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Poly(allylammonium acrylate) as a drug-releasing matrix

II. Release of drugs entrapped into the polysalt structure

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Summary

The release of drugs, entrapped into the poly(allylammonium acrylate) (PAAC) polyelectrolyte complex structure, was tested for vitamin B_{12} (VitB12) and tetracycline (TCY). The PAAC-drug "composites" were obtained by synthesizing PAAC in the presence of either VitB12 or TCY. Weighed samples of the "composites" were sintered as tablets, which were dipped into Dulbecco's PBS (pH 7.3); the release was followed spectrophotometrically. The tests show very low limiting release values, with different kinetic behaviours for TCY and VitB12. The results are discussed and attributed to strong ionic interactions between the polyelectrolyte complex and the dipolar ions VitB12 and TCY.

Introduction

In Part I, we reported a first attempt to use a poly(allylammonium acrylate) complex (PAAC), obtained by radical polymerization of sodium acrylate (NaAA) onto polyallylamine hydrochloride (PAAM·HCl) (1), for the controlled release of drugs (2). The lack of control found was attributed to the technique used to make the specimens with which the releasing tests were carried out: the drugs were mixed, in the form of powder, with PAAC and sintered as tablets. So, a not uniform distribution of the drug in the polycomplex matrix was present.

To assure a more uniform distribution, we tried to entrap the drugs into the polyelectrolyte complex structure of PAAC, by synthesizing PAAC in the presence of vitamin B_{12} (VitB12) and tetracycline (TCY), two substances having both a dipolar ion structure, but different molecular dimensions (see Scheme 1). In this paper we report the results of some tests, concerning the release of such entrapped drugs into Dulbecco's PBS (pH 7.3 ± 0.3).

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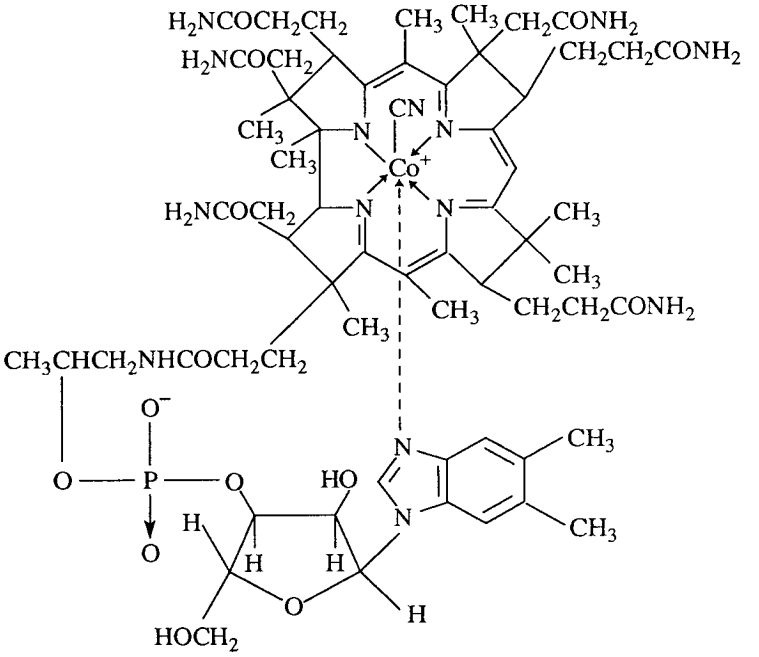
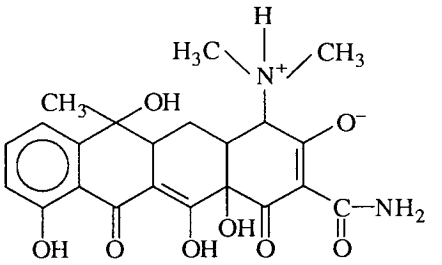


(a)



(b)

Scheme 1. Structural formulas of VitB12 (a) and TCY (b).

2. Experimental

Entrapping of drugs into the PAAC structure

The purification of the reagents was carried out as already described (1). The synthesis of PAAC in the presence of either VitB12 or TCY was carried out at 37°C by a procedure similar to that used by other authors to synthesize drug-containing collagen-

poly(hydroxyethyl methacrylate) networks (3). In a typical run, aqueous 0.5 M NaAA was polymerized onto 0.5 M PAAM·HCl in the presence of the drug (0.3 g/l), using the redox couple 0.056 M $(NH_4)_2S_2O_8$ plus 0.134 M $Na_2S_2O_5$ as a radical initiator. The amount of drug not entrapped into the precipitated polysalt was measured spectrophotometrically, at 361 nm for VitB12 and 355 nm for TCY.

Drug-releasing tests

The tests were carried out on tablets, sintered by the already described vacuum-compression procedure (2). The release of each drug was measured spectrophotometrically. The percentage of each drug released at time t, $\%A_t$, was calculated by adding the drug concentrations found in the eluates, dividing by the theoretical concentration corresponding to a complete release of the same drug, and then multiplying by 100.

