Absorption and Bioavailability of Diclofenac after Rectal Administration of Diclofenac-Na Gel Preparation in Rat and Man

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Abstract: In order to evaluate diclofenac-Na (DC-Na) micro-enema, DC-Na gel preparations were administered to rats and man. When DC-Na gel preparations were rectally administered at various pH (pH 5–8) to rats, their bioavailability increased at higher pH. The bioavailability of DC-Na gel preparations (pH 8.0) in rats was significantly higher than that with conventional suppository bases, Witepsol H-15 and polyethylene glycol 1000 (PEG 1000). In man, the DC-Na gel preparation showed higher C_{max} and higher bioavailability than commercial suppository made with an oily base. DC-Na gel preparations containing 10 % v/v oleic acid showed a prolonged action. The irritative effect of DC-Na gel preparation on rectal mucosa in rats was weaker than that of PEG 1000, but similar to that of Witepsol H-15. Therefore, the present results suggest that gel preparation is a favorable form for rectal administration of diclofenac-Na.

Diclofenac-Na (DC-Na), a nonsteroidal anti-inflammatory (NASAI) drug, has been widely used for rheumatoid arthritis, osteoarthritis and acute musculoskeletal disorders. The tablets and capsules of DC-Na represent the common pharmaceutical preparations, but recently suppositories of DC-Na prepared with oily base have been introduced. Rectal administration of NASAI drugs is favorable for patients with peptic ulcer, infants and children, since the oral administration carries the risk of GI irritation. We have previously described the rectal administrations of ibupurofen (1), flurbiprofen, ketoprofen and indomethacin (2) with polyacrylic acid gel bases as a new effective method for administering NASAI drugs. pH values and viscosity of the polyacrylic acid gel can be changed over a wide range according to the types of drugs to be used (3).

In this study, a DC-Na gel preparation was designed to obtain high bioavailability without causing side effects of the drug after rectal administration.

Materials and Method

Materials – Polyacrylic acid (Carbopol® 941) was obtained from B. F. Goodrich Chem. Co. Oh. USA. and diclofenac Na (DC-Na), 74-177 μm particle size, from Hishiyamaseiyaku Co. Ltd. Osaka, Japan. The other reagents were of the best commercially available grade.

Preparations – Polyacrylic acid gel base was prepared with Carbopol® 941 presoaked in distilled water at room temperature as previously described (3). In the case of the gel base containing oleic acid, the oleic acid was emulsified at concentrations of 5 and 10 % v/v. DC-Na was dispersed into the polyacrylic acid gel base, and the DC-Na gel preparations were adjusted to pH 5.0, 6.5 and 8.0 by addition of 10 % w/v NaOH solution. Final concentrations of polyacrylic acid in the gel preparations were adjusted to 0.5, 1.0 and 2.0 % w/v by the addition of water. For comparative study, DC-Na was dispersed into the molten base [Witepsol H-15 and polyethylene glycol 1000 (PEG 1000)].

Release Experiments – The release of DC from the preparation at 37°C was determined with a dissolution-test apparatus for suppositories (Toyama Sangyo Co., Ltd., Japan) according to the method of Muranishi et al. (4). Two hundred ml phosphate buffer (pH 7.4), the dissolution medium, was pipetted into releasing glass vessels and maintained at 37° C under stirring at 100 rpm. A 5 ml gel preparation was placed on a membrane filter (FR 250 micro filter, Fuji Photo Film, Co. Ltd., Japan) fitted at the lower end of a plastic cylindrical cell. The preparation phase was not stirred. An aliquot of 1 ml dissolution medium was sampled, and the medium was replenished with the same volume of phosphate buffer. The amounts released were followed by means of UV spectrophotometry.

