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The Kinetics of Adsorption of Some Organic Cations on to an Insoluble Sodium Polyphosphate

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ABSTRACT

The kinetics of adsorption of the hydrochlorides of chlorpromazine, propranolol, quinine, and quinidine on to an insoluble sodium polyphosphate, Maddrell's phosphate type II (MPI), have been studied in vitro. The data have been fitted to a three-compartment model, in which one compartment represents the aqueous solution of adsorbate and the other two compartments represent hypothetical adsorption sites. One site is labile, i.e., adsorption (and desorption) occur very rapidly, while the second site is a sink at which the adsorption density slowly increases until it eventually dominates the total adsorption density. The initial adsorption rates of the cations increase with temperature and, with the exception of quinidine, are very rapid. The adsorption densities obtained for the drugs substantially exceed the predicted densities and it is suggested that the drugs may form an adhesive layer of insoluble (drug-polyphosphate) complex at the MPI surface which then acts as a diffusion barrier to further uptake.

INTRODUCTION

Maddrell's phosphate type II (MPI) is a long-chain sodium polyphosphate which is very slowly soluble in water. It is one of a group of polyphosphates (many of which are water soluble) which are employed in various food industries and which are classified by the Food and Drug Administration (FDA) as being "generally recognized as safe" (1). Since MPI is polyanionic, a variety of cationic drugs will interact with it and adsorb on to the surface of the MPI particles. We consider that MPI may be a useful tableting excipient. This paper

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reports the kinetics of the adsorption of several cationic drugs on to MPI.

Studying the adsorption kinetics of organic molecules on to the surface of MPI is complicated by the potential micellization of the drugs and the lack of detailed knowledge of the degree of hydration of the molecules and of their effective hydrated size.

Micellization of the drugs is important since it is desirable to know whether monomers or micelles are adsorbed, or whether hemimicelles are adsorbed or develop on the surface after adsorption. Hemimicelles of ionic surfactants form near an oppositely charged surface, at bulk concentrations less than the critical micelle concentration (CMC). This is due to the Coulombic attraction of monomers by the surface to such a degree that the local concentration exceeds the CMC (2).

The degree of hydration of the cations, the effective size of the hydrated cations, and the extent of dehydration of the surface and the cation during adsorption will influence both the rate and extent of adsorption. Little information is available on such factors.

The initial rapidity of the adsorption process makes the collection of sufficient samples at early times difficult. Therefore the mathematical analysis of the process may be inaccurate during the initial period of adsorption.

In a previous paper (3) we reported the adsorption kinetics of calcium and magnesium on to MPI, presented a mathematical analysis of the data, and proposed a mechanism of adsorption. That treatment resulted in the extraction of kinetic parameters based upon the fitting of the data to a three-compartment model. More specifically, the data were fitted to a biexponential equation:

$$Q_T/Q_{ZERO} = k + A \exp(-\alpha t) + B \exp(-\beta t) \qquad (1)$$

where k, A, B, α, and β are the fitted model-independent parameters determined by NONLIN (4,5). Q_T and Q_{ZERO} are the amount of adsorbate in solution at any time during the experiment and at the beginning of the experiment, respectively. At equilibrium, Eq. (1) reduces to $Q_T/Q_{ZERO} = k$. This is conceptually pleasing, since it predicts that a fraction of the available adsorbate will remain free in solution at equilibrium.

MATERIALS AND METHODS

Materials

The identity of the drugs—chlorpromazine HCl, quinine HCl, quinidine HCl (Sigma Chemical Co., USA), and propranolol HCl (donated by Alphapharm, Australia)—was confirmed by infrared spectroscopy and melting point determination. The insoluble sodium polyphosphate glass—i.e., Maddrell's phosphate type II—was also obtained from the Sigma Chemical Co. and was used as obtained. Fundamental physical and spectroscopic properties, particle size, specific surface area, pycnometric density, appearance (by scanning electron microscopy), x-ray diffraction (CuKα radiation), infrared (2% in KBr) and ^{31}P NMR spectroscopy were reported previously (3).

