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COMMUNICATION

Studies of Ion-Exchange Resin Complex of Chloroquine Phosphate

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ABSTRACT

High-potency adsorbates of chloroquine phosphate (CQP) were prepared by the batch method using a polyacrylic acid ion-exchange resin. Taste evaluation of the adsorbates shows significant masking of the bitterness of the drug. The complex formation was complete at pH 6.0. Stability studies at 37°C, 45°C, and 60°C indicated that the complex was stable at all conditions for 1 month. In vitro release studies revealed complete drug elution from the complex at pH 1.2 and 2.0.
Key Words: *Chloroquine phosphate; Drug release; Ion-exchange resin; Stability; Taste masking.*

INTRODUCTION

The breadth and scope of ion-exchange resins (IERs) seem inexhaustible: Their use as solid insoluble chemicals in the manufacturing industries is growing with today's search for improved processing methods. Use of IERs in drug formulations for stabilization of sensitive components (1), taste masking (2–4), sustained release of drug (4), and as tablet disintegrants (5,6) is described.

IERs are water-insoluble, cross-linked polymers containing salt-forming groups in repeating positions on the polymer chain. Drug is bound to the resin by repeated exposure of the resin to the drug in a chromatographic column or by prolonged contact of the resin with the drug solution. The resins form insoluble adsorbates or resinates through weak ionic bonding with oppositely charged drugs. Drug release from the drug resin complex depends on the ionic environment (i.e., pH and electrolyte concentration) within the gastrointestinal (GI) tract, as well as the properties of the resin (4,7).

Drug molecules attached to the resin are released by exchanging with appropriately charged ions in the GI tract (depicted in Eqs. 1 and 2), followed by diffusion of the free drug molecule out of the resin (8).

$$\text{Resin}^+ - \text{Drug}^- + x^- \rightarrow \text{Resin}^+ - x^- + \text{Drug}^- \quad (1)$$

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or

$$\text{Resin}^- - \text{Drug}^+ + y^+ \rightarrow \text{Resin}^- - y^+ + \text{Drug}^+ \quad (2)$$

where x^- and y^+ are ions in the GI tract.

In this paper, we deal with taste masking of chloroquine phosphate (CQP), which is a commonly used antimalarial drug that has an intense bitter taste. There are literature reports on the interaction of amine drugs with polycarboxylic acid ion-exchange resin (2,9) that indicated these resins might be very useful in taste masking. One study indicated that saliva, with an average pH of 6.7 and a cation concentration of 40 meq/L (2), would only elute a few percent of drug from polycarboxylic acid resin adsorbate. These studies also revealed that drugs containing a tertiary amino group give much higher selectivity coefficients than those with primary, secondary, or quaternary amines (10). Thus, taste coverage should be more efficient with tertiary amine drugs same being the case with CQP. The complex is, however, weak enough to be broken down by gastric juice present in the stomach. While passing through the mouth, the drug remains in the complex form; there is very little or no taste. We selected weak acid cation-exchange resin because of the exchangeable cationic moiety of the drug (11,12).

EXPERIMENTAL

Materials

For the cation-exchange resin, a polyacrylic acid ion-exchange resin with a particle size of 72–147 μ, a matrix of cross-linked acrylic copolymer having exchangeable potassium of 5.25 meq/g was purchased from Ion Exchange (I) Limited. Also used were chloroquine phosphate USP and hydrochloric acid AR grade.

Adsorbate Preparation

For the preliminary study, we optimized the ratio of resin to drug at 2:1. An accurately weighed amount of resin (3 g) was added to demineralized water (25 ml), and the pH was adjusted to 4, 4.5, 5, 5.5, 6, 6.5, 7, and 8 for different samples. The drug (1.5 g) was added, and the slurry was transferred to 100-ml volumetric flasks. The samples were kept in a water bath shaker for 1 hr at a constant temperature of 30°C. At the end of 1 hr, samples were filtered and washed with demineralized water to remove the free drug; the wet adsorbate was transferred to glass pans. It was then dried in a vacuum oven at 50°C to a constant weight.

Assay

An accurately weighed amount of complex was transferred to a 50-ml volumetric flask; the volume was made with 5 N HCl to break the complex. The volumetric flask was kept in a sonicator for 30 min. The samples were diluted suitably and filtered, and absorbance was measured at 343 nm.

Temperature Effect on Formation of Complex

Adsorbate was prepared at different temperatures (i.e., 25°C, 30°C, 35°C, 45°C, and 60°C) with 1 hr shaking at a constant pH of 6.0.

