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The Effect of pH and Ionic Strength on the Release of Quinine Adsorbed on to an Insoluble Sodium Polyphosphate

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ABSTRACT

The preparation and evaluation of a potential prolonged-release drug delivery system with the model drug quinine HCl adsorbed onto an insoluble sodium polyphosphate (Maddrell's phosphate type II) is described. The delivery system was prepared by equilibration of the drug with a suspension of the polyphosphate and then compressing the dried adsorbed complex into disks. It was shown that the extraction of the drug from the loose powder was enhanced by increasing the sodium ion concentration and by reducing the pH. The effect of sodium ion concentration upon release of the drug from compressed disks depended upon the pH of the dissolution fluid. At low pH, which slowly dissolved the disks, the zero-order release of quinine was reduced as the ionic strength of the dissolution medium was increased. At near-neutral pH, the release of quinine was first-order at sodium concentrations greater than 0.025 M and was zero-order at sodium concentrations lower than 0.025 M. The release was promoted by an increase in the ionic strength.

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INTRODUCTION

There are a myriad of reports and reviews on the use of synthetic polymers in prolonged-release formulations (e.g., Ref. 1). The polymers may act as an inert matrix for the drug or as a coating for a drug core, or may have the drug covalently or ionically bound as pendant groups. Although most of the polymers employed are organic, there have been some reports on the use of inorganic polymers. This report focuses particularly on the sodium polyphosphates.

Kaplan and Buckwalter (2) reported the preparation and physicochemical properties of tetracycline hexametaphosphate (THMP). Other reports have shown that acute or chronic oral administration of THMP produced significantly higher blood levels than the hydrochloride salt with no significant toxic side effects (3–7).

The Bayer Company and the Meiji Confectionary Co. have patented sustained-release preparations of the hexametaphosphate derivatives of streptomycin and kanamycin respectively (reported in Ref. 8). It has been demonstrated that although there was no difference in the peak plasma concentrations of quinidine in dogs when the drug was administered as the sulfate, hexametaphosphate, or polymetaphosphate derivatives, the area under the curve (AUC) of the phosphate derivatives was 15–32% greater than the sulfate (9). An 8–26% increase in the AUC of papaverine in dogs occurred when administered as the same phosphate derivatives, compared to the hydrochloride salt (10).

There have been reports on the formation of insoluble hexametaphosphate and polyphosphate derivatives of a variety of organic cationic drugs and demonstrations that there may be prolonged dissolution of the drugs from such complexes (8–11). Sodium polyphosphate and other phosphates such as hydroxyapatite and mixed calcium phosphates have been employed as carriers or matrices from which the sustained release of verapamil, adriamycin, and some antibiotics has been recently reported (e.g., Refs. 11–14).

We have reported that Maddrell's phosphate type II (MPI), an insoluble sodium polyphosphate, can rapidly adsorb significant quantities of a variety of cations, such as quinine, quinidine, propranolol, and chlorpromazine (15). This paper reports the equilibrium adsorption of a model drug quinine onto MPI and the effects that the dissolution medium has on the release of the drug from this delivery system.

MATERIALS AND METHODS

Materials

The Maddrell's phosphate type II (MPI) and the quinine hydrochloride, obtained from Sigma Chemical Co., USA, were used as received. All other reagents were analytical grade. The MPI was identified by infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy, and also physically characterized prior to use. The powder has a mean size (determined by laser diffraction with a Malvern 2600D) of 11.3 μm and geometric standard deviation of 2.61, and a pycnometric density in water of 2.69 g/cm^3 (16). The identity of the quinine HCl was confirmed by IR and ultraviolet (UV) spectroscopy.

Adsorption Isotherm for Quinine on to MPI

The adsorption of quinine HCl from water was determined by equilibration of 1 g of MPI with 10 ml of different quinine HCl solutions. The suspensions were sealed in glass vials and rotated at 15 rpm in a water bath at 25°C. After 8 hr, the vials were centrifuged, and the supernatant was assayed for quinine by UV spectroscope as described below.

