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Report

Adsorption of Inorganic and Organic Ions to Polycarbophil as a Means of Sustained-Release Dosage Formulation

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The adsorption and desorption of drugs and inorganic ions to and from polycarbophil (PC), a polymer, were investigated to determine if PC would be a suitable carrier for sustained-release dosage formulations. Both *in vitro* and *in vivo* experiments with a polycarbophil–atropine sulfate complex demonstrated the gradual-release properties of this system. Adsorbed Cr^{3+} ions, like atropine, are released slowly. In contrast, $^{51}CrO_4^{2-}$ ions are predominantly bound in an irreversible manner. A third group of drugs minimally adsorbed to PC under the conditions studied. We conclude that PC under both *in vitro* and *in vivo* conditions is able to bind certain ions and drugs and then release them over a period of time in a predictable and repeatable manner.

KEY WORDS: polycarbophil; sustained release; adsorption; polymer.

INTRODUCTION

The concept of preparing a sustained-release dosage formulation of a drug by binding it to a polymer such that the drug is slowly leached from the polymer is well known (1). Examples of this principle include ion-exchange resins, biodegradable polymers, and some bioerodible polymer dosage forms. In each case, a large molecule is used as a support for a small releasable molecule. When placed in aqueous solution, the small molecule is released into solution in a sustained and controlled manner.

Polycarbophil (PC) is a hydrophilic polymer. It has both laxative and antidiarrheal properties (2) by virtue of its ability to absorb and hold water. PC consists of repeating subunits of *n*-butyric acid, polymerized at the 2 and 4 positions. It swells when mixed with water to yield hydrated, separable, gel-like particles. The amount of water that a given quantity of dry polycarbophil will absorb is dependent upon the pH and ionic strength of the hydrating solution. During hydration, polycarbophil is capable of adsorbing certain ions irreversibly (3).

The present studies were performed to characterize the adsorptive properties of PC; the compound was also examined with regard to its potential usefulness as a support matrix for sustained drug release (patent applied for by Wisconsin Alumni Research Foundation).

MATERIALS AND METHODS

In Vitro Experiments

The initial experiments involved adsorption of radioactive chromium (^{51}Cr) to the acid form of polycarbophil (PC; gift from A. H. Robins Co., Richmond, Va.) followed by successive rinses to determine if the ligand could be easily removed. Experiments were conducted using both $^{51}CrCl_3$ and $Na_2{}^{51}CrO_4$. The method for quantitation of $Na_2{}^{51}CrO_4$ adsorption and desorption has been published (3). This same procedure was used in experiments involving $^{51}CrCl_3$. Briefly, the PC was hydrated in saline containing the radioactive salt for 1 hr and a sample of the hydrated PC was collected. The remainder of the gel was stirred in 300 ml of nonradioactive saline for 2 hr. The filtering–sampling–washing process was repeated at intervals of 1, 2, 4, 6, 8, and 10 hr after the initial hydration. The samples taken were dried and the radioactivity per gram of PC (dry weight) remaining was expressed as a percentage of the activity originally associated with the unrinsed polymer.

Experiments were also conducted to measure binding and release of atropine sulfate (Sigma Chemical Co., St. Louis, Mo.) to and from PC. Adsorption was studied by dissolving a known quantity of the drug in 50 ml of pH 7.0 phosphate buffer solution (3.68 g NaH_2PO_4 and 5.68 g Na_2HPO_4 per liter) and using this solution to hydrate 0.250 g of PC. This mixture was stirred on a magnetic stirrer for 30 min and the PC was collected by filtration. A sample of the filtrate was collected and the weight of the adsorbed drug was calculated after the concentration of the filtrate was determined using UV spectrophotometric analysis.

A binding isotherm for atropine sulfate was determined as follows. Fifty-milligram samples of PC were hydrated at room temperature with 10 ml each of atropine sulfate solutions of six different concentrations. The mixtures (which had been allowed to reach equilibrium) were then filtered through a Millipore filter, and the filtrates were analyzed spectrophotometrically for atropine sulfate concentration.

To measure the rate of atropine release, 0.375 g of PC was hydrated in 75 ml of 1.6×10^{-2} *M* atropine sulfate in phosphate buffer for 30 min. The mixture was filtered, and

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the gel was rinsed, filtered again, and dried. The amount of adsorbed atropine was calculated. After the dry gel was weighed, 0.190 g of the PC–atropine complex was placed in a stainless-steel U.S.P. dissolution basket, and the basket was submerged in a jacketed water bath containing 120 ml of phosphate buffer. The buffer was maintained at 37°C. The basket was suspended about 0.5 cm above the bottom of the beaker and was rotated at a constant rate of 80 rpm. Five-milliliter samples of the solution were removed at intervals of 1, 5, 10, 20, 30, 45, 60, 75, 90, 105, and 120 min, each being immediately replaced with 5 ml of fresh buffer. These samples were then assayed on a UV spectrophotometer at 257 nm to determine the amount of atropine in solution, which, after accounting for the drug removed in the samples, indicated how much atropine had been released at each time interval.