Results and discussion

A more controlled drug-releasing system might be a polyelectrolyte complex having a drug entrapped into its structure: to this purpose, we synthesized PAAC in the presence of either VitB12 or TCY. The spectrophotometrical evaluation of the amount of drug not entrapped into the precipitated polyelectrolyte complexes indicates that the two products contain 0.96 mg/g of VitB12 and 1.96 mg/g of TCY, respectively. The difference between these two values can be attributed to steric factors (see Scheme 1).

The presence of the drug in the polysalt structure of PAAC enhances very strongly its hydrophilicity; during the first two days of dipping, the tablet absorbs a relevant amount of PBS solution, assuming a hydrogel consistency and spreading over the bottom of the vessel. Concerning the drug release, it is much slower than with the PAAC-drug mechanical mixtures, and never complete. Contrary to the corresponding mechanical mixture (2), TCY release (Fig. 1, point curves) is very regular and reproducible, although stops at 13-13.5% of the total amount of drug initially contained in the tablet. This percentage of the initial amount seems a true "limiting value" for the TCY release; so, carrying out the first order kinetic analysis, as made in Part I for the mechanical mixtures (2), an a_0 value equal to such percentage of the initial TCY must be inserted in the equation:

$$\ln(a_0/a_t) = kt \qquad 1)$$

The experimental data fit well the logarithmic equation, giving a $k = 2.36 \times 10^{-4}$ min^{-1} = 0.34 days^{-1}; this value has been inserted in the equation:

$$\%A_t = \%A_f \times (1 - e^{-kt}) \qquad 2)$$

By using 13.25 instead of 100 as the final limiting value $\%A_f$, it is possible to calculate the continuous curve in Fig. 1, fitting both series of experimental points very well. Conversely, VitB12 releasing curves (Fig. 2) appear S-shaped with maximum rates at about 8 days of dipping, are less reproducible at dipping times greater than 6 days, and stop at very low release percentages (2.03% and 2.65%, respectively).

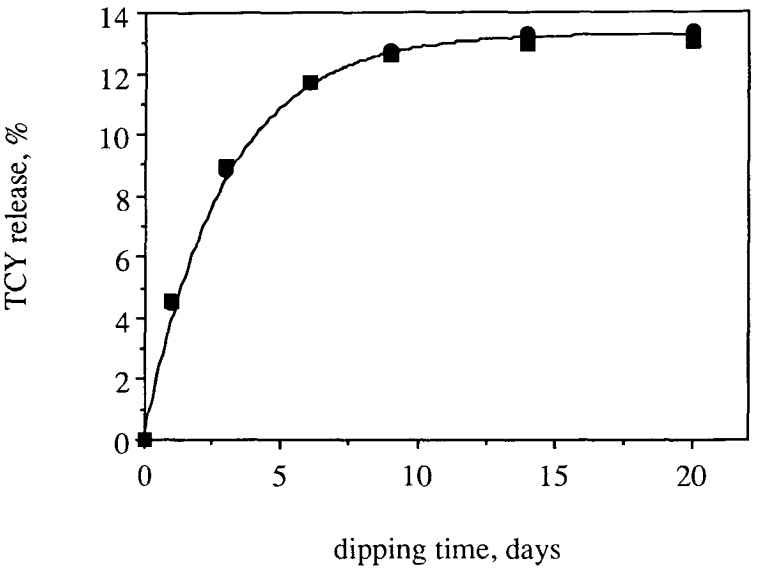


Fig. 1. Release of TCY by two tablets of a PAAC-TCY "composite", obtained by synthesizing PAAC in the presence of TCY, and containing 1.96 mg/g TCY. Point curves: experimental data of the first (●) and of the second (■) series of measurements. Continuous curves calculated by equation 2), using the $\%A_f$ and k values in the text.

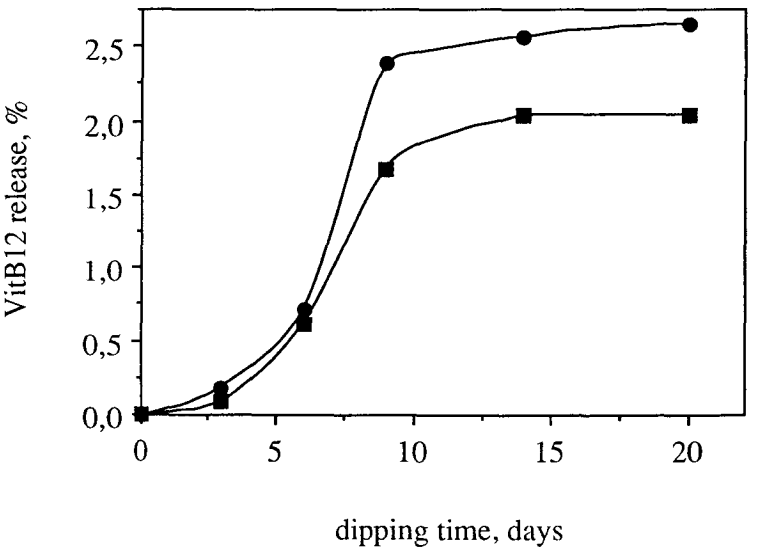


Fig. 2. Release of VitB12 by two tablets of a PAAC-VitB12 "composite", obtained by synthesizing PAAC in the presence of VitB12, and containing 0.96 mg/g VitB12.

