adsorption of unionized base can be excluded in the pH range under investigation.

Neutral electrolytes. The adsorption of propantheline cations onto the silica surface is enhanced in the presence of neutral electrolytes such as NaCl or $NaNO_3$ (Fig. 3). It is evident that at pH 3.6 NaCl is more effective at promoting the

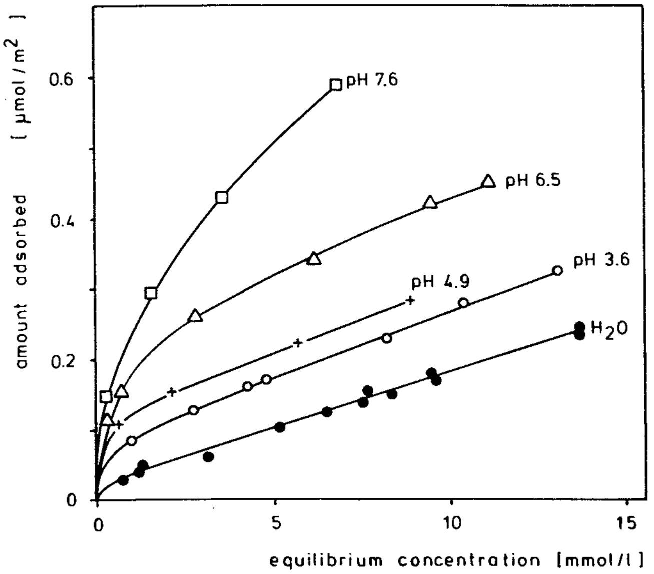

Fig. 2 Adsorption of propantheline cations onto 1 % silica at different pH values at 21° C.

Table I. Propantheline Cations Adsorbed on Silica (Kr 36) at Different pH Values, Adjusted with Phosphate Buffer, 50 mmol/l; Equilibrium Concentration 5 mmol/l.

pH of the dispersion	3.6	4.9	6.5	7.6
Propantheline adsorbed (μmol/m²)	0.170	0.208	0.310	0.512
Negative adsorption sites (μmol/m² according to Bolt (14))	0.530	0.667	0.921	1.28
$Q = \frac{\text{[propanth. ads.]}}{\text{[neg. ad. sites]}}$	0.32	0.31	0.33	0.40

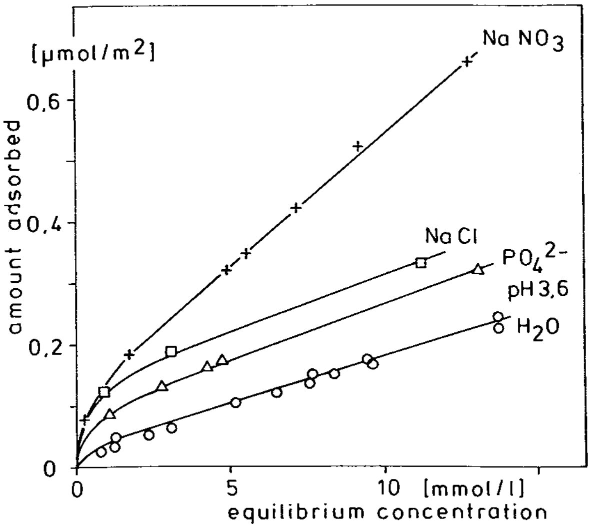

Fig. 3 Adsorption of propantheline cations onto 1 % silica in the presence of neutral electrolytes (50 mmol/l) at 21° C.

propantheline adsorption than equivalent amounts of phosphate buffer. After the addition of equivalent amounts of $NaNO_3$, however, the extent of propantheline adsorption is greater than that found with either NaCl or phosphate buffer.

These high adsorption values of the drug cannot be explained by an ion-exchange mechanism alone, since the pH of 3.6 in the aqueous phase reduces the number of silanol groups capable of ion-exchange to 5 % of the total number. The measured drug adsorption exceeds this value by far; for example at 10 mmol/l equilibrium concentration the amount adsorbed is 10 fold greater. The enhancement of propantheline adsorption by neutral electrolytes may be related to several different phenomena, namely the properties of the electrical double layer at the silica interface, the aggregating properties of the drug and the specific mechanism of cationic surfactant adsorption at the silica surface. We shall outline each of these three factors briefly, before discussing the adsorption mechanism.