Preparation, Analysis, and Characterization of Quinine Adsorbed System

Quinine HCl was adsorbed from 100 ml of a 0.05 M solution on to 5 g of MPI at 37°C. After an 8-hr equilibration period the suspension was vacuum filtered and washed with 50 ml of warm distilled water. The powder was vacuum dried at 20°–25°C for 12 hr, lightly ground, and passed through a 75-μm sieve. The powdered complex (Q-MPI) was stored in a dessicator at 20°C.

Accurately weighed quantities (about 100 mg) of the Q-MPI were dissolved with the aid of gentle heat in 20 ml of 0.1 M HCl solution before being quickly cooled and diluted to 50 ml with 0.01 M HCl solution. This solution was further diluted with 0.01 M HCl and analyzed by UV spectroscopy to determine the quinine content of the Q-MPI. The UV spectra of the solutions were identical with samples of the pure drug.

Scanning electron microscopy (Phillips Model 505, Phillips Industries, Holland) was performed on the MPI and Q-MPI in both the powder form and as compressed disks.

Release Determination Procedures

Accurately weighed quantities of Q-MPI as loose powder (about 220 mg) were dispensed into 10-ml glass vials and were subjected to two different tests. The vials were rotated at 15 rpm in a constant temperature bath at 37°C.

1. The samples were equilibrated with solutions of sodium chloride over a concentration range of 0–0.1 M at a constant pH of 1.8 for 6 hr.
2. The powder samples were equilibrated for 18 hr with solutions in which the sodium chloride concentration was 0.025 M and the pH was adjusted over a range of 6.0 to 1.72 by adding small volumes of a 1 M HCl solution.

As well, the required weights of the Q-MPI were compressed in a hydraulic press (RIIC, England) and IR punch and die set (Beckman–RIIC, Scotland) at a pressure of 187 MPa for 2 min. The disks were subject to dissolution testing immediately. Dissolution was measured by placing the disks in a rotating basket (Erweka DT-D, Erweka-Appartebau, Germany). The rate of revolution employed was 50 rpm and the temperature was 37°C. The media used were: (a) aqueous solutions of sodium chloride at pH 6, and (b) modifications of Gastric Fluid, Simulated, TS (USP) without pepsin in which the concentration of sodium chloride was varied. The volume of medium was 900 ml, and the sample aliquots (which were replaced) of 1 ml were diluted with 0.01 M HCl before assay by UV spectroscopy.

Analytical Procedure

All samples were diluted in 0.01 M HCl and analyzed by UV spectroscopy (Pye PU8600, Pye Unicam, England) at 318 nm. It had been previously determined that quinine obeyed Beer's law over the range of 0–0.24 μmol ml^{-1}, and that the MPI did not interfere with the measured absorbances at the concentrations present during the adsorption or release studies.

RESULTS AND DISCUSSION

Adsorption Isotherm

The isotherm for quinine on MPI at 25°C is shown in Figs. 1(a) and 1(b). The data shown in Fig. 1(a), adsorption density (i.e., x/m, expressed as micromoles quinine adsorbed/gram of MPI) plotted against the equilibrium concentration of quinine (expressed as micromoles/milliliter), were plotted according to the linear form of the Langmuir isotherm shown in Eq. (1).