Animal Experiments – Wistar strain male rats weighing 250–350 g were fasted for 17 hours prior to the experiments. Following pentobarbital (50 mg/kg) anesthesia, the DC-Na preparations were administered into the rectal loop (5 cm section above anus), which was isolated by ligation. The dosage of the DC-Na preparations was 1 ml/kg body weight. For comparison, oral administration of DC-Na and rectal administration of DC-Na in Witepsol H-15 and polyethylene glycol 1000 (PEG 1000) were also performed with separate groups of rats. DC-Na was also administered orally with 1 % w/v carboxymethyl cellulose (CMC) solution. Blood samples (1.5 ml) were collected from the inguinal vein at 0.25, 0.5, 1, 2 and 3 hours after administration.

Human Experiments – The subjects were four healthy male volunteers, age 22 to 56 years, with a weight of 61 ± 2 kg. Each subject received three rectal administrations, first the regular gel preparation, second the suppository and third the gel preparation containing oleic acid. The drug-free interval between experiments was at least two weeks. Both gel preparations and the suppository (Voltaren® Suppo., Ciba-Geigy (Japan) Ltd.) contained 50 mg DC-Na. Blood samples (2 ml) were collected at 0.25, 0.5, 1, 2 and 3 hours after administration.

Assay Procedure – The plasma samples were obtained by centrifugation of heparinized blood samples. The quantity of DC was determined by the high performance liquid chromatographic (HPLC) method of Yaginuma et al. (5).

Morphological Study on Rectal Tissue – DC-Na was administered with polyacrylic acid gel, Witepsol H-15 and PEG 1000 to the rat rectum. At 1 hour after administration,

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rectal tissues were isolated and fixed with 10 % formalin. Slices were stained with hematoxylin-eosin solution and examined under an optical microscope.

Calculation of the AUC – Area under the curve (AUC) was calculated according to the method of Kaplan et al. by means of the trapezoidal rule (6).

Results

Release Experiments

Figure 1 shows the results of release experiments of DC-Na gel preparations at pH 6.5 and 8.0. Linear relations between the amount released and the square root of time were obtained with each preparation. The release rates of DC-Na were not significantly different between two different concentrations of polyacrylic acid in the gel preparations. On the other hand, the effect of pH of the gel preparation was evident; slower release of DC was seen with the lower pH preparation.

Figure 2 shows the results of DC release experiments from DC-Na gel preparations containing oleic acid. The release rates of DC decreased with increasing the concentration of oleic acid from 0 to 10 % in the gel preparations.

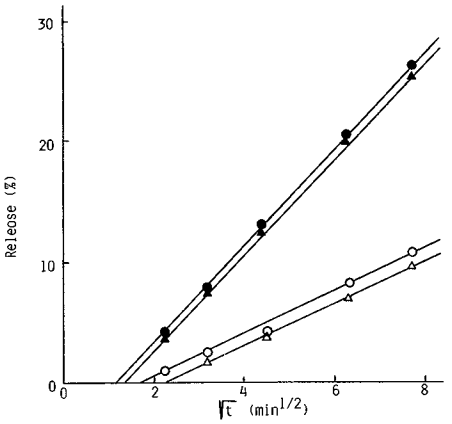

Fig. 1 Effects of polyacrylic acid concentration and pH on the release of diclofenac from dicrofenac-Na gel preparations.
1 % w/v polyacrylic acid: ○ pH 6.5, ● pH 8.0.
2 % w/v polyacrylic acid: △ pH 6.5, ▲ pH 8.0.

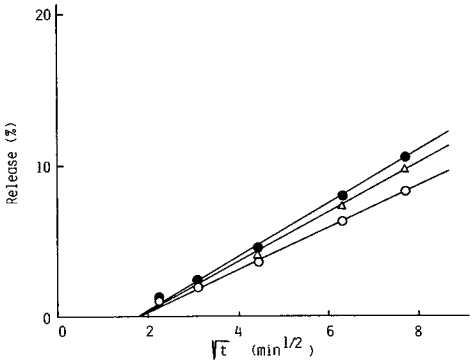

Fig. 2 Release of diclofenac from diclofenec-Na gel preparations containing oleic acid at various concentrations.
● 0 % v/v oleic acid, △ 5 % v/v oleic acid, ○ 10 % v/v oleic acid. The concentration of polyacrylic acid in diclofenac-Na gel preparation was 1 % w/v, with a pH 6.5.

