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# DESIGN AND CHARACTERIZATION OF SEVELAMER HYDROCHLORIDE: A NOVEL PHOSPHATE-BINDING PHARMACEUTICAL

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## ABSTRACT

Sevelamer hydrochloride (polyallylamine crosslinked with epichlorohydrin) is a polymeric hydrogel that has been developed as an oral pharmaceutical to prevent the absorption of dietary phosphate by kidney dialysis patients. It has been found to bind to phosphate *in vitro*, and to do so more effectively than a wide range of other cationic polymers. It shows a preference for phosphate over other intestinal anions, such as chloride and bicarbonate. The preference for phosphate is believed to be due to its dianion character, and may also involve hydrogen bonding. The absorption of phosphate *in vitro* is rapid (less than a minute) relative to the time of passage of such a drug through the small intestine (hours). It has also been found to prevent the absorption of dietary phosphate *in vivo* and in humans, and is presently awaiting FDA approval.

## INTRODUCTION

Elevated serum phosphate levels are a significant problem for patients with renal failure. Current treatments effectively prevent the uptake of dietary

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phosphate through formation of insoluble calcium or aluminum phosphates in the gastrointestinal tract [1]. Unfortunately, these treatments can lead to undesirable serum levels of either calcium or aluminum. In order to prevent absorption of dietary phosphate without these drawbacks, we have developed a crosslinked organic polymer that is capable of binding phosphate in the gastrointestinal tract.

Sevelamer hydrochloride consists of polyallylamine that has been crosslinked with epichlorohydrin to form a hydrogel. Under physiologic conditions, both *in vitro* and *in vivo*, this polymer has been shown to bind significant quantities of phosphate [2, 3]. It has also been shown to be an effective treatment for hyperphosphatemia in human clinical trials, and is presently awaiting FDA approval [4]. Since it is a crosslinked hydrogel that cannot be absorbed from the gastrointestinal tract, the possibility of toxic side effects are greatly reduced compared to systemic medications.



During the discovery phase of sevelamer hydrochloride, a large number of cationic polymers were investigated. Sevelamer hydrochloride was found to be the most potent of these phosphate-binding polymers under physiologic conditions.

It is believed that two of the most important criteria in developing a phosphate binding polymer as a pharmaceutical are the number of positive charges per unit weight, and the spacing between those charges. The number of charges is important in order to keep the required human dose from becoming too large (more than a few grams per day). The spacing is important in order to permit a preference of the polymer for phosphate over the much higher concentrations of chloride and other ions present in the gastrointestinal tract.

## EXPERIMENTAL

Polyallylamine hydrochloride was polymerized from allylamine hydrochloride in water using azobis(amidinopropane) dihydrochloride as the initiator [2]. Polyallylamine was crosslinked with epichlorohydrin (at various levels) in aqueous solution, and then washed with water to remove any residual impurities [2]. Other polymers were also synthesized as described previously [2].

Phosphate binding isotherms were carried out in aqueous solution containing 80 mM sodium chloride, 30 mM sodium carbonate, and the desired level of phosphate as phosphoric acid. The polymer (0.10 g) was added to the solu-

tion (20 mL), and the mixture was adjusted to pH 7 (or other pH as noted) with conc. HCl or 50% aqueous NaOH as necessary. After stirring for 1 hour, the pH was again adjusted, if necessary, and the gel was removed by filtration.

Kinetics experiments were carried out by placing the polymer (0.2 g) in a solution containing 100 mM NaCl and 24 mM phosphate at pH 7.1 (100 mL). The mixture was stirred for various lengths of time, and the polymer removed by passing the solution through a syringe filter. The solution was then analyzed for phosphate.

The liquid samples were analyzed for phosphate spectrophotometrically using a standard molybdate assay [5]. In the case of isotherms, the results were then plotted as millimoles of phosphate bound per gram of polymer (determined by difference from the starting solution), vs the unbound phosphate concentration.

## RESULTS AND DISCUSSION

The phosphate-binding isotherm for crosslinked polyallylamine is shown in Figure 1. The amount of phosphate bound is a strong function of the unbound phosphate concentration, rising to about 2.7 mmoles/g at 5 mM phosphate (a typical physiologic concentration of phosphate in the intestine).