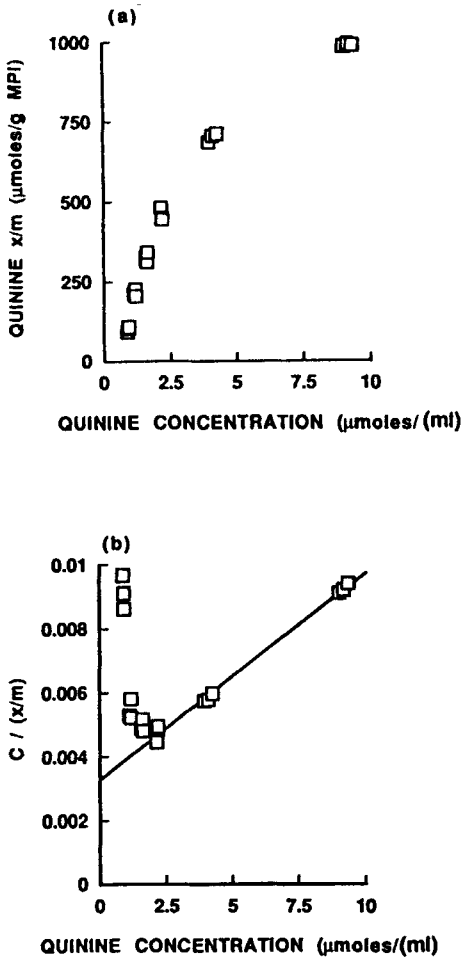

Figure 1. (a) The adsorption isotherm of quinine HCl on to MPI in water at 25°C. Triplicated data are shown. (b) The adsorption isotherm of quinine HCl on to MPI "linearized" according to the Langmuir isotherm shown in Eq. (1).

$$C/(x/m) = C/Q_{max} + 1/(KQ_{max}) \quad (1)$$

where K is the adsorption affinity parameter with units of reciprocal concentration and Q_{max} is the estimated maximum adsorption density. The "linearized" results are shown in Fig. 1(b). It is clear that at concentrations less than 2.5 μmol/ml the data do not conform to the Langmuir model. This suggests that the adsorption pro-

cess is cooperative and that at low equilibrium concentrations the adsorption densities are less than the Langmuir model predict. The linear portion of the plot (with the positive slope) indicates that Q_{max} has a value of about 780 μmol/g MPI. Clearly this value of Q_{max} underestimates the adsorption densities which are attainable since Fig. 1(a) shows that the maximum density attained was about 980 μmol/g MPI. The latter density corresponds to a drug load of about 28% w/w.

Sample Characteristics and Extraction from Loose Powder

The dried and powdered sample Q-MPI contained a 26.9% w/w loading of quinine, which is very close to the maximum loading shown in the isotherm above. Therefore 220 mg of Q-MPI contain almost 60 mg of active drug. Scanning electron micrographs of both the MPI and the Q-MPI as loose powder showed no sign of any surface alteration due to the adsorption of the quinine on to the MPI.

Based upon preliminary experiments, an equilibration period of 6 hr was chosen to assess the influence of sodium concentration on the extraction of drug from Q-MPI at a constant pH of 6 at 37°C. The results are presented in Fig. 2, in which, for ease of plotting the wide range of sodium ion concentrations, the pNa, and not molarity, is employed. The pNa is defined as $-\log_{10}[S]$, where [S] is the molar concentration of sodium chloride.

The maximum extraction of quinine at pNa 1.12 (i.e., 0.075 M) was 21.4%. About 5–6% of the quinine was extracted at pH of 6.0 and pNa greater than 1.6. The coefficient of variation of triplicate determinations of the extractions was 0.4%. The good reproducibility may be due to the fact that the Q-MPI did not aggregate. When the pH is near neutral and dissolution is negligible, the extraction of drug is dictated by ion-exchange processes.

Figure 2 also shows the effect of varying the pH at a constant pNa of 1.602 (0.025 M). The low concentration of sodium was chosen since this will contribute minimally to the extraction process. At pH less than 5, the Q-MPI became very adhesive and aggregated readily. To compensate for the adhesion and aggregation, the equilibration time was increased to 18 hr. Below pH 3, the extraction of quinine increased quite dramatically; at a pH of 1.7, the extraction of quinine was 70.9%. At pH greater than 3.5, extraction of quinine was essentially constant at about 6–8%. Clearly, the extraction of quinine is more profoundly influenced by low pH than pNa. This is because the powder undergoes acid-induced dissolution.