On the basis of the theory of electrical double layers at a solid-aqueous interface, potential determining ions such as peptizing agents or surfactant ions are expected to be adsorbed onto the solid surface to a greater extent after the addition of neutral electrolytes (16). The surface charge density σ is increased by the addition of such ions according to:

$$\sigma = \frac{D \cdot p}{4\pi} \psi_o$$

where the surface potential ψ_o remains constant, D is the dielectric constant and the Debye Hueckel factor p is given as:

$$p = \left(\frac{4 \cdot \pi \cdot e^2 \cdot n_o \cdot Z^2}{D \cdot k \cdot T}\right)^{1/2}$$

Assuming that the number of ions n_o is proportional to the neutral salt concentration and the other parameters (e = electronic charge, Z = ionic valency, k = Boltzmann constant, T = temperature) are constant, the surface charge density may be more simply expressed:

$$\sigma = K \cdot (C_{neutral})^{1/2}$$

With cationic surfactant the sudden increase in their adsorption onto the silica surface in the region of the CMC is due to hydrophobic interactions, producing adsorbates with a hemimicellar structure at the surface (18, 19).

We propose, therefore, that in addition to the ion-exchange reaction at the silica surface further propantheline cations are adsorbed by hydrophobic bonding to the primary bound species which are oriented perpendicular to the surface, as shown in Fig. 4. They are probably attached with their ring systems parallel and adjacent to each other, the best position for strong mutual interaction of their π-electron systems. This adsorption is counterbalanced by the electrostatic repulsion of the positively charged headgroups of propantheline. Neutral salts reduce [according to the DLVO-theory (16)] this repulsion between neighboring cations, and since the surface potential remains constant, the surface charge density and, consequently, the adsorbed amount of propantheline increases.

The large differences observed between the effect of equivalent concentrations of $Cl^\ominus$ and $NO_3^\ominus$ on propantheline adsorption may be discussed on the basis of the aggregation phenomena of cationic surfactants in the aqueous phase (20). The water structure-breaking $NO_3^\ominus$ ions with their disorganized hydration shells may come closer to the vicinity of the aggregated propantheline ions in the adsorption layer. Thus, charge neutralization in the adsorption layer by the counterions should be better effected by $NO_3^\ominus$ than by the water structure-preserving $Cl^\ominus$ ions. Charge-neutralization is subsequently the precondition for close packing of the propantheline ions in the adsorption layer.

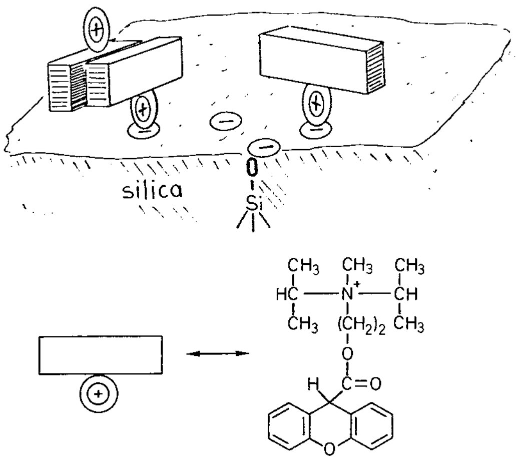

Fig. 4 Proposed configuration of adsorbed propantheline cations at the silica surface.

In contrast to the alkyl chain surfactants, propantheline is reported to aggregate poorly in water with gradually increasing aggregation numbers at higher concentrations and without a definite CMC value (17). Therefore, the sudden increase in amount adsorbed seen in the adsorption isotherm in the region of the CMC, which is typical for surfactants, is not valid for propantheline. The almost linear slope of the adsorption isotherm of propantheline – after the initially steep increase – in the presence of neutral electrolyte is probably due to this gradual increase in aggregation both in solution and at the surface.

Hydrolysis

In aqueous solutions propantheline bromide decomposes by hydrolysis, following pseudo first-order kinetics according to Horioka et al. (21). The degradation is catalyzed by hydroxyl ions (Fig. 5), for the higher the pH the more rapidly the hydrolysis proceeds. The pH profiles show straight lines when the logarithm of apparent rate constant is plottet versus the pH (22) in the temperature range between 21° C and 61° C (Fig. 6), in accordance with Horioka (21).