In Vivo Atropine Sulfate Experiments

A study involving rats was also utilized to demonstrate a sustained release of atropine from PC. Male rats (Sprague–Dawley, Madison, Wis.) weighing 135–150 g were anesthetized with ether and underwent celiotomy. A 5- to 7-mm incision was made in the duodenum and a No. 5 gelatin capsule containing the appropriate treatment was inserted. The incision was closed with 3-0 silk. The rats were deprived of food and water for the duration of the experiment.

The rats received one of three encapsulated treatments. The capsules contained either (1) atropine solution alone, (2) atropine solution plus 25 mg of dry polycarbophil (PC) granules, or (3) 25 mg of PC granules plus 0.1 ml of saline as a control. Atropine sulfate (5 mg/kg) was dissolved in 0.9% NaCl to provide the dose required in about 0.1 ml.

The duration of atropine release was assessed by monitoring the duration of mydriasis. The pupil diameter of each rat was estimated at 0.5, 1, 2, 4, 6, 8, 10, 12, 14, and 24 hr after dosing.

RESULTS

In Vitro Study

The *in vitro* experiments indicated that the adsorbed cation, $^{51}Cr^{3+}$, was slowly released from the polycarbophil (Table I). The radioactivity per gram of gel decreased by about 20% with each successive rinse (mean percentage remaining after each rinse: 75, 59, 41, and 22). In contrast, repeated washed released only approximately 20% of the adsorbed anion, $^{51}CrO_4^{2-}$. The remaining approximately 80% appeared to be irreversibly bound (Table I).

The slow release of $^{51}Cr^{3+}$ from PC suggested that this system might be suitable for providing gradual release of drug molecules. Adsorption was attempted with pentobarbital sodium, atropine sulfate, sodium salicylate, caffeine, cimetidine HCl, and Mg $(OH)_2$. Of these drugs, only atropine sulfate exhibited significant adsorption under the conditions studied. Atropine was adsorbed in a predictable and consistent manner, although only about 15% of the drug present in the hydrating solution adsorbed to the polycarbophil. The binding data for the PC–atropine sulfate system are presented in Table II.

To measure the rate of *in vitro* atropine sulfate release, 0.190 g of PC–atropine sulfate complex (calculated to contain 34 mg of adsorbed atropine sulfate) was placed in a U.S.P. dissolution test basket, and the rate at which the drug came off the polymer was measured. The average results of two such experiments are shown in Table III.

In Vivo Study

The data from the atropine-induced mydriasis in the rat are presented in Table IV. Significant pupil dilation was still evident 14 hr after treatment of the rats with the PC–atropine mixtures. In contrast, rats treated with atropine sulfate solution alone exhibited mydriasis for a maximum of 4 hr. No appreciable mydriasis was evident after more than 24 hr in any treatment group.

DISCUSSION

Since polycarbophil is a polymer with repeating carboxylate groups, it might function as a cation exchanger. The adsorption and release of Cr^{3+} may be controlled by electrostatic interaction with the carboxylate groups, although some covalent character is probably present; complexes of Cr^{3+} with numerous carboxylates are known (4).

The binding of the chromate ion CrO_4^{2-} with polycarbophil appeared to be essentially irreversible. The mechanism of this process must be different from that for Cr^{3+}. In the chromate ion the metal is Cr (VI), and the structure is tetrahedral, all four oxygens being equivalent (5). It is known that chromate undergoes oxygen exchange with water (6) and that it is subject to acid-catalyzed nucleophilic substitution (7). The overall reaction of an anionic nucleophile X^- with chromate is

$$X^- + HCrO_4^- \rightarrow CrO_3X^- + OH^-$$

Table I. Effect of Successive Saline Rinses on the Radioactivity per Gram of $^{51}CrO_4^{2-}$- and $^{51}Cr^{3+}$-Labeled Polycarbophil Gel

	% of original radioactivity remaining (average of 3 experiments)	
Time (hr)	$^{51}CrO_4^{2-}$ [a]	Cr^{3+} [b]
0	100	100
1	90	75
2	86	59
4	86	41
6	81	22
8	77	—
10	80	—

[a] As Na_2CrO_4.
[b] As $CrCl_3$.