Administrations of DC-Na in Rat

Figure 3 shows the influence of pH of the DC-Na gel preparations when administered rectally in rats. Higher plasma concentrations of DC-Na were obtained at higher pH. The mean plasma concentration of DC peaked at 30 min after rectal administration with gel preparations of pH 8.0 and pH 5.0, and at 1 hour with those of pH 6.5, and then decreased rapidly.

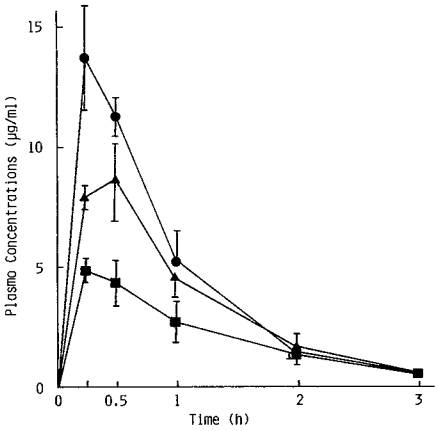

Fig. 3 Plasma concentrations of diclofenac following rectal administrations of diclofenac-Na gel preparations of various pH in rats.
The pH values were pH 5.0 (■), pH 6.5 (▲) and pH 8.0 (●). The concentration of polyacrylic acid in the gel preparation was 1 % w/v. The ▲ dose of diclofenac-Na was 10 mg/kg rat. Each value represents the mean ± S. E. of at least 4 rats.

Figure 4 shows the influence of polyacrylic acid in the gel preparations on DC concentrations in plasma when DC-Na gel preparations were rectally administered in rats. DC plasma profiles and peak plasma concentrations were similar between 1 % w/v and 2 % w/v polyacrylic acid in the gel preparations at both pH 8.0 and pH 6.5. Therefore, the effect of polyacrylic acid in the DC-Na gel preparation was negligible.

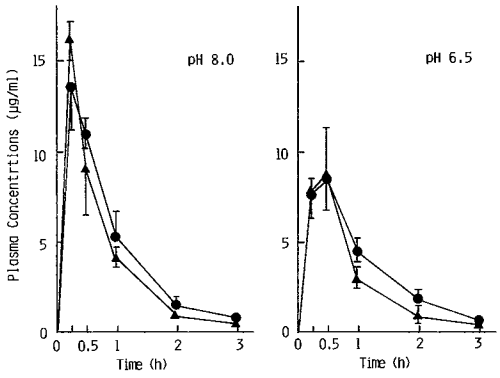

Fig. 4 Plasma concentrations of diclofenac following rectal administration of diclofenac-Na in polyacrylic acid gel (pH 6.5 and pH 8.0) at various concentrations of polyacrylic acid in rats.
The concentrations of polyacrylic acid were 1 % w/v (●) and 2 % w/v (▲). The dose of diclofenac-Na was 10 mg/kg rat. Each value represents the mean ± S. E. of at least 4 rats.

Figure 5 shows the DC plasma concentrations in rats after rectal administration of DC-Na gel preparations (pH 6.5) containing oleic acid at the concentration of 5 % v/v and 10 % v/v. The DC plasma profile after administering DC-Na gel

preparations with 5 % v/v oleic acid did not change compared with that without oleic acid. The peak plasma level obtained with the 10 % v/v oleic acid preparation was decreased but DC plasma levels were increased at 2 and 5 hours.

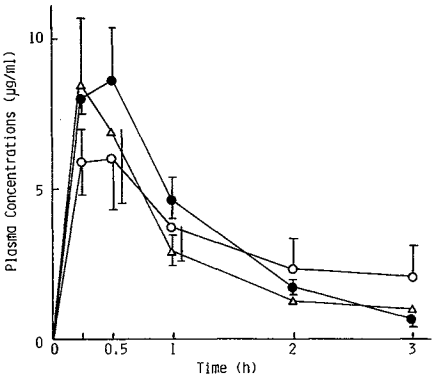

Fig. 5 Plasma concentrations of diclofenac following rectal administrations of diclofenac-Na gel preparations containing oleic acid in rats.
● 0 % v/v oleic acid, △ 5 % v/v oleic acid, ○ 10 % v/v oleic acid. The concentration of polyacrylic acid in the diclofenac-Na gel preparation was 1 % w/v, with a pH 6.5. The dose of diclofenac-Na was 10 mg/kg rat. Each value represents the mean ± S. E. of at least 4 rats.