Stability Studies of Complex

The complex was kept at different temperatures (i.e., 37°C, 45°C, and 60°C) for 1 month and assayed.

Taste Evaluation

Bitterness was measured by consensus of a trained taste panel (13), with 20 mg of each sample held in the mouth for 5 to 10 sec, than spat out; the bitterness level was then recorded. A numerical scale was used with the following values: 0 = tasteless, 0.5 = very slight, 1.0 = slight, 1.5 = slight to moderate, 2.0 = moderate, 2.5 = moderate to strong, 3 = strong, and 3+ = very strong.

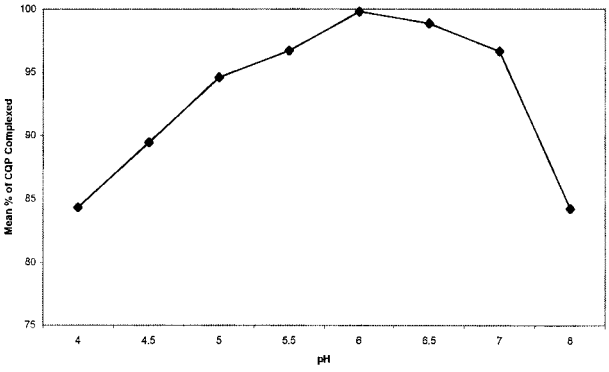

Figure 1. Effect of pH on amount of chloroquine phosphate exchanged.

Table 1

Bitterness Evaluation by Taste Panel

	1	2	3	4	5	6
Pure drug	3+	3+	3+	3+	3+	3+
Adsorbate (5 sec)	0.5	0.0	0.0	0.5	0.5	0.0
Adsorbate (10 sec)	0.5	0.0	0.5	1.0	0.5	0.0

In Vitro Release Study

Drug release was determined by adding adsorbate equivalent to 100 mg of drug to 900 ml of dissolution medium in a USP 23 dissolution apparatus using a paddle at 100 rpm. The dissolution medium of varied pH (i.e., 1.2, 2, 3, 4) was used, and samples were withdrawn at suitable time intervals. The filtrates were then assayed by UV spectroscopy.

RESULTS

It is evident from Fig. 1 that, with increasing pH up to 6, the complex formation increased, and it decreased at higher pH. Complexation up to 98% was obtained in the pH range of 5.5 to 6.5. Since complete formation of complex occurred at all studied temperatures, it can be inferred that complex formation was independent of temperature. Further, stability studies of drug resin complex up to 1 month showed that the complex was stable at varied temperatures.

Bitterness Evaluation

Bitterness evaluation results made by the consensus of trained persons are listed in Table 1. The table shows that there is very little or no bitterness imparted with adsorbate with reference to pure drug since a person is not able to keep the pure drug in the mouth even for 5 sec.

In Vitro Release

Figure 2 shows that drug release from the complex was 100% within 5 min at pH 1.2, while the same occurred in 10 min at pH 2.0. The release was slightly slow at pH 3; at pH greater than 4.0, no release of drug occurred. This suggests that, in the mouth, there should be no release of drug, and IER was proved effective in taste masking of CQP.

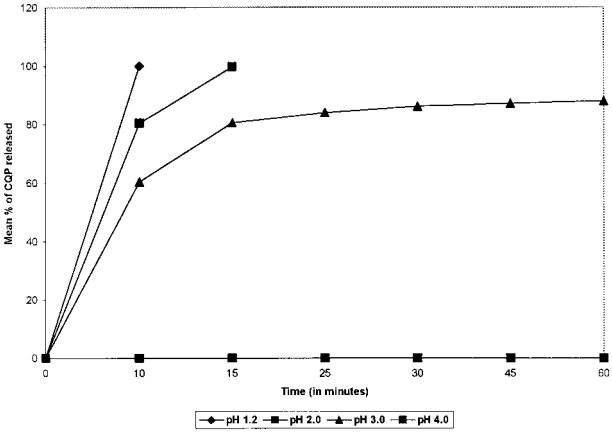

Figure 2. Influence of pH on in vitro release of chloroquine phosphate from the drug resin complex.

CONCLUSIONS

The drug resin complex was stable at pH 4.0 to 7.0. There was complete taste masking of CQP by suitable IERs. The study also suggests that an ion-exchange resin system is a useful alternate for palatable suspensions and various other oral dosage forms. The results of this study can be extrapolated to other intensely bitter drugs by suitable selection of IERs.

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