Table II. Binding of Atropine Sulfate to Polycarbophil at pH 7.0

Equilibrium drug concn. (*M*)	μg of drug bound/mg of polycarbophil
0.0042	115
0.0082	242
0.025	694
0.061	1260
0.087	1800
0.48	2857

Table III. Atropine Release from Polycarbophil: Atropine Complex Average of Two Trials

Minutes	Cumulative amount of atropine released (mg)[a]
1	0
5	0
10	7.5
20	25.5
30	27.1
45	30.7
60	32.2
75	32.8
90	33.1
105	33.3
120	34.0

[a] Corrected for 16 mg of drug that had been dissolved in the water of hydration and was therefore associated with the PC but was not adsorbed to it.

Among the nucleophiles that have been studied as reactants in this process are phosphate, thiosulfate, thiocyanate (8–10), and chromate itself (the product being the dichomate ion) (11,12). It seems possible that a similar reaction may take place between chromate and polycarbophil.

The drugs studied here included neutral, anionic, and cationic species. The only drug to show significant binding was atropine sulfate. This observation is not readily accounted for; the mechanism of small-molecule binding to polycarbophil is a major question that is beyond the scope of the present work.

Simply as a means of expressing the extent of atropine binding in a quantitative form (without suggesting stoichiometric or structural meanings), the data in Table II were fitted to the hyperbolic relationship

$$y = \frac{KYc}{1 + Kc} \quad (1)$$

where c is the equilibrium molar concentration of atropine in solution, y is the amount of drug bound (as micrograms per milligram of PC), K is an apparent binding constant having the units M^{-1}, and Y is the maximum binding capacity. Nonlinear least-squares regression by the method of Duggleby (13) yielded the parameters $K = 10.7 \pm 1.2\ M^{-1}$ and $Y = 3440 \pm 160$ μg/mg. These parameters satisfactorily reproduce the binding data when used in Eq. (1).

When the dry polycarbophil is hydrated to form a gel, the water of hydration (water associated with the gel) contains dissolved drug. The gel was rinsed once prior to drying, removing about 85% of the dissolved drug. The portion of dry PC–atropine complex used in the *in vitro* atropine release-rate experiments therefore contained about 16 mg of nonadsorbed atropine sulfate, in addition to the 34 mg of adsorbed atropine sulfate. The nonadsorbed atropine would have dissolved as soon as the polycarbophil was fully hydrated; all of it was accounted for in the first 5–10 min. About 50 mg of atropine sulfate eventually appeared in solution. Allowing for about 16 mg of nonadsorbed drug that appeared in solution within a few minutes, it can be seen in Table III that the adsorbed atropine was essentially released within 75 min in this assay.

Table IV. Effect of Polycarbophil (PC) on the Duration of Atropine-Induced[a] Mydriasis in the Rat

	Mean degree of mydriasis (hr)[b]									
Treatment	0.5	1	2	4	6	8	10	12	14	24
PC/saline	0	0	0	0	0					
Atropine soln.	3	3	3	1.3	0					
PC/atropine	2.9	3	3	2.9	2.6	2.6	2.3	2	1.8	0.5

[a] Atropine, 5 mg/kg body weight.

[b] Scale: 0 = pinpoint; 1 = <½ maximum; 2 = >½, <maximum; and 3 = maximum pupil dilation. N, six to eight rats per treatment.

It is unknown how closely the *in vitro* release system modeled drug release inside the intestinal tract of a rat, but it demonstrated that atropine adsorbed to polycarbophil is released over a significant period of time. It is clear that the apparent duration of atropine release in the rat was significantly longer than that measured in the *in vitro* system. This is an indication not that the *in vivo* assay is more sensitive but, rather, that the amount of free water available in the rat intestine for hydration and solubilization is much less (relative to the volume of the atropine–polycarbophil complex) than was present *in vitro*. Therefore, the rate at which the drug was leached from the polycarbophil was slower.

PC is retained in the stomach for a long time period (14) relative to other macromolecules such as guar gum and psyllium (15). Controlled-release properties of orally administered PC might therefore be manifested in a variety of ways. A drug coadministered with PC could adsorb to the polymer and be slowly leached from it. Even in the absence of adsorption, PC might retard the passage of the majority of a solid dosage form from the stomach, allowing it to dissolve slowly and gradually enter the small intestine, the organ from which most drug absorption occurs. In addition, our results indicate that a drug can associate with PC in two ways: (1) the drug dissolved in the water of hydration is quickly released, acting as a loading dose, while (2) the drug adsorbed to the polymer is released at a much slower rate, providing a sustained release effect.

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