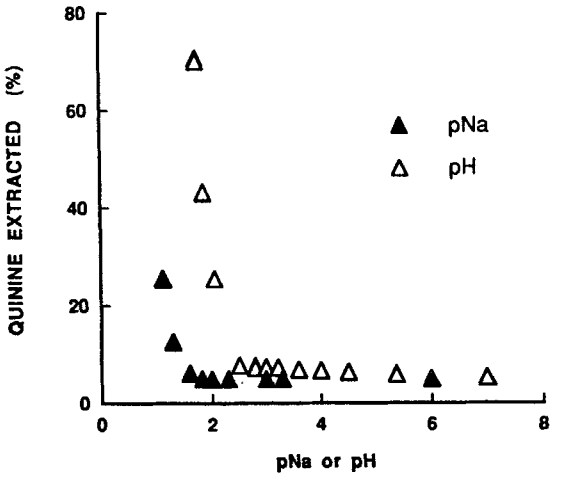

Figure 2. The percentage of quinine extracted from 220 mg of Q-MPI at 37°C. When the pNa was varied, pH was constant (=6) and equilibration time was 6 hr. When the pH was varied, the sodium concentration was constant (=0.025 M; i.e., pNa 1.601) and equilibration time was 18 hr. Triplicated data are shown.

Release from Compressed Disk in a Neutral Medium

Figure 3 shows the release profiles of quinine from disks into aqueous solutions of sodium chloride (0–

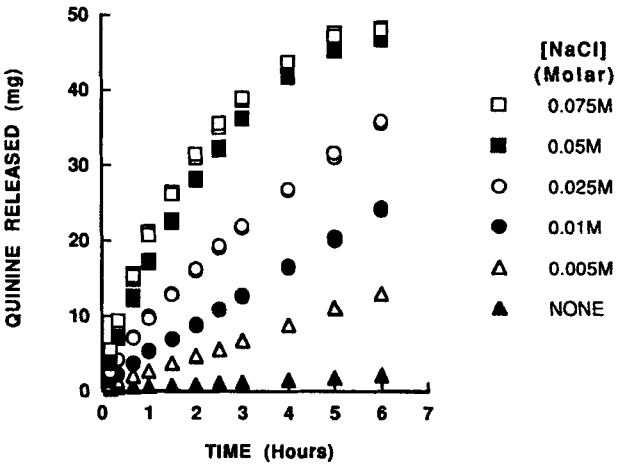

Figure 3. The effect of variation in sodium concentration (over the range of 0–0.075 M) on the release of quinine from discs of Q-MPI (220 mg, compressed at 187 MPa), at pH 6 and 37°C. Triplicated data are shown.

0.075M) at a pH of 6. The release into near-neutral solutions increases with the sodium ion concentration. At low concentrations of sodium chloride the release is apparently zero-order, but not at higher concentrations of sodium chloride. The same data were redrawn in Fig. 4(a), and the linearity of all the plots suggests that the release process is first-order. From data in the excellent review presented by Osterheld (17) on the nonenzymic hydrolysis of polyphosphates, it is apparent that sodium has no effect on the hydrolytic breakdown of long-chain polyphosphates. Furthermore, from the half-lives and activation energies (presented at 60°C) a calculation based on the Arrhenius theory indicates that the half-life of hydrolytic breakdown of very long polyphosphates is greater than 1000 hr at a near-neutral pH. Since the solubility of the polyphosphates is largely related to chain length (18), it is very likely that dissolution and hydrolysis are intimately linked. At low ionic strengths (<0.025 M) there was no perceptible dissolution of the disk, but there were visible suspended particles of MPI. In a neutral environment, the release of drug is probably due to ion exchange and was not augmented by dissolution of the carrier.