Accelerating effects on propantheline degradation are found in the presence of silica at the same pH in the aqueous phase at 21° C and 41° C (Fig. 7). This catalytic effect is also related to the silica concentration, with a marked acceleration occurring with increasing silica content in the mixture up to 1 %.

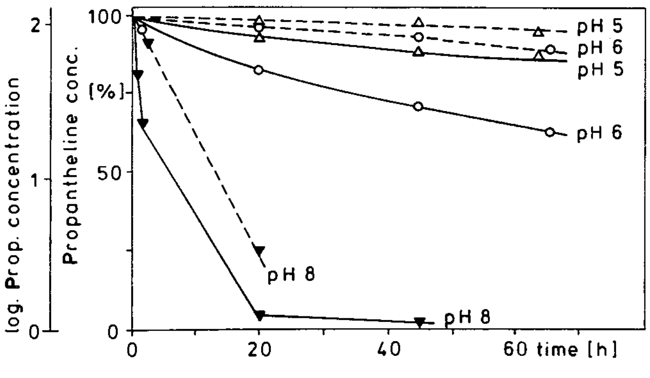

Fig. 5 Propantheline degradation in aqueous solutions at 21° C at different pH values (adjusted with phosphate buffer, 50 mmol/l). Solid lines: linear scale; dashed lines: log scale.

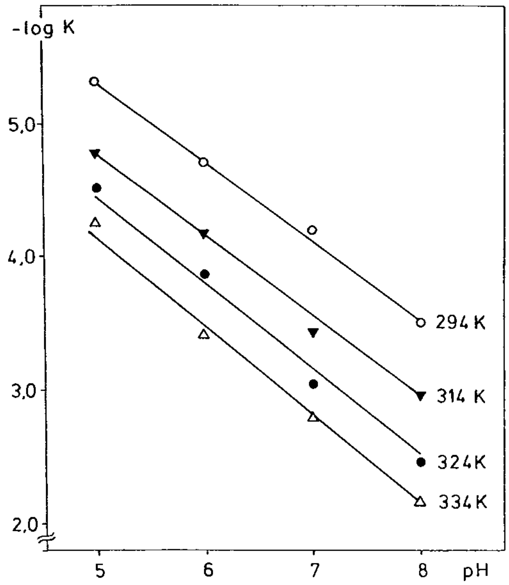

Fig. 6 Rate constants of propantheline hydrolysis at different pH values (adjusted with phosphate buffers 50 mmol/l) in the temperature range 21–61° C.

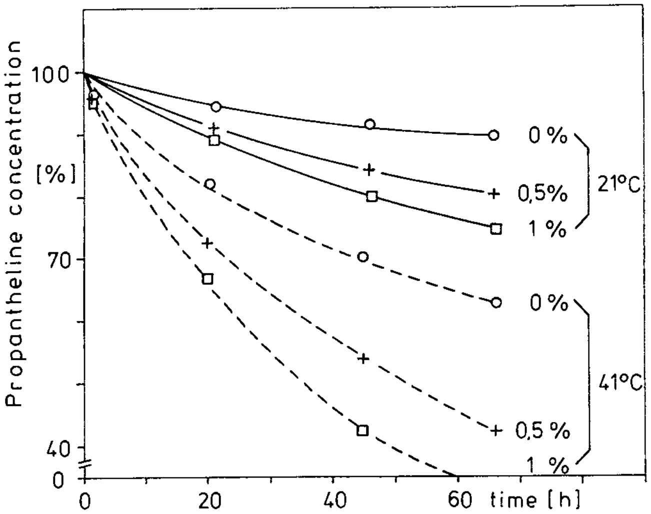

Fig. 7 Propantheline degradation in aqueous silica suspensions at pH 6 and different silica concentrations.

Figure 8 illustrates the total loss of propantheline seen in aqueous silica suspensions at various pH values of phosphate buffers. Although the strong influence of the hydroxyl ion concentration in the aqueous phase on drug hydrolysis is evident, the hydrolysis rates suggest that silica acts as a catalyst even in weakly alkaline media, which by themselves produce high degradation rates.