Kinetic Procedures

The method employed has been previously described in detail by us (3) and was only slightly modified. A water-jacketed glass reaction vessel was used, in which either 50 or 100 ml of the adsorbate solution was stirred magnetically with a Teflon-coated bar. The temperature within the reaction vessel was maintained within 0.1°C of the nominated temperature, namely 25°, 37°, or 49°C.

The experiment was started by adding either 2.5 or 5 g of MPI all at once. Ten to 30 sec before the required sampling time, the stirrer was turned off to allow the aggregated suspension time to settle and reveal sufficient supernatant for sampling. A 0.2-ml sample was taken within ±3 sec of the nominated time. The procedure was continued until equilibrium was reached or the suspensions became impossibly aggregated. The sample volume was not replaced, but the total sample volume was never more than 8% of the initial volume. The residual amounts of adsorbate were determined by the analytical procedures described below, and the calculation of the amount adsorbed allowed for that quantity of adsorbate removed in the sample aliquots. All experiments were performed in duplicate. Control experiments confirmed that the cations were stable and did not adsorb on to the experimental apparatus.

Analytical Methods

The solvents chosen were either freshly distilled water or 0.01 M hydrochloric acid. The analytical wavelengths (solvent and concentration range over which Beer's law was obeyed) were: chlorpromazine 306 nm (water, 0–0.2 μmol/ml), propranolol 293 nm (water, 0–0.2 μmol/ml), and both quinine and quinidine 318 nm (0.01 M HCl, 0–0.24 μmol/ml). All ultraviolet (UV) analyses were performed with either a Cary 219 (Varian Associates, USA) or a Pye PU8600 (Pye Unicam, England).

Data Analysis

At any sampling time, the solution concentrations of the cations were expressed as a fraction of the initial solution concentration and were then analyzed by NONLIN (4), which has been modified to run on a PDP11-34 with the RSX-11 operating system (5). Three different polyexponential equations were fitted to the data (3), and statistical criteria and methods which have been previously described (6) were used to select the most suitable equation.

RESULTS

Chlorpromazine

The kinetics of adsorption of chlorpromazine (50 ml of a 0.05 M solution) onto 2.5 g of MPI (giving an initial loading of 1000 μmol/g MPI) were studied at 25°C and 37°C. The profiles are presented in Fig. 1. The adsorption densities are very high and are virtually independent of the temperature. The initial rates of adsorption are quite rapid, and although slightly slower at 25°C than at 37°C, both profiles reached plateaus representing 90% of the equilibrium adsorption density (i.e., EAD) within 20 min. The adsorption process was accompanied by aggregation of the MPI which was more severe at 37°C than at 25°C. The aggregates were very adhesive and sedimented within seconds of the stirrer being turned off.

Propranolol

The kinetic profiles of the adsorption of propranolol (1000 μmol/g MPI) from a 0.05 M solution at 25°, 37°, and 49°C are shown in Fig. 2. The rates depend upon the temperature, but the EAD (810–850 μmol/g MPI) are relatively independent of temperature. Adsorption reached 90% EAD within 90 min. Aggregation of the MPI occurred but was not very severe, even at the highest temperature.

Quinine and Quinidine

A similar pattern is presented in Fig. 3, which shows adsorption from a 0.05 M solution of quinine (1000 μmol/g MPI) at 25° and 37°C. Again, the EAD (860–870 μmol/g MPI) is independent of temperature while both the rapid and slow rates are dependent on temperature. The process was fairly rapid; 90% EAD was achieved within 160 min. Figure 3 also shows the adsorption of quinidine (1000 μmol/g MPI) from a 0.025 M solution at 37°C. The EAD of 445 μmol/g MPI, is far lower than those found in the other system. The equilibrium adsorption densities and the times to reach

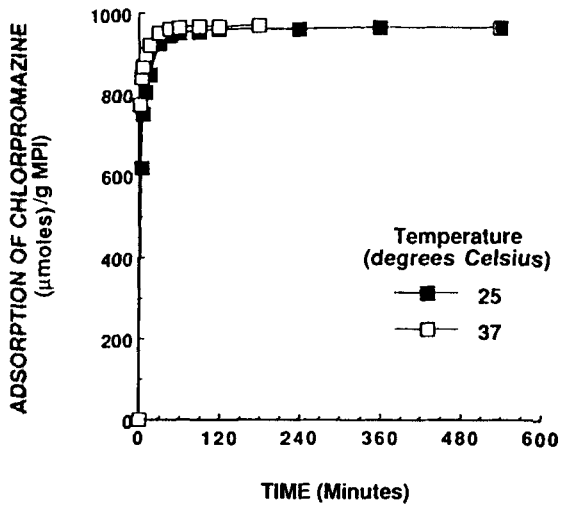

Figure 1. The adsorption kinetics of 1000 μmol of chlorpromazine onto MPI at 25° and 37°C. The means of duplicate determinations are shown; the point size encompasses the experimental variation.