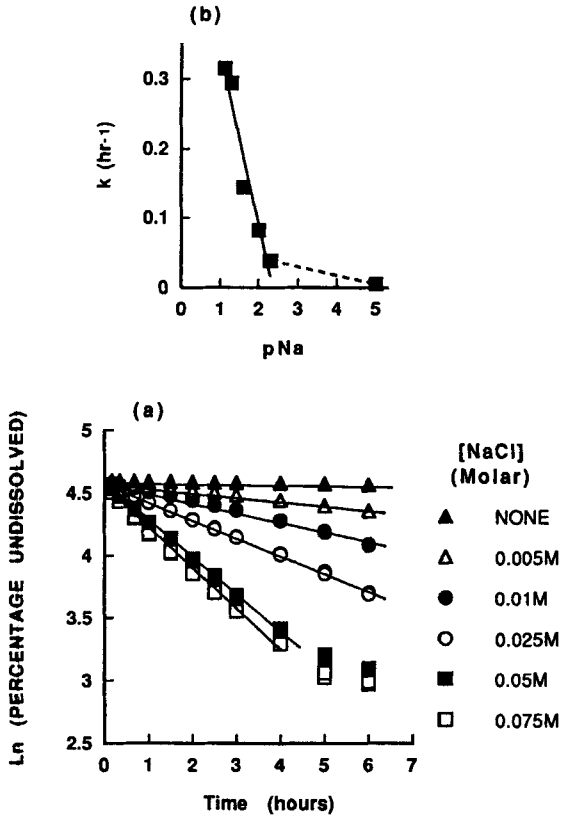

Figure 4. (a) First-order plots of the percentage of quinine unreleased from disks of Q-MPI (220 mg, compressed at 187 MPa) at pH 6 and 37°C. The concentration of sodium ranged from 0 to 0.075 M. Triplicated data are shown. (b) The first-order rate constants plotted against the pNa. The value when no sodium was added is arbitrarily plotted at pNa = 5.

Since ion exchange is a stoichiometric process, the release of quinine would be expected to be first-order and to be enhanced by an increase in the ionic strength of the dissolution medium. In Fig. 4(b), the first-order rate constants are plotted against the pNa of the dissolution medium, showing an apparent linear relationship between release rate and pNa. The rate constant in water ([Na] = 0) is arbitrarily plotted at a pNa of 5. The results in Fig. 4(b) correlate with those in Fig. 2, in that both show a marked increase in release at low pNa.

At low ionic strengths, there was minimal attrition of the disks which would result in only a slight reduction of the surface area at which ion exchange occurred. This probably accounts for the apparent zero-order release. As the ionic strength was increased, the disks appeared to suffer greater abrasion and ultimately disruption of their integrity. Compressed disks of pure MPI readily disintegrated under similar conditions of pH and ionic strength. It appears that the Q-MPI is very cohesive and produced a more stable disk, which as it was converted to MPI (due to ion-exchange-mediated release of quinine) became more unstable and prone to abrasion.

Some disks of Q-MPI or MPI were prepared, and it was shown that while the breaking strength of the MPI disks was about 2–3 kg, the Q-MPI disks remained intact at 15 kg. Clearly, the Q-MPI disks are sustantially stronger than the MPI disks.

Release from Compressed Disks in an Acidic Medium

Figure 5(a) shows the quinine release profiles obtained with Q-MPI disks in modified (no pepsin) Gastric Fluid Simulated TS (USP) with variable concentrations of NaCl. The release of quinine was initially quite rapid, but after about 30 min, decreased to a constant rate which was maintained for some 3–5 hr. In contrast to the results presented above in Figs. 4(a) and 4(b), the release of quinine is suppressed by an increase in ionic strength (decreased pNa) and Fig. 5(b) indicates that the zero-order rate constant may be linearly related to the pNa of the dissolution medium. The disks became very adhesive to touch and seemed to have a soft gel layer on their surface after they had been exposed to the acidic environment for about 15 min; the disks remained