In view of the fact that details of the degradation mechanism of propantheline in the vicinity of silica particles and at the silica surface are not available, it seemed reasonable to choose the $t_{90\%}$ stability level (7) as a parameter to describe the influence of silica on hydrolysis. The corresponding data are summarized in Table II, and the ratios of $t^s_{90\%}$ – the stability in the presence of silica – over $t^o_{90\%}$ – the corresponding aqueous solution value – at the same temperature and pH are listed.

Shifting the pH in the silica-propantheline mixtures from 5 to 8, both at 0.5 % and 1 % silica, causes the ratio $t^s_{90\%}/t^o_{90\%}$ to increase (Fig. 9). If one accounts for the fact that the data obtained at elevated temperatures and at pH 8 may be of limited value because of limits of the analytical method under these conditions, the $t^{s}_{90\%}/t^{o}_{90\%}$ appear to approach unity as the pH increases. This suggests that the catalytic effect of silica is gradually reduced at higher $OH^{\ominus}$ concentrations.

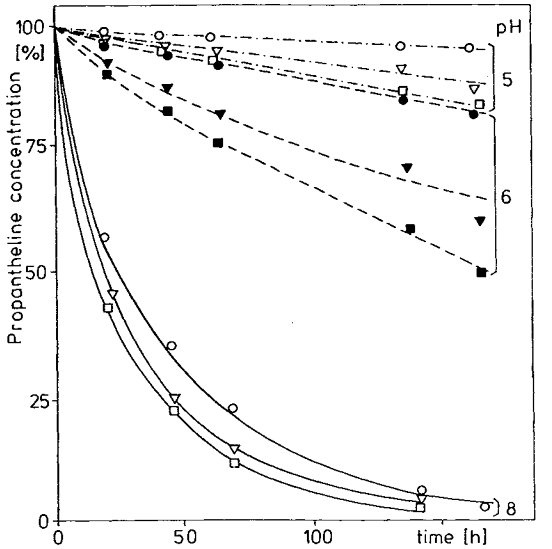

Fig. 8 Propantheline degradation in aqueous silica suspension at different pH and silica concentration. Symbols: without silica: circles, 0.5 % silica: inverted triangles, 1 % silica: squares.

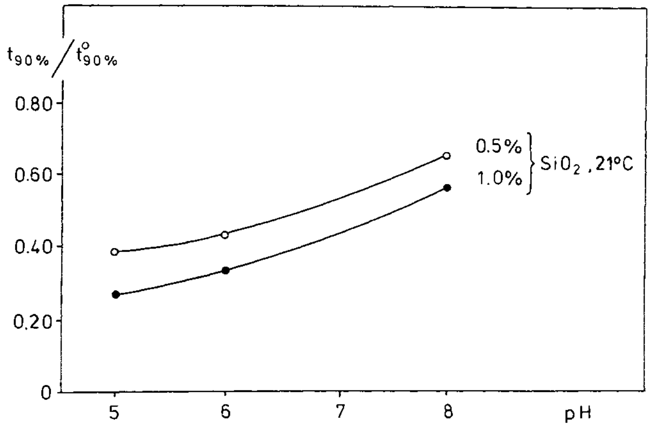

Fig. 9 Ratio of $t_{90\%}$ values for propantheline stability in the presence of silica.

Figure 10 depicts the relationship among the logarithm of the $t_{90\%}$ stability values and the silica concentration at different pH values and temperatures. All curves reveal that the catalytic activity of silica is enhanced by increasing its concentration up to 1 %, although not in a linear fashion.

The lower than expected catalytic activity at higher silica concentrations needs to be considered together with the corresponding adsorption data (Table II).

At a total concentration of 2.34 mmol/l propantheline in the mixture the surface coverage of the silica with the drug (expressed as θ (23)) was found to be higher at 0.5 % silica than at 1 % silica throughout the degradation of propantheline. A constant difference of about 0.05 was observed (θ is related to the monolayer capacity). However, the absolute amount of adsorbed propantheline with 1 g silica in 100 ml mixture (30 % total drug) ist greater than with 0.5 g silica (20 % total drug) in the same mixture volume.

