J. Pharm. Pharmacol. 1980, 32: 525–532 Received November 19, 1979

On the anomalous sorption behaviour of chlorhexidine with poly(2-hydroxyethyl methacrylate)

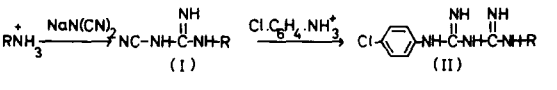
B. S. PLAUT*, B. J. MEAKIN AND D. J. G. DAVIES†

Pharmaceutics Group, School of Pharmacy and Pharmacology, University of Bath, Bath, BA2 7AY, U.K.

General observations of solute: plastic interactions would suggest that the sorption of the cationic preservative, chlorhexidine, with poly (2-hydroxyethyl methacrylate) (PHEMA) is not only unexpected but also atypical in its properties. The polymer and preservative were investigated independently and the sorption of PHEMA with simple solutes, namely benzoic acid, benzocaine and aniline found to exhibit conventional properties. The single exception was the uptake of small amounts of benzocaine and aniline cations at acidic pH's. In order to elucidate the sorption characteristics of chlorhexidine a series of N^1-(*p*-chlorophenyl)-N^5-alkylbiguanide acetates were synthesized. The anomalous sorption behaviour observed between PHEMA and the bis biguanide, chlorhexidine, was also found to be characteristic of these monofunctional biguanide derivatives. The extent of the interactions increased with increasing alkyl chain length (R = methyl to n-octyl), this being interpreted in terms of an interaction binding mechanism via the biguanide functional group stabilized by van der Waal's forces between the alkyl chain and the polymer backbone. Atypical sorption behaviour was observed for simple organic cations, biguanide and N^1-phenylbiguanide acetate with PHEMA, a possible inference being that this is a general characteristic of all cationic sorption with PHEMA.

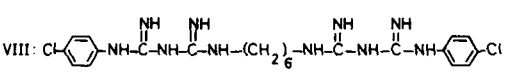
Most soaking solutions that are designed for the disinfection of soft, hydrophilic contact lenses include chlorhexidine as the antibacterial agent. Its widespread use can be attributed to its high antimicrobial efficiency (Davies 1978) and the relatively low level of irritation observed when its solutions are used with hydrogel lenses (Browne et al 1974, 1975; Callender 1978). The interaction between chlorhexidine and the hydrophilic lens polymer poly (2-hydroxyethyl methacrylate) (PHEMA) has been characterized (Richardson et al 1978, 1979; Plaut et al 1980) and found to exhibit properties not usually observed for solute: plastic interactions. This anomalous sorption behaviour is seen in three ways. Firstly, the interactions of all the chlorhexidine salts examined show some degree of irreversibility (Plaut et al 1980). Secondly, the cycling of PHEMA in a single concentration of chlorhexidine solution results in levels of preservative being accumulated within the polymer that are significantly in excess of the values predicted for the relevant concentration from the basic isotherm (Plaut et al 1980; Richardson et al 1979). Lastly, any deviation from the polymer weight: solution volume ratio that is adopted routinely in most experiments (0·2 g PHEMA: 10 ml solution) gives data that do not lie on the isotherm generated under these standard conditions. We considered that the source of this unusual behaviour stemmed either from the polymer or the preservative. In order to examine the first possibility, we decided to study the sorption of PHEMA with two simple aromatic solutes, benzoic acid and benzocaine (ethyl *p*-aminobenzoate) whose interactions with other plastics are already defined and known to follow classical principles (Kapadia et al 1964; Richardson & Meakin 1974).

An alternative source of the atypical sorption characteristics is the solute, chlorhexidine. Because of the symmetry of the chlorhexidine molecule (VIII in Scheme 1), a polymer: preservative interaction mechanism involving the two functional groups is readily envisaged in which case bridge linkages could be formed between adjacent polymer chains. We investigated the sorption of a series of monofunctional biguanide derivatives, N^1-*p*-chlorophenyl-N^5-alkylbiguanides (II in Scheme 1), in order to examine the effect of the bifunctionality. Another unusual aspect of the polymer: preservative



(I) (II)

III: R = methyl V: R = isopropyl
IV: R = n-propyl VI: R = n-amyl VII: R = n-octyl



* Financial support from Burton, Parsons and Co. Inc. is gratefully acknowledged.
† Correspondence.

interaction is the very existence of the sorption process. The preservative exists as a di-cation in aqueous solution and charged molecules in solution generally show negligible affinity for the solid phase (Kipling 1965; Kapadia et al 1964; Richardson & Meakin 1974). Chlorhexidine, however, is a more complex molecule than those previously studied and as a result of the hexamethylene chain possesses the ability to form aggregates in solution (Heard & Ashworth 1968). Therefore homologous alkyl biguanides were synthesized with alkyl chains ranging from one to eight carbon atoms, thus permitting us to see if any correlation exists between the surface activity of the solute and the extent and characteristics of their sorption with PHEMA.