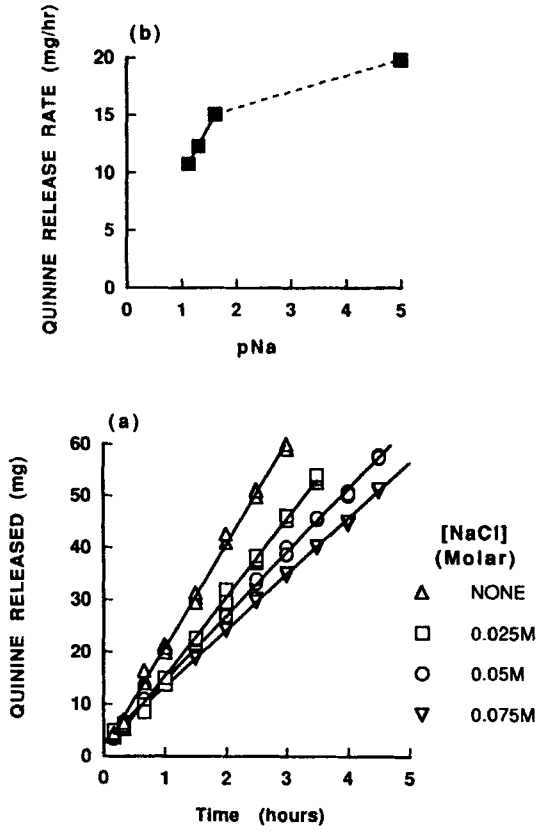

Figure 5. (a) The effect of sodium ion concentration on the release of quinine from disks of Q-MPI (220 mg, compressed at 187 MPa). The temperature was 37°C and the dissolution medium had a pH of 1.26. Triplicated data are shown. (b) The zero-order release rate constants (mg/hr) plotted against the pNa. The value when no sodium was added is arbitrarily plotted at pNa = 5.

nonadhesive in the neutral medium. Although the disks progressively dissolved, they maintained their structural integrity in the acidic medium for several hours before they broke up and completely dissolved. It is not known whether the gel layer is progressively sloughed off, or whether there was substantial conversion of the disk to gel before it was abraded. The initial "burst" may be due to ion-exchange-mediated release before the gel layer forms.

A comparison of the release profiles shows that the release of quinine in both acidic and neutral medium depends on the ionic strength. When there is no sodium chloride present, the rates of release are very different, but as the ionic strength is increased the profiles approach each other. When 0.075 M of sodium chloride is present, the rate of release of quinine in the neutral medium is greater than in the acidic medium, but over the time scale studied, release in the neutral medium is only about 80% complete.

The release profiles of quinine in an acidic medium shown in Fig. 5(a) are probably due to different (possibly conflicting) chemical and physical mechanisms. There will be an ion-exchange component, which presumably will be first-order and through which an increase in ionic strength would act to increase release. However, the acidic conditions will markedly increase the rate of hydrolysis of MPI and result in dissolution of the carrier. From the data presented in the review by Osterheld (17), it can be calculated that the overall half-life of polyphosphate hydrolysis is about 2.1 hr at 37°C and pH 1. This correlates well with our observation that the disks extensively dissolved in the acidic medium over about 3–5 hr. Although sodium does not specifically influence the rate of hydrolysis of polyphosphates (17), the increase in ionic strength may suppress the hydrolysis nonspecifically. Therefore, since the net release curves in Fig. 5(a) are linear with time and show that increased sodium concentrations suppress release, we conclude that the suppression of hydrolysis due to increased ionic strength and the almost constant surface area of the intact disks are the dominant factors in controlling release in acidic media.

CONCLUSIONS

Quinine is adsorbed extensively and fairly rapidly on to Maddrell's phosphate type II. We have shown that the release of quinine from Q-MPI adsorbed systems as loose powder and compressed disks depends upon both the pH and ionic strength of the medium. The compressed disks of the adsorbed systems possess greater strength than those of pure Maddrell's phosphate type II.

Our research demonstrates some of the unusual physical properties and the potentially useful release characteristics of the adsorbed systems. Although the release mechanisms remain to be fully elucidated, it is apparent that these systems deserve further investigation to establish whether a broader range of cationic drugs can have their release sustained by the same means. Further work toward this goal is being undertaken.

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