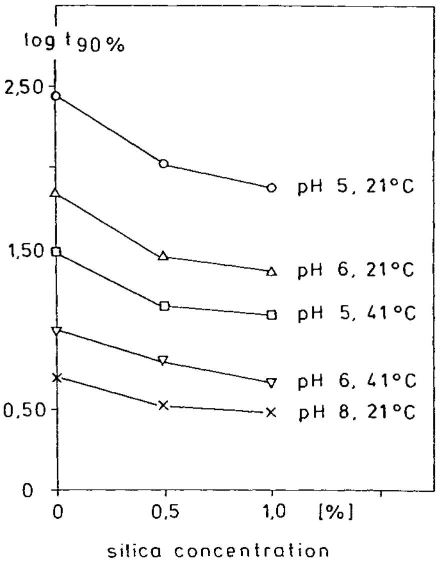

Fig. 10 Log $t_{90\%}$ values for propantheline stability in aqueous silica suspension at different pH values and temperatures.

Table II. Stability Values of Propantheline Bromide in Aqueous Solution ($t^{o}_{90\%}$) and in the Presence of Silica ($t^{s}_{90\%}$).

	Silica concentr. %	$t^{o}_{90\%}$[hr]	log $t_{90\%}$	$t^{s}_{90\%}/t^{o}_{90\%}$
	0	279	2.446	1.000
pH 5; 20°C	0.5	109	2.037	0.391
	1.0	74.5	1.872	0.267
	0	67	1.826	1.000
pH 6; 20°C	0.5	28.5	1.455	0.425
	1.0	22	1.342	0.328
	0	5	0.698	1.000
pH 8; 20°C	0.5	3.2	0.505	0.64
	1.0	2.8	0.447	0.56
	0	31	1.491	1.000
pH 5; 40°C	0.5	14.8	1.170	0.477
	1.0	13.4	1.127	0.432
	0	9.7	0.987	1.000
pH 6; 40°C	0.5	6.0	0.778	0.618
	1.0	4.0	0.662	0.474

Discussion of Hydrolysis

The accelerating effect of silica on propantheline degradation in aqueous mixtures depends on the adsorption of the drug onto the silica surface.

It has been proposed (26) that binding to a surface can weaken bonds in an adsorbed molecule. In this way the activation energy of cleavage is reduced, and consequently the rate of degradation is further enhanced. This effect is typical of heterogenous catalysis, and requires a distinct positioning of the adsorbed species on the surface. As discussed above, propantheline cations are adsorbed to the silica surface partly by ion exchange and partly by hydrophobic bonding. This results in a different binding mechanism when only a single propantheline species is present, with active binding sites, such as the quaternary ammonium groups, separated from the ester linkage. Therefore it was excluded that weakening of the ester linkage by adsorption forces may be an essential rate-determining factor for propantheline degradation.

Table III. Adsorption of propantheline cations to the silica surface during decomposition. Initial concentration of propantheline: 2.34 mmol/l; pH 6 (phosphate buffer), 20° C; monolayer capacity $m_{max} = 0.492$ µmol/m²; $\Theta = \frac{m}{m_{max}}$.

Time	0.5 % silica				1 % Silica			
	Propantheline cations adsorbed							
[h]	Absolute [µmol]	Per surface units of SiO_2 [µmol/m²]	% of total prop.	Θ	Absolute [µmol]	Per surface units SiO_2 [µmol/m²]	% of total prop.	Θ
21	8.6	0.168	19	0.34	15.6	0.153	36	0.31
46	9.4	0.184	22	0.37	14.2	0.139	36	0.28
66	8.0	0.156	19	0.32	13.6	0.133	36	0.27
138	6.6	0.129	21	0.26	11.0	0.107	41	0.22
167	6.0	0.118	19	0.24	6.6	0.064	26	0.13
191	5.2	0.102	21	0.21	7.2	0.071	38	0.14

$t_{90}^{0.5} = 28.5$ h $t_{90}^{1.0} = 22$ h
$t_{90}^{0} = 67$ h

The reason for this catalytic effect seen with silica is most likely due to the fact that hydroxyl ions can be preferably adsorbed both on silica surfaces (3) and at the surfaces of aggregation-colloids such as micelles of cationic surfactants (24). Thus, the accelerating effects on ester hydrolysis in the presence of solubilizing cationic surfactants may be explained by a high concentration of $OH^{\ominus}$ ions present at the surface of the aggregates, acting there as a catalyst (25). In the presence of silica it is therefore suggested that the accelerated degradation of propantheline is due to a more alkaline microenvironment surrounding the silica particles at the surface of which the drug is adsorbed, when compared to the drug in the bulk solution.

Acknowledgements

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