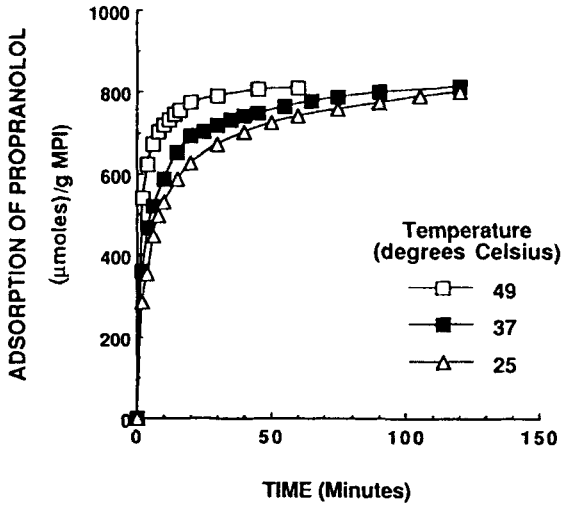

Figure 2. The adsorption kinetics of propranolol (1000 μmoles/g MPI) PI at 25°, 37°, and 49°C. The means of duplicate determinations are shown; the point size encompasses the experimental variation.

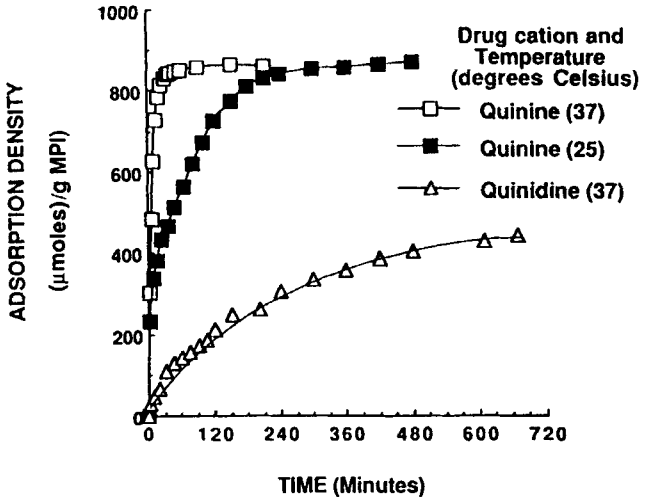

Figure 3. The adsorption kinetics of quinine and quinidine (1000 μmol/g MPI) at 25° or 37°C. The means of duplicate determinations are shown; the point size encompasses the experimental variation.

90% EAD for all drugs studied are summarized in Table 1.

DISCUSSION

The Kinetics of Adsorption

Equation (1) describes the situation in which the adsorbate is present in a solution compartment and adsorbs on to two adsorption sites either simultaneously or sequentially (3). Site 1 is labile; i.e., adsorption and desorption occur rapidly. At site 2 the adsorption density increases slowly and at equilibrium becomes the dominant site. Successful fitting of the data to the equation does not define the mechanism of the adsorption process. Since the analytical method determines the total amount adsorbed and does not distinguish between the two possible adsorption sites, it is not possible to define a particular model. Therefore, only the fitted, model-independent parameters, and not the microconstants, are considered.

The rate of adsorption of the organic cations on to MPI increased as the temperature was increased and occurred more rapidly than for calcium and magnesium ions. The rapidity of the process made difficult the acquisition of sufficient data to enable the accurate determination of the initial adsorption phase. Therefore, some of the adsorption experiments were performed over a more limited range of temperatures than the experiments with the inorganic ions. Table 2 shows the computer estimates of the kinetic parameters (k, α, and β) and the mean half-lives of the fast (alpha) and slow (beta) adsorption phases; for comparison, some data for calcium (3) are also shown.