The enhancement of the PAAC hydrophilicity and the kinetics of the drug release give information about the entrapping of VitB12 and TCY into the polysalt structure of PAAC. The enhanced hydrophilicity, in comparison with that of PAAC as such (4), indicates that the drugs are entrapped within "cavities" formed between the polycationic and the polyanionic chains of the polyelectrolyte complex (1), so that the drug-containing polysalts can absorb much more aqueous solution than the pure one. In other words, the synthetic procedure employed gives products similar to PAAC-drug composites, which, obviously, give releasing kinetics totally different from those given by the mechanical mixtures previously examined. The nature of such "composites" can be inferred from the chemical structures of the two drugs. The molecule of VitB12 (Scheme 1a) contains in its structure both a Co^+ cation and a phosphoric diester monoanion, which can link ionically the $—COO^-$ groups of the polyacrylate chain and the $—NH_3^+$ groups of the polyallylammonium chain of PAAC, respectively. As regarding TCY molecule, it exists mainly as the inner salt shown in Scheme 1b (5,6), containing a negative enolate ion at carbon 3 and a positive dimethylammonium ion at carbon 4. Such a "zwitterion" can be linked ionically by the polysalt structure of PAAC in the same manner as VitB12, but less strongly. The dimethylamino group at carbon 4 is a very weak base, having $K_b \cong 5 \times 10^{-7}$ (5), so that a very low fraction of it is protonated at pH 7.3; although the enolic hydroxyl group at carbon 3 is an acid even stronger than a carboxylic one, with $K_a \cong 5 \times 10^{-4}$ (5), the negative charge of the corresponding enolate anion is delocalized throughout the conjugated π system between the oxygen at carbon 1 and that at carbon 3 (6); so, its interaction with the $—NH_3^+$ groups of PAAC is lower than that of the less delocalized negative charge of VitB12.

Regarding the releasing kinetics, it can be reasonably explained by the nature of the bonds existing between the drugs and PAAC. The strong ionic interactions of VitB12 with both PAAC moieties make it very difficult its detachment by the PBS pH 7.3 buffer, so that only a small percentage of this drug can be released. Moreover, the large dimensions of the entrapped molecule (see Scheme 1a) can hinder its going out the "cavity" of the "composite", so slowing down the release in the first days of dipping (see Fig. 2). Conversely, TCY is a relatively small dipolar ion (see Scheme 1b), which on one side can form only few ionic bonds with the carboxylate groups of PAAC, and on the other side has delocalized negative charges interacting quite weakly with the ammonium groups of PAAC. Consequently, the smaller dimensions and the weaker interactions make TCY more free than VitB12 to escape from the "composite" into a high ionic strength solution. The ionic interactions between such a solution and PAAC are stronger than those between PAAC and TCY, so giving a limiting value of drug release higher than that found with VitB12 (see Figs 1 and 2).

The attribution of these two limiting values to acid-base interactions led us to test the influence of pH on the drug release. To avoid the decomposition of the polyelectrolyte complex by an excessive neutralization of either $—COO^-$ or $—NH_3^+$ groups, we used a CH_3COOH/CH_3COONa pH 5.4 buffer and a Na_2HPO_4/NaH_2PO_4 pH 8 buffer to carry out the tests. In both cases no significant enhancement of the drug release was observed.

The absence of any pH effect on the drug release can be explained by the relative strengths of the acids and the bases present in the system. Poly(acrylic acid) is known (7) to have a dissociation constant of the same order as propionic acid ($K_a = 1.4 \times 10^{-5}$), its model molecule. Therefore, one can reasonably suppose that also polyallylamine could

have a basic constant of the same order as its model molecule, *n*-propylamine ($K_b = 3.8 \times 10^{-4}$). Since the phosphoric diester of VitB12 and the enolic hydroxyl at carbon 3 of TCY are both quite stronger acids than the carboxyl groups of PAAC, at pH 5.4 their anions are protonated not enough to be detached from the PAAC ammonium groups, which moreover are more numerous than at pH 7.3. At pH 8 the dissociation of the acid groups of VitB12 and TCY is enhanced, so counterbalancing the lower protonation of the PAAC ammonium groups. Most likely, the extraction of the drugs by an acidic or basic solution is possible only at pH values such to destroy the polysalt structure of PAAC.

Since the acidity constants of TCY are dependent on the ionic strength of the medium (6), one might attempt to vary the drug release kinetics by using extraction media having ionic strengths different from that of Dulbecco's PBS ($I \cong 0.16$ M). However, such ionic strengths would be too different from the physiological one, so that the tests could give no useful information about the drug release in the human body.

Conclusions

The results of the releasing tests show that the release of drugs by PAAC is very difficult to be controlled, with the drugs used and under the experimental conditions. The lack of a well-controlled release is attributable to the nature of the chemical interactions between the drugs and the poly-ionic complex matrix.

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