Materials

Benzoic acid (Analar) and benzocaine (Reagent grade) were obtained from BDH Ltd. Aniline (Analar, BDH Ltd.) was used from a freshly opened bottle. Sodium dicyanamide, n-propylamine (98%), n-amylamine (99%), biguanide (95%), N^1-phenylbiguanide (94%) and 4-chloroaniline (99%+) were obtained from Aldrich Chemical Co. Ltd. N^1-(*p*-chlorophenyl)-N^5-methylbiguanide hydrochloride, N^1-(*p*-chlorophenyl)-N^5-isopropylbiguanide (proguanil) hydrochloride and chlorhexidine acetate were gifts from ICI Pharmaceuticals. All other salts were of Analar quality.

Preparation of PHEMA

PHEMA was obtained and prepared as described previously (Plaut et al 1980). Isotherms for all biguanides were derived from a single batch of PHEMA in order to negate the effects of batch to batch variation.

Instrumentation

pH's of solutions from completed sorption studies were read as described previously at the temperature of the sorption experiment (Plaut et al 1980). In the most sensitive region of the pH dependence studies of benzoic acid and benzocaine ($pK_a \pm 1.5$ pH units), the pH difference between the highest and lowest concentrations for an individual isotherm was never more than 0·05 units. For the biguanide derivatives, the pH's all lay in the range 5·6 to 6·2, being at least two pH units away from either pK_a.

Mass spectra were obtained from an AEI MS12 spectrophotometer with a direct probe operating at 70 eV and an accelerating voltage of 8 kV. The ion source temperatures were 121 °C (compound III, Scheme 1), 129 °C (IV), 140 °C (VI) and 115 °C (VII).

N.m.r. spectra were run on a Perkin Elmer R12B (60 MHz) instrument using tetramethylsilane as an internal standard.

Melting points were read using a Gallenkamp apparatus No. 889339.

Preparation of N^1-(p-*chlorophenyl*)-N^5-*alkylbiguanide (II) hydrochloride*

The synthetic approach was based on that of Curd et al (1948), outlined in Scheme I, omitting the isolation of the intermediate alkyldicyandiamide (*I*).

The appropriate alkylamine (0·1 mol) was dissolved in 100 ml of 1 M HCl (0·1 mol), evaporated to dryness and the hydrochloride salt so obtained dissolved in n-butanol (50 ml). Sodium dicyanamide (8·9 g, 0·1 mol) was added to the butanolic solution and refluxed with stirring for 4 h. The sodium chloride formed was removed from the cooled suspension by filtration. *p*-Chloroaniline hydrochloride (16·4 g, 0·1 mol) was prepared from the base in the same manner as the alkylamine hydrochloride and refluxed for 5 to 6 h with the butanolic solution of the alkyldicyandiamide (I). The hydrochloride salt of II which precipitated as a white solid was separated from the cooled reaction mixture by filtration and recrystallized from water.

Conversion of N^1-(p-*chlorophenyl*)-N^5-*alkylbiguanide (II) hydrochlorides to acetates*

The hydrochloride salt (0·01 mol) was dissolved in water and the pH adjusted to 12 by the addition of 1 M NaOH solution. For the methyl derivative (III), the free base was obtained as a precipitate and collected by filtration. In all other cases (IV to VII inclusive), the base was extracted into chloroform (3 × 100 ml) and the solvent evaporated from the combined chloroform layers. For compounds III to VI, the base was dissolved in acetone to which glacial acetic acid (0·6 g, 0·01 mol) was added. The white solid which formed was filtered off and recrystallized. The basic form of the octyl derivative (III) was recrystallized directly from a 20% w/v solution of acetic acid. Melting points are shown in Table 1. Compounds were stored over phosphorus pentoxide in a desiccator before use.

Analytical data were as follows: N^1-(*p*-Chlorphenyl)-N^5-methylbiguanide acetate: ^{1}H-n.m.r. (DMSO-d_6): δ 1·71 (3H, s, CH_3COO^-); 2·67 (3H, s, CH_3N–); 7·21 (2H, d, aromatic H); 7·47 (2H, d, aromatic

H); 6·9–9·0 (6H, m, biguanide H) p.p.m. Mass spectrum: m/z 225 ($M^+ - CH_3COOH$).