The most striking feature of the results in Table 2 is that the organic ions, with the exception of quinidine, are adsorbed more rapidly than calcium ions. At 37°C the alpha and beta half-lives for quinidine are about 7.5 and 15 times slower than for quinine, and the beta half-life of quinine is about 10 times slower than the alpha phase, while for quinidine the beta half-life is about 20 times slower. Both propranolol and calcium showed decreased k values as the temperature was increased from 25° to 37°C, but further temperature increases did not decrease k proportionately. The value of k for chlorpromazine is virtually insensitive to temperature changes.

Table 1

Summarized Data for the Adsorption of Various Organic Cations on to MPI

Drug	MPI Weight (g)	Temperature (°C)	EAD[a]	Time at 90% EAD[a] (min)
Chlorpromazine	2.5	25	967	16
	2.5	37	970	6
Propranolol	5.0	25	850	80
	5.0	37	815	35
	5.0	49	810	12
Quinidine	2.5	37	445	440
Quinine	5.0	25	872	160
	5.0	37	862	18

[a]Equilibrium adsorption density (quoted as micromoles per gram of MPI).

Table 2

The Kinetic Parameters Obtained by Nonlinear Least Squares Regression of the Adsorption Data; for Comparison, Some Parameters for Calcium Are Also Shown

Cation	Temperature (°C)	k^a	Half-lives[a,b] α	Half-lives[a,b] β
Chlorpromazine[c]	25	0.0380	1.08	10.74
	37	0.0332	0.50	8.02
Propranolol[c]	25	0.164	2.37	30.49
	37	0.202	1.13	13.72
	49	0.192	0.6	6.85
Quinine[c]	25	0.120	4.29	63.90
	37	0.139	1.43	13.91
Quinidine[c]	37	0.513	10.61	206.78
Calcium[c,d]	25	0.141	5.46	165.43
	37	0.109	2.65	61.89
	49	0.110	0.95	20.13

[a]The means of duplicate results are reported.
[b]Half-lives are in minutes.
[c]Concentration of adsorbate applied to MPI, 1000 μmol/g MPI.
[d]Mean data from Ref. 3.

The difference between both the k values and kinetic half-lives of quinine and quinidine at 37°C suggests that stereochemical differences have considerable influence on the adsorption process.

The Equilibrium Adsorption Densities

The crystal radii of inorganic ions are well known, and even the hydrated radii can be reasonably estimated. Although the dimensions of many organic molecules are well characterized, the effective hydrated size of the same molecules in aqueous solution is not as clear. Estimates of the effective area of surface active molecules can be made from surface tension data and the Gibbs isotherm.

It is reasonable to employ literature estimates of the effective areas of the adsorbate molecules, namely, propranolol 62×10^{-20} m^2 (7) and chlorpromazine 66.3×10^{-20}/m^2 (8). No data could be found for quinine and quinidine, but it is unlikely that the effective areas would be considerably smaller than the figures quoted above.

If we assume that the adsorbate molecules behave as rigid monodisperse spheres arranged in hexagonal close packing, only 84.2% of the surface area is available for adsorption. Based upon an estimate of the total specific surface area of 2 m^2/g MPI, measured by the adsorption of helium gas and reported previously by us (3), the predicted coverage of the drugs is about 5 μmol/g MPI. From the data in Table 1, it is apparent that the measured adsorption densities are far higher.

Allingham et al. measured adsorption densities of some cationic dyes (including the phenothiazine derivative methylene blue) on to silica and observed that the measured densities were some 20–70 times greater than the predictions (9). They proposed that this was due to the preferential adsorption of micelles, which have a higher mobility due to their high charge/radius ratio.