Figure 6 shows the DC-plasma concentrations in rats after rectal DC-Na administration with the conventional suppository bases, Witepsol H-15 and PEG 1000, and after oral administration in 1 % w/v carboxymethyl cellulose (CMC) solution. The DC plasma concentration after administration of DC-Na in Witepsol H-15 base was lower than that in polyacrylic acid gel (1 % w/v, pH 8.0), and it was even lower after rectal administration of DC-Na in PEG 1000. The lowest concentrations were obtained after oral administration.

Rectal Administrations of DC-Na in Man

Figure 7 shows the plasma concentrations of DC in healthy human subjects, who were administered rectally with the DC-Na gel preparation without oleic acid, a DC-Na gel preparation containing 10 % v/v oleic acid and commercial DC-Na suppositories (Voltaren Suppo.®) Table I summarizes the areas under the curves (AUC) from 0 to 3 hours and the relative bioavailability of the gel preparations compared with that of the commercial suppository of DC-Na in man.

As can be seen from Fig. 7, rectal administration of the DC-Na gel preparation (1 % w/v, pH 8.0) caused a much higher and

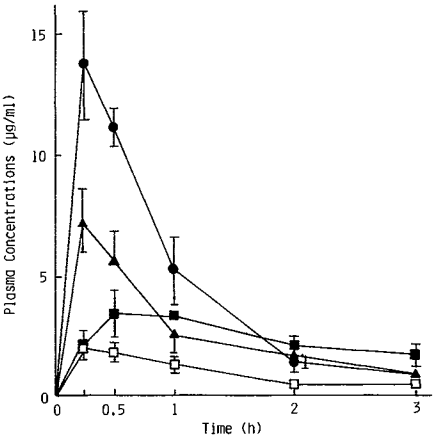

Fig. 6 Plasma concentrations of diclofenac following rectal administrations of diclofenac-Na gel preparation, diclofenac-Na with conventional suppository base and oral administration in rats.
● Gel preparation (1 % w/v, pH 8.0), ▲ Witepsol h-15, ■ PEG 1000, □ oral administration.
The dose of diclofenac-Na was 10 mg/kg rat weight. Each value represents the ± S. E. of at least 4 rats.

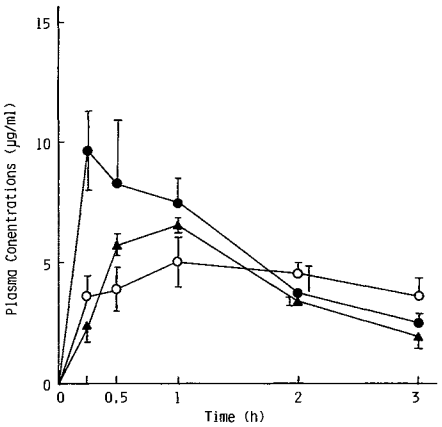

Fig. 7 Plasma concentrations of diclofenac following rectal administrations of diclofenac-Na gel preparations and a commercial suppository (Voltaren Suppo.®) in man.
● Diclofenac-Na gel preparation (pH 8.0), ○ Diclofenac-Na gel preparation containing 10 % v/v oleic acid, ▲ Commercial suppository.
The dose of diclofenac-Na was 5 mg/body. Each value represents the mean ± S. E.

Table I. Relative bioavailability following rectal administration of diclofenac-Na preparations in man.