N^1-(*p*-Chlorophenyl)-N^5-n-propylbiguanide acetate: ^{1}H-n.m.r. (DMSO-d_6): δ 0·87 (3H, t, CH_3–CH_2–, J = 7·3 Hz); 1·1–1·8 (2H, m, CH_3–CH_2–CH_2); 1·71 (3H, s, CH_3COO^-); 3·04 (2H, t, –CH_2–NH–, J = 6·7 Hz); 7·22 (2H, d, aromatic H); 7·45 (2H, d, aromatic H); 7·2–8·9 (6H, m, biguanide H) p.p.m. Mass spectrum: m/z 253 ($M^+ - CH_3$ COOH).

N^1-(*p*-Chlorophenyl)-N^5-n-amylbiguanide acetate: ^{1}H-n.m.r. (DMSO-d_6): δ 0·86 (3H, m, CH_3 –CH_2–); 0·9–1·7 (6H, m, CH_3–(CH_2)$_3$–CH_2–); 1·70 (3H, 3, CH_3 COO^-); 3·05 (2H, t, –CH_2–NH–); 7·23 (2H, d, aromatic H); 7·42 (2H, d, aromatic H); 6·0–8·5 (6H, m, biguanide H) p.p.m.). Mass spectrum: m/z 281 ($M^+ - CH_3$ COOH).

N^1-(*p*-Chlorophenyl)-N^5-n-octylbiguanide acetate: ^{1}H-n.m.r. (pyridine-d_5): δ 0·83 (3H, m, CH_3–CH_2–); 0·9–1·8 (12H, m, CH_3–(CH_2)$_6$–CH_2–); 2·25 (3H, s, CH_3 COO^-); 3·32 (2H, t, –CH_2–NH–); 7·24 (2H, d, aromatic H); 7·45 (2H, d, aromatic H); 7·8–9·8 (6H, m, biguanide H) p.p.m. Mass spectrum: m/z 323 ($M^+ - CH_3COOH$).

Preparation of biguanide acetate. Biguanide was recrystallized from methanol–water and then 0·02 mol (2·02 g) dissolved in methanol. Glacial acetic acid (0·02 mol; 1·2 g) was added and the solvent removed by evaporation. The solid was recrystallized from acetone–ethanol.

Preparation of N^1*-phenylbiguanide acetate.* N^1-Phenylbiguanide (0·03 mol, 5·32 g) was dissolved in acetone and the small amount of insoluble material removed by filtration. Glacial acetic acid (0·03 mol, 1·8 g) was added and the acetate salt separated as white crystals. These were collected and recrystallized from acetone–methanol.

Assay procedures

The concentrations of all solutes were estimated by u.v. spectrophotometry using a Pye Unicam SP1800 spectrophotometer. Beer Lambert plots were constructed for each experiment and the extinction coefficient obtained from the gradients (s.d.: slope ratio was always less than 0·6%) used to calculate solute concentrations. Average values for the molar extinction coefficients for benzoic acid, benzocaine and aniline as well as the assay conditions are summarized in Table 2. The biguanide acetate solutions were diluted appropriately with distilled water and their extinctions read at the wavelength of maximum absorbance as quoted in Table 1.

pK_a determination

pK_a's were determined under the same conditions as the sorption studies, i.e. 30 °C and 0·5 M ionic strength. The pK_a's for benzoic acid and aniline were estimated spectrophotometrically (Albert & Sergeant 1971) and found to be 4·00 and 4·75 respectively. A value of 2·57 for benzocaine had previously been determined at 30 °C and 0·5 M ionic strength (Richardson & Meakin 1974).

Sorption studies with PHEMA

Stock solutions of benzoic acid (8 mM), benzocaine (6 mM) and aniline (4 mM) were prepared in buffers as listed in Table 2. Dilutions in the appropriate buffer were prepared so that the experimental concentrations ranged from that of the stock solution to around a tenth of this value. Unbuffered, aqueous solutions of the biguanide acetates (2 mM) were prepared and dilutions in water made to cover the concentration range 0·02 to 2·0 mM.