### pH Effects

The amount of phosphate bound by crosslinked polyallylamine is dependent upon the pH of the solution. Figure 2 shows the relationship between the

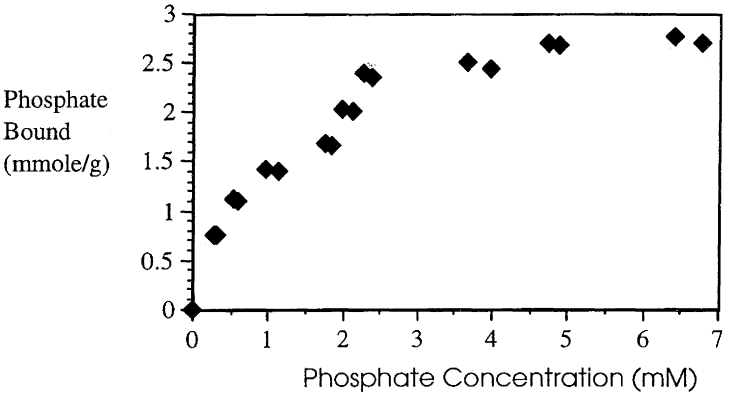


**Figure 1.** Phosphate binding isotherm for 12 mole percent crosslinked polyallylamine at pH 7.

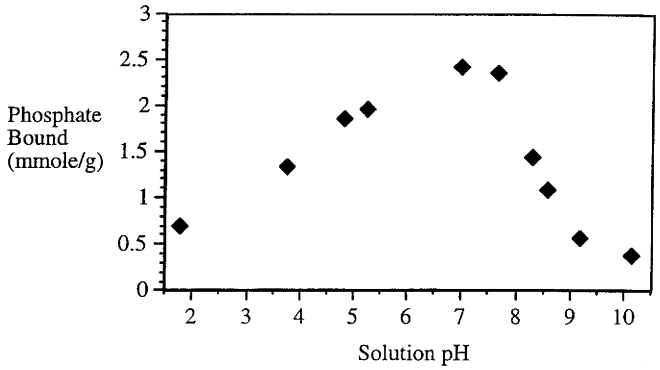


**Figure 2.** Phosphate binding as a function of pH for crosslinked polyallylamine when 0.1 g of polymer is added to 20 mL of 20 mM phosphate solution.

solution pH and the amount of phosphate bound when 0.1 g of polymer is added to 20 mL of 20 mM phosphate. The binding clearly shows a maximum between pH 6 and 8, and is significantly lower above and below this range.

One straightforward interpretation is that above pH 7 the polymer exists as a mixture of the free amine and the amine hydrochloride. An acid/base titration of the crosslinked polymer (Figure 3) indicates that the protonation of the amines takes place over the broad pH range of 7-12. As the pH is raised, more and more of the amines are present as the free amine, and are unable to act as counterions for phosphate. Consequently, the binding of phosphate is reduced at elevated pH.

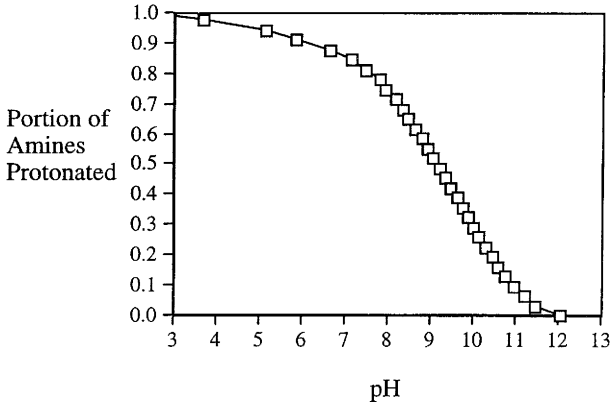


**Figure 3.** Portion of amines protonated in polyallylamine crosslinked with epichlorohydrin as a function of the solution pH. The portion protonated was determined by aqueous pH titration.

Likewise, below pH 7, the phosphate ion will begin to exist primarily in the monoanion form, rather than the dianion. We speculate that it is the dianion that binds to the polymer, and that reducing the concentration of the dianion by reducing the pH has the effect of reducing phosphate binding.