	Dose (mg)	N	C_{max} (μg/ml)	t_{max} (h)	AUC_0^3 (μg·h/ml)	BA (%)
DC-Na Suppository (Voltaren Suppo®)	50	4	0.649±0.031	1	1.20±0.04	100
DC-Na gel Preparation (pH 8.0)	50	4	0.962±0.164	0.25	1.53±0.26	127.5
DC-Na gel Preparation containing 10 % v/v oleic acid	50	4	0.505±0.107	1	1.25±0.21	104.2

Each value represents the mean ± S.E. Statistical significance of difference from the DC-Na suppository (Voltaren Suppo®) is $p < 0.05$.

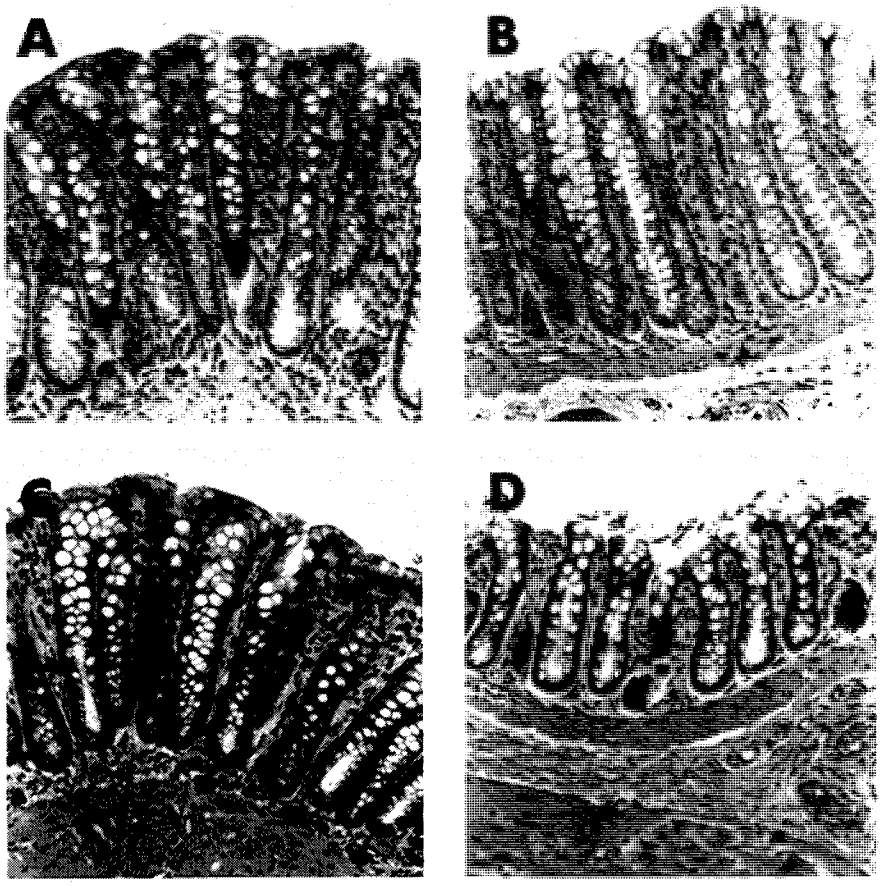

Fig. 8 Light microphotographs of rectal mucosa at 1 hour after rectal administrations of various preparations.
A: Polyacrylic acid gel (1 % w/v, pH 6.5),
B: Diclofenac-Na gel preparation (pH 6.5),
C: Diclofenac-Na with Witepsol H-15,
D: Diclofenac-Na with PEG-1000.
Hematoxylin-eosin stain was used.

earlier peak in plasma concentration than the commercial suppository. On the other hand, the DC-Na gel preparation containing 10 % v/v oleic acid yielded lower plasma concentrations than the commercial suppository at 0.5 to 1 hour after administration, but it maintained the DC plasma concentrations near maximum levels between 1 to 3 hours.

As shown in Table I, the bioavailability of the DC-Na gel preparation (pH 8.0) and the DC-Na gel preparation containing 10 % v/v oleic acid, relative to the commercial suppository, was 127.5 and 104.2 %, respectively.