Sorption studies were carried out as described previously (Plaut et al 1980) whereby, unless otherwise stated, 0·2 g aliquots PHEMA powder were incubated at 30 °C with 10 ml of solution. With the exception of benzocaine at low pHs, discussed below, an equilibrium time of 24 h was adopted. The supernatant solutions were withdrawn via glass tubes fitted with number three glass sinters and assayed. Where desorption was also followed, 5 ml of solution was removed and replaced by an equal volume of either water (in the case of biguanide derivatives) or buffer of the same pH and ionic strength as the sorption study. After incubation for a further 24 h, solutions were withdrawn as before and assayed. The experimentally adopted equilibration times were verified for all substrates by following sorption and desorption at each concentration studied for 48 h. For benzoic acid, benzocaine and aniline this was done only at a single pH which corresponded to the maximum uptake by PHEMA.

The equilibration time for benzocaine at pH's less than two was modified since a loss of absorbance in the u.v. at 286 nm was observed for stock solutions following incubation at 30 °C for 24 h. Losses were small (5% or less) and probably reflect degradation by acid-catalysed ester hydrolysis, the aromatic degradation product, *p*-aminobenzoic acid, having a λ_{max} at 266 nm in alkaline solution. A shorter time of 5 h was found to be sufficient and no loss of benzocaine activity, as evidenced by the absorbance at 286 nm, could be detected even at the lowest pH studied (0·38).

Table 1. Physicochemical parameters for biguanide acetates. a. Warner et al (1976), b. Curd & Rose (1946), c. Fisher et al (1975).

Compound (acetate salt)	R	Recrystallization solvent	Melting point (°C)	Literature value (°C)	λmax (nm)	Molar $E_{1\,cm}^{M}$	s.d.*
Biguanide	—	acetone–ethanol	175–176		231	13 746	15
N^1-Phenylbiguanide	—	acetone–methanol	187		243	14 224	42
III	methyl	acetone	148	149[a]	253	15 445	34
IV	n-propyl	acetone–ethanol	164–166	165–166[a]	253	15 548	26
V	isopropyl	acetone–ethanol	184–185	184–185[b]	253	15 154	21
VI	n-amyl	acetone	129–130		253	14 821	34
VII	n-octyl	see text	126–127	132[a]	253	14 956	89
Chlorhexidine	—	acetone–ethanol	172	170·5–172[c]	253	28 889	174

* Standard deviations refer to the slopes of single Beer Lambert plots.

Table 2. Experimental conditions for the sorption of benzoic acid, benzocaine and aniline with PHEMA.

	Ultraviolet assay					pH conditions		
Solutes	Conditions for u.v. assay	λmax (nm)	molar $E_{1\,cm}^{M}$	No. of Beer Lambert plots	s.d.	Buffer 1 (pH range)	Buffer 2 (pH range)	Buffer 3 (pH range)
Benzoic acid	0·1 M HCl	274	944	8	18	Sørensens citrate* (2·3–6·0)		
Benzocaine	0·01 M NaOH	286	16 810	8	220	HCl/NaCl* (0·38)	glycine/ HCl* (0·7–3·0)	Sørensens* citrate (2·3–5·0)
Aniline	0·01 M NaOH	280	1368	3	13	McIlvaine citrate/ phosphate† (2·0–7·5)		

† Buffers were adjusted to ionic strength 0·5 M by the addition of sodium or potassium† chloride.

Despite the fact that the PHEMA powder was cleaned by Soxhlet extraction (Plaut et al 1980), a small amount of u.v. absorbing material was released into solution. For this reason, at least two blanks were run alongside sorption and desorption stages of each experiment by equilibrating 0·2 g PHEMA with 10 ml of water or buffer as relevant. These were treated and assayed exactly as for the other samples and subtracted from the experimental values. With benzoic acid, benzocaine and aniline, the blank correction was most significant for aniline because of its low uptake by PHEMA (Table 3). The mean absorbance at 280 nm of eight sorption determinations was 0·016 (s.d. = 0·007). This standard deviation corresponds to an uptake of 0·25 mmol kg^{-1} which is a constant error throughout the concentration range studied and affects the position of intercept on the ordinate but not the value of the slope or sorption constant. For the biguanide derivatives, the blank correction was greatest for biguanide itself owing to the low wavelength of the sorption maximum of 231 nm. The mean absorbance of four readings was 0·117 (s.d. = 0·009), the standard deviation corresponding to an uptake of 0·03 mmol kg^{-1} which was not considered to be significant.

RESULTS AND DISCUSSION

The uptakes of benzoic acid and benzocaine by PHEMA are related linearly to their concentrations in solution at equilibrium (Fig. 1A and B respectively). According to the classification of Giles et al (1974) these curves may be considered as C type or partitioning isotherms which implies that the solute actually penetrates into the polymer matrix during the sorption process. PHEMA appears to follow the behaviour of polyvinyl chloride and nylon with the same two solutes, C type isotherms being reported in all cases (Rodell et al 1966; Bray & Meakin 1975; Richardson & Meakin 1974, 1975).