Further, we believe that it is the dianion character of phosphate that permits it to be bound so strongly by this and other polycations (perhaps in conjunction with hydrogen bonding to other parts of the phosphate). Monoanions, such as chloride, are unable to interact with multiple cationic sites, and are more weakly bound. The data in Figure 1 actually represent a competition between phosphate and the monoanions chloride and bicarbonate. In Figure 1, when $[PO_4^{3-}] = 5$ mM the phosphate comprises only 4.3% of the total anions (with the remainder being chloride and bicarbonate), and yet the phosphate occupies between 25 and 50% of the available cationic sites (depending upon whether it is believed that each phosphate occupies one cationic site or two).

The spacing between the negatively charged oxygen atoms in a phosphate dianion is about 2.5 Å. The spacing between positive charges in polyallylamine is variable, but molecular models show that it can match this value (2.5 Å) in certain configurations. Consequently, the phosphate dianion can readily interact with two cationic sites at a time.



## Other Polymers

We have also examined a wide range of other polymers as potential phosphate binders. Table 1 shows the amount of phosphate bound (at 5 mM unbound phosphate) for some of these polymers. In each case, an isotherm similar to Figure 1 was determined, and the amount of phosphate bound at 5 mM was determined.

From these and other polymers examined, it appears that quaternary amines are especially not useful for binding phosphate. In a number of cases,

TABLE 1. Phosphate-Binding of Various Polymers at 5 mM Phosphate

| Polymer | Phosphate Bound (meq/g) |
|---|---|
| Polyallylamine/epichlorohydrin | 3 |
| Polyethyleneimine/acryloyl chloride | 1.2 |
| Diethylenetriamine/epichlorohydrin | 1.5 |
| Poly(dimethylaminoethylacrylamide) | 0.8 |
| Poly(trimethylammoniomethylstyrene chloride) | 0.7 |
| Poly(allyltrimethylammonium chloride) | 0.3 |

such as with polyallylamine and poly(allyltrimethylammonium chloride), we have made the same polymer with and without quaternization of the amines present. In every case, the binding of phosphate is significantly reduced upon quaternization. In the case above, it is reduced far more than the simple diluent weight of the three methyl groups and the chloride ion would predict. We believe that the poor binding provided by quaternary amines may stem from their inability to engage in hydrogen bonding with the phosphate ion.

### Kinetics

The kinetics of binding of phosphate to sevelamer hydrochloride is shown in Figure 4. In this case, the polymer is added to a phosphate-containing solution, and the free phosphate concentration is monitored. For this polymer, the binding of phosphate is faster than the experiment can be carried out (30 seconds).

The final amount of phosphate bound after 17 hours corresponds to 6.4 mmoles/g, at a final phosphate concentration of 11.4 mM. Similar experiments carried out at lower initial phosphate concentrations show similarly rapid kinetics. Consequently, the kinetics of phosphate binding is far faster than the transit times through the gastrointestinal tract (hours) and can safely be ignored with respect to human efficacy.

## CONCLUSION

Crosslinked polyallylamine is a potent phosphate binding polymer, and is well suited for use as a pharmaceutical. It shows maximum phosphate bind-

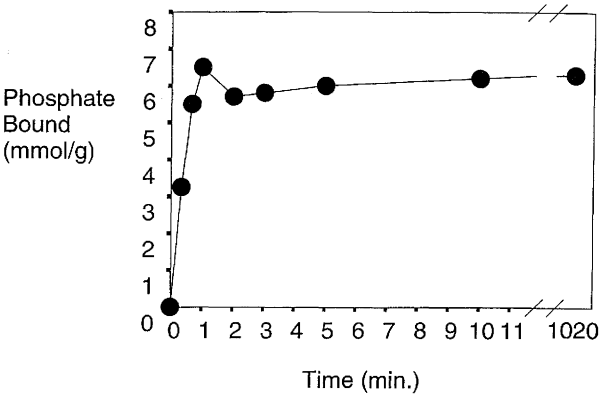


**Figure 4.** Free (unbound) phosphate concentration as a function of time after sevelamer hydrochloride is added to a phosphate-containing solution.

ing in the pH range present in the small intestine, it binds more phosphate than other polymers under physiologic conditions, and is essentially nontoxic as it is a nonabsorbed hydrogel. It has a preference for phosphate over other ions in the gastrointestinal tract (such as chloride and bicarbonate), which is probably due to the fact that phosphate, being a dianion, can interact with two of the cationic sites at a time. Hydrogen bonding between the polymer and the phosphate ion may also be important for binding.

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