Histopathology of Rectal Epithelium

In order to detect any histological changes in the rectal tissue, the epithelium was observed under the microscope following rectal administration of DC-Na with various vehicles. As shown in Fig. 8, in the rats treated with the DC-Na gel preparation and Witepsol H-15, significant histopathological changes did not occur, while rectal administration of DC-Na with PEG 1000 base damaged epithelium from the lamina propria and caused slight membrane perturbations.

Discussion

It was previously reported that the rectal administration of diclofenac-Na produced a higher bioavailability than its oral administration (5). However, DC has a relatively short plasma half-life compared with other NASAI drugs (8). Prolonged action and higher bioavailability of DC after rectal administration was desired to permit a decreased dosing frequency. In this study, the rectal administration of a DC-Na gel preparation and a DC-Na gel preparation containing 10 % v/v oleic acid gave markedly higher bioavailability and prolonged action, respectively, in rats and healthy human subjects.

In rat experiments, a more rapid absorption and higher C_{max} of DC was achieved at the higher pH level (pH 8) of the DC-Na gel preparation (Fig. 3). This result is caused by the greater degree of ionization and solubility of DC (pK_a 4.0) in the gel preparation at higher pH with a concomitant increase of the DC release rate from the gel (Fig. 6). Moreover, this result agrees with our previous data with other NASAI drugs (1, 2). On the other hand higher concentrations of polyacrylic acid in the gel preparation resulted in higher gel viscosity, lower drug release rates and slower drug absorption in our previous studies (1, 2). In contrast, the concentration of polyacrylic acid in the gel preparation did not affect the release rate of DC (Fig. 1) and its bioavailability after rectal administration of the DC-Na gel preparation (Fig. 4).

Diclofenac-Na gel preparations containing 10 % v/v oleic acid resulted in slow absorption and prolonged DC plasma levels (Fig. 5). This effect parallels the in vitro release rate of DC which was slightly delayed for the gel preparation containing 10 % v/v oleic acid (Fig. 2).

Rectal administration of the DC-Na gel preparation gave a more rapid absorption and higher AUC than those with conventional suppository base, Witepsol H-15 or PEG 1000 in rats (Fig. 6). Compared with the commercial suppository, the rectal administration of the DC-Na gel preparation in healthy human subjects induced rapid absorption and higher C_{max}, while DC-Na gel preparation containing 10 % v/v displayed markedly prolonged plasma levels (Fig. 7).

Mucosal irritation occurs not only upon oral administration but also rectal administration of NASAI drugs (5). The rectal administration of DC-Na with PEG 1000 caused histological

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.

References

(1) Hirano, E., Morimoto, K., Takeeda, T., Nakamoto, Y., Morisaka, K. (1980) Chem. Pharm. Bull. 28, 3521–3526.
(2) Kamiya, E., Morimoto, K., Takeeda, T., Nakamoto, Y., Morisaka, K. (1983) Int. J. Pharm. 17, 273–281.
(3) Morimoto, K., Hama, I., Nakamoto, Y., Takeeda, T., Hirano, E., Morisaka, K. (1980) J. Pharm. Dyn. 3, 24–32.
(4) Muranishi, S., Okubo, Y., Sezaki, H. (1979) Yakuzaigaku 39, 1–7.
(5) Yaginuma, H., Nakata, T., Toya, N., Murata, T., Yamazaki, M., Kamada, A., Shimazu, H., Makita, I. (1981) Chem. Pharm. Bull. 19, 3326–3333.
(6) Kaplan, S. A., Jack, M. L., Cotler, S., Alexander, K. (1973) J. Pharmacokinet. Biopharm. 1, 197–216.
(7) Ogiso, T., Iwaki, M., Tamaki, F. (1983) J. Pharm. Dyn. 7, 392–399.
(8) Degen, P., Faigle, J. W., Geraridin, A., Moppert, J., Asllmann, A., Achmid, K., Schweizer, A., Sucl, M., Theobald, W., Wagner, J., (1978) Scan. J. Rheumatology, Suppl. 22, 17–29.
(9) Kakegawa, K., Ikumoto, H., Yamauchi, Y., Ikeda, H., Shirami, K., Yagi, M. (1981) Gastro Enterological Surg. 4, 1493–1501.

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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