Table 3. Sorption of aniline (pK_a 4·75) by PHEMA at 30 °C from buffer of ionic strength 0·5 M.

pH	Sorption constant K (litre kg^{-1})	(s.d.)	Intercept (mM kg^{-1})	(s.d.)	Proportion Aniline unionized %
2·10	1·11	(0·07)	−0·04	(0·17)	0·22
7·47	6·07	(0·11)	−0·32	(0·21)	99·8

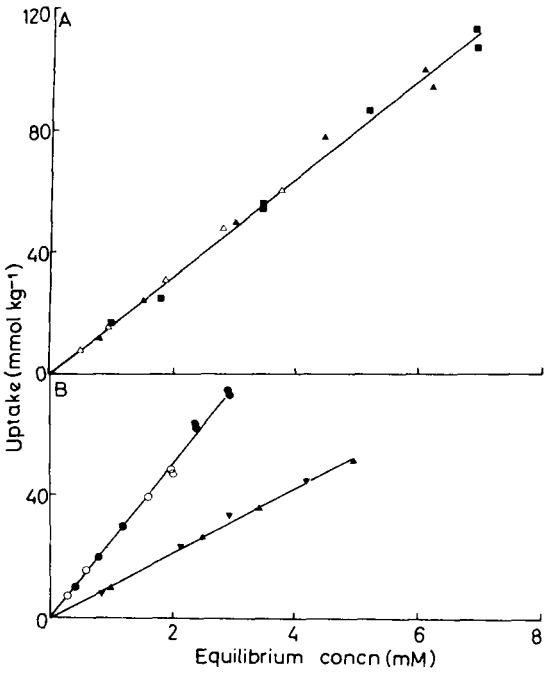


FIG. 1. Sorption of benzoic acid (A: pH 2·32) and benzocaine (B: pH 4·69, circles, and 2·34, triangles) with PHEMA at 30 °C, ionic strength 0·5 M. PHEMA (0·2 g) was incubated with either 5 ml (▼), 10 ml (● ○ ▲ △) or 20 ml (■) of solution. Closed symbols represent sorption and open symbols desorption data.

In order to expose any atypical sorption behaviour, some of the data in Fig. 1 were generated by varying the volume of solution which was equilibrated with the usual weight of PHEMA (0·2 g). Unlike the sorption of chlorhexidine, these values lie on the isotherms obtained under standard conditions (0·2 g PHEMA: 10 ml solution). In addition, the collinearity of the sorption and desorption isotherms demonstrates that both benzoic acid and benzocaine interact with PHEMA in a freely reversible manner as would be expected for any sorption process mediated by physical bonding.

The sorption of chlorhexidine by PHEMA is unusual in that electrically charged species are not generally sorbed from aqueous solution by polymers. This led us to investigate the behaviour of PHEMA with other positively and negatively charged ions. Isotherms for benzocaine and benzoic acid were constructed over a range of pH's that spanned the pK_a of the solute. All the individual isotherms fulfilled the criterion of linearity applied by Richardson & Meakin (1974) in that the curves possessed intercepts (derived from least squares regression analyses) that lay within two standard deviations of the origin. These lines were characterized by their slopes or sorption constants which have been plotted as a function of pH in Fig. 2. The lines in the Figure were calculated using pK_a values determined at 30 °C and 0·5 M ionic strength and assuming that only the unionized species interacted with the PHEMA. The sorption constants for benzoic acid (Fig. 2B) fit the theoretical lines closely thus validating the premise that the negatively charged benzoate ion is not sorbed by the polymer. In addition, the pH dependence of the interaction between benzocaine and PHEMA (Fig. 2A) also illustrates the preferred affinity of the polymer for unionized molecules. These results are consistent with general theoretical considerations in that ions would be expected to exist preferentially in a polar aqueous medium as opposed to the relatively hydrophobic polymer environment. An anomaly is visible however for the benzocaine:PHEMA interaction