A successive bilayer model has been proposed to explain the adsorption of cationic surfactants on to silica (10) and propantheline on to silica (11). The arrangement of surfactant molecules at the surface allows the total binding to be due to a combination of electrostatic interaction with the negative surface and cooperative hydrophobic bonding between the hydrocarbon chains. It is not clear whether the aggregation occurs in solution or is induced to occur at the interface. Although it is well known that chlorpromazine and propranolol form micelles in aqueous solution (12,13), the large measured adsorption densities imply that if adsorption as micelles occurred, the micelles contain several hundred monomers. The aggregation numbers of chlorpromazine and propranolol in aqueous solution, reported by the above authors, are in the range of 8–36. If we assume that the

drugs initially adsorb very rapidly as a bilayer or as micelles or hemimicelles, the net result will be the formation of an adsorbed "layer" which could present a hydrophobic surface to the aqueous solution. In that situation, particle aggregation would be almost inevitable.

It has been suggested that a gel layer of hydrolysates is present at the solution/oxide interface (e.g., Ref. 14). The layer is about 50×10^{-10} m thick and provides a medium in which further adsorption of inorganic cations occurs. Since MPI is very slowly soluble in water (15), some dissolution and/or hydrolysis may occur at the solution/MPI interface to form a stagnant layer of polyphosphates. Since it is well known that the drugs studied here can form adhesive insoluble complexes with soluble polyphosphates (16–18), chemisorption could occur within that layer.

Alternatively, the presence of the adsorbed cations at the surface may promote the localized dissolution and/or hydrolysis processes which form the reactive gel layer. Since the cation–polyphosphate complexes are very adhesive, they would bind to the surface of the particles and stabilize the development of the gel layer, which would impose a diffusion barrier to the adsorption of further ions. We have previously suggested that adsorption and/or complexation within a layer about 150×10^{-10} m thick may account for the high adsorption densities obtained with calcium and magnesium (3).

Assuming that the hydrated molecular diameter of chlorpromazine approximates that of methylene blue (12.5×10^{-10} m, Ref. 19), we can estimate the total molecular volume of 970 μmol of adsorbed chlorpromazine. If we then assume that chlorpromazine occupies half of the available volume and since the specific surface area of MPI is 2 m^2/g, the thickness of the layer of reacted MPI would be about 0.6 μm. Since the mean particle diameter of MPI is 11.3 μm (3), a layer of that thickness is physically realistic.

CONCLUSIONS

The organic cations, chlorpromazine, propranolol, quinine, and quinidine are all apparently adsorbed by MPI. The initial rate of uptake of chlorpromazine and propanolol is more rapid than that of calcium. The initial rapid uptake of the cations is probably due to the adsorption of micellar aggregates on to the polyanionic MPI particles promoted by Coulombic attraction. Quinine and quinidine have not been reported to micellize in aqueous solution and this may be the reason that the adsorption rates of quinine are only slightly faster than those of calcium. The initial uptake would be represented in the adsorption model as the more labile site and is probably best described by the alpha half-lives. That different drugs are adsorbed at different rates and to different degrees, must be related to the different affinities of the drugs for the MPI. If the whole uptake process were simply adsorption due to the Coulombic attraction between oppositely charged species, then there would probably be no great difference in the initial uptake rates. However, the differences between quinine and quinidine at 37°C show that molecular structure is very significant.

Upon exposure of the MPI to the cations for several hours, a much slower uptake phase occurs. This phase could simply be the slow development of an equilibrium and be due to the increasing difficulty of adsorption of cations on to a surface with significantly less anionic character. However, the large adsorption densities indicate that the physical capacity of the surface to adsorb the ions is vastly exceeded. This suggests that these organic cations, once adsorbed on to the surface, either complex with a preformed layer of polyphosphate hydrolysates or catalyze the formation of such a layer before complexing within it. The original MPI particles are therefore progressively converted to a nucleus of MPI coated with a layer of adhesive insoluble complex. Since all of the drugs studied have been reported to form cation polyphosphate complexes, with stoichiometries of 0.85–1.0, the layer of complex would be neutral or slightly anionic and hence impose a diffusion barrier to further uptake. Diffusion through the complex layer and interaction with the underlying MPI surface would be a far slower process and corresponds to the slow beta phase and the hypothetical second adsorption site.

We believe that MPI warrants further investigation as an adsorbent for cationic drugs. Other studies from our laboratories have shown that the release of adsorbed drug can be sustained for several hours from tablets containing MPI alone (20) or in combination with other excipients (21). Further work is in progress in our laboratories to study the uptake of drugs and to elucidate the mechanism(s).

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