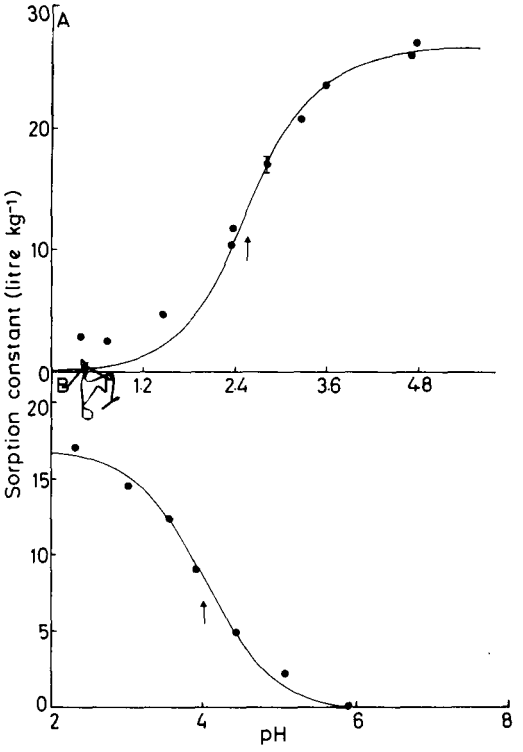


FIG. 2. pH dependences for the sorption of benzocaine (A) and benzoic acid (B) with PHEMA at 30 °C in ionic strength 0·5 M buffer. Lines were drawn using experimentally determined pK_as of 2·57 and 4·00 respectively, as shown by arrows, and assuming that only the unionized species interacted with the polymer. Standard deviations are within symbols unless indicated by error bars.

at pH's less than two where the sorption constants deviate markedly from the theoretical line. This trend could reflect loss of benzocaine activity as a result of acid-catalysed ester hydrolysis during the sorption study. However, for the shortened equilibration times adopted at these low pH's, no reduction in drug concentration was detected indicating that the cationic benzocaine ion is being sorbed by the hydrogel. This result contrasts with the sorption of benzocaine by nylon where only the uncharged species interacted (Richardson & Meakin 1974). The sorption of another cationic solute, aniline, was followed and the same trend observed. This interaction was studied at pH's that spanned either side of the pK_a (4·75) by at least two pH units. Both isotherms were linear, the relevant parameters being summarized in Table 3. At pH 2·10 where aniline is more than 99% protonated, the solute still showed an appreciable affinity for PHEMA. It is possible, therefore, that the sorption of organic cations, although atypical of substrates in general, is a property of this particular polymer.

In every other respect, however, the PHEMA: solute interactions showed classical sorption patterns, serving to focus our attention on the properties of chlorhexidine. A series of monofunctional chlorhexidine analogues were synthesized (see Table 1), the n-propyl derivative (compound IV) being of particular interest in that it represents exactly half the chlorhexidine molecule. Its interaction with PHEMA is illustrated in Fig. 3A and, to facilitate comparison its sorption isotherm is shown alongside that of the parent molecule in Fig. 3B. The 'half molecule' is taken up to a slightly lesser extent than chlorhexidine itself possibly because the chlorhexidine molecules have the ability to bind with PHEMA via both functional groups which could result in an enhanced affinity for the polymer. However, the most important features of the sorption of N^1-(*p*-chlorophenyl)-N^5-n-propylbiguanide acetate with PHEMA are the distinct sorption and desorption isotherms which indicate a high degree of irreversible binding and the non-isothermal points generated by pertubing the solution volume : polymer weight ratio. It is evident, therefore, that the anomalous sorption behaviour of chlorhexidine is not linked to its bufunctionality. A further property of chlorhexidine which was considered to be of potential relevance is its surface activity. Heard & Ashworth (1968) cite a c.m.c. for the acetate salt in the region of 0·011 M. Although this concentration is well

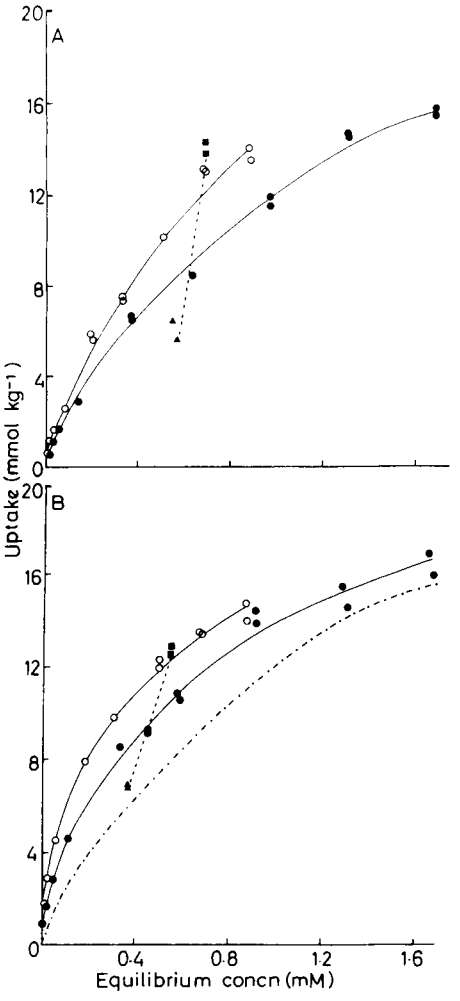


Fig. 3. Interaction of N^1-(*p*-chlorophenyl)-N^5-n-propyl biguanide (IV) acetate (A) and chlorhexidine (VIII) acetate (B) with PHEMA powder from simple aqueous solution at 30 °C. Solution volumes were 5 ml (▲), 10 ml (● ○) and 25 ml (■) respectively, closed symbols representing sorption and open symbols desorption data. The sorption isotherm from A is shown in B as a stippled line. Sorption points from 0·8 mM solution are connected by a broken line.

outside the range of these sorption experiments, the solute concentrations at the polymer : water interface are unknown. We decided to look at the interactions of N^1-(*p*-chlorophenyl)-N^5-methylbiguanide, biguanide and N^1-phenylbiguanide acetates with PHEMA (Fig. 4). As none of these compounds possess extensive hydrocarbon regions, it was thought unlikely that they would be surface active, a prediction reinforced by the surface pressure

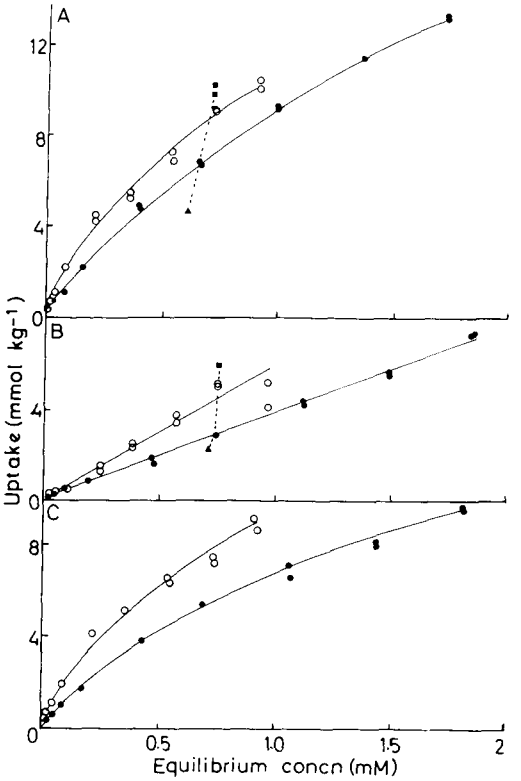


FIG. 4. Sorption of the acetate salts of N^1-(*p*-chlorophenyl)-N^5-methylbiguanide (A), biguanide (B) and N^1-phenylbiguanide (C) with PHEMA in simple aqueous solution at 30 °C. Symbols as for Fig. 3.

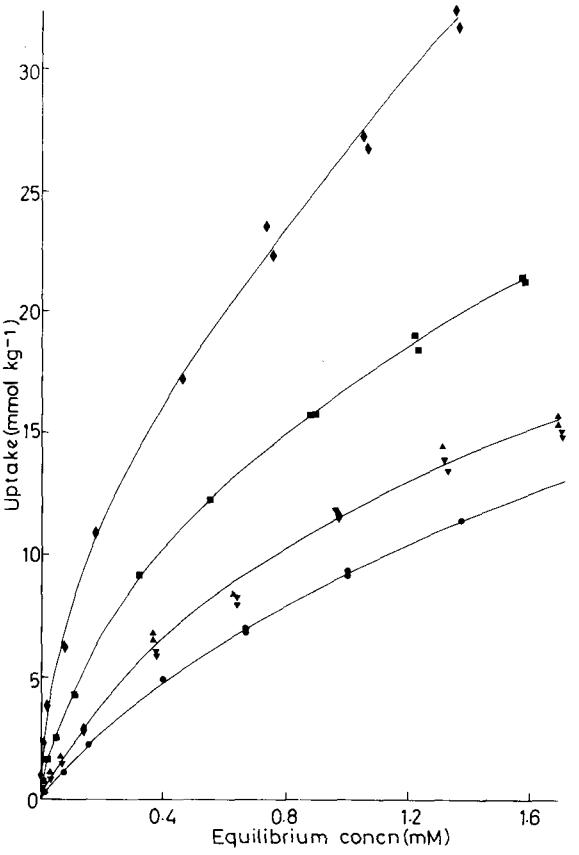


FIG. 5. Sorption isotherms from aqueous solution, 30 °C for the acetate salts of various N^1-(*p*-chlorophenyl)-N^5-alkylbiguanides with PHEMA where the alkyl substituent was methyl (III, ●), n-propyl (IV, ▲), isopropyl (V, ▼), n-amyl (VI, ■) and n-octyl (VII, ◆).

measurements of Fisher et al (1975) on a similar series of biguanide derivatives. All three compounds exhibited anomalous sorption behaviour as judged by the same criteria that were applied to the n-propyl (IV) derivative. This indicates that solute aggregation is not an important aspect of the problem. The sorption isotherms for all five N^1-(*p*-chlorophenyl)-N^5-alkylbiguanides are shown in Fig. 5. The interactions of all these compounds with PHEMA were characterized by distinct sorption and desorption isotherms and by the 'volume effects' which have been described for chlorhexidine and other biguanide derivatives. Increasing affinity for the polymer appears to be related to the extent of the solute hydrocarbon region, the isomeric biguanides IV and V generating collinear isotherms. It is possible that chlorhexidine and its congeners bind to PHEMA via the biguanide grouping which we have shown to interact with the polymer (Fig. 4B). If this is the case, it could imply the existence of negatively charged binding sites on the polymer which would account for the affinity exhibited by PHEMA for the positively charged ionic forms of benzocaine and aniline. The increasing uptake accompanying increasing solute chain length illustrated in Fig. 5 probably reflects the fact that the interactions are stabilized by van der Waal's forces operating between the hydrocarbon groups and the polymer backbone and maybe also by hydrophobic bonding. As a result of the anomalous sorption observed for simple cations, biguanide and N^1-phenylbiguanide, it is tempting to suppose that this could be a feature of the sorption of all positively charged ions with PHEMA. However, in order to validate this supposition it will be necessary to investigate the sorption of other organic cations choosing compounds that have a higher affinity for PHEMA than aniline and having pK_a's that permit studies in the pH range around 6 characteristic of aqueous chlorhexidine solutions.

REFERENCES

Albert, A., Serjeant, E. P. (1971) The Determination of Ionisation Constants. 2nd ed. Chapman and Hall, London

Bray, C. S., Meakin, B. J. (1975) J. Pharm. Pharmacol. 27: 68P

Browne, R. K., Anderson, A. N., Charvez, B. W. (1974) The Optician 167: 19–24

Browne, R. K., Anderson, A. N., Charvez, B. W., Azzarello, R. J. (1975) Toxicol. Appl. Pharmacol. 32: 621–627

Callender, M. (1978) Contact Lens J. 7: 2–6

Curd, F. H. S., Rose, F. L. (1946) J. Chem. Soc. 729–737

Curd, F. H. S., Hendry, J. A., Kenny, T. S., Murray, A. G., Rose, F. L. (1948) Ibid. 1630–1636

Davies, D. J. G. (1978) J. Appl. Bacteriol. 44: Suppl. 19–28

Fisher, R. G., Quintana, R. P., Boulware, M. A. (1975) J. Dent. Res. 54: 20–24

Giles, C. H., Smith, D., Huitson, A. (1974) J. Colloid Interface Sci. 47: 755–765

Heard, D. D., Ashworth, R. W. (1968) J. Pharm. Pharmacol. 20: 505–512

Kapadia, A. J., Guess, W. L., Autian, J. (1964) J. Pharm. Sci. 53: 28–34

Kipling, J. J. (1965) Adsorption from solutions of non-electrolytes. Academic Press, London.

Plaut, B. S., Davies, D. J. G., Meakin, B. J. (1980) J. Pharm. Pharmacol. 32: 453–459

Richardson, N. E., Meakin, B. J. (1974) Ibid. 26: 166–174

Richardson, N. E., Meakin, B. J. (1975) Ibid. 27: 145–151

Richardson, N. E., Davies, D. J. G., Meakin, B. J., Norton, D. A. (1978) Ibid. 30: 469–475

Richardson, N. E., Plaut, B. S., Davies, D. J. G., Norton, D. A., Meakin, B. J. (1979) Proc. Third Int. Conf. Plastics in Medicine and Surgery 22.1–22.11

Rodell, M. B., Guess, W. L., Autian, J. (1966) J. Pharm. Sci. 55: 1429–1434

Warner, V. D., Lynch, D. M., Ajemian, R. S. (1976) Ibid. 65: 1070–1072