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Poly(allylammonium acrylate) as a drug-releasing matrix

I. Release of drugs mixed and sintered with the polyelectrolyte complex

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Summary

A poly(allylammonium acrylate) complex was tested for drug release in aqueous solution. Sintered tablets of the polyelectrolyte complex, mixed respectively with human serum albumin, vitamin B_{12}, 5-fluorouracil and tetracycline, were made and dipped into Dulbecco's PBS (pH 7.3). The release kinetics, followed spectrophotometrically, is poorly reproducible and very different for the different drugs. An explanation of such behaviours is proposed, based on the chemical structures of the drugs and of the polyelectrolyte complex, as well as on two concurrent processes: the drug extraction and the saturation by the buffer of the poorly uniform drug-complex mechanical mixtures.

Introduction

Polyelectrolyte complexes were proposed as biomaterials for blood-contacting devices (1), immobilization of proteins, enzymes, DNA and liposomes (2), and drug-releasing systems (3). Their thermal condensation products were proposed for the manufacturing of membranes for dialysis (4). Some years ago we studied the physicochemical properties of a poly(allylammonium acrylate) complex (PAAC), obtained by radical polymerization of sodium acrylate onto polyallylamine hydrochloride as a template (5). The non-cytotoxicity of PAAC was later ascertained, as well as that of its condensation product poly(*N*-allyl acrylamide) (PAAD), obtained by thermally crosslinking PAAC at 200°C (6,7). We also tested the ability of PAADs, having different crosslinking degrees, to absorb water from buffer solutions having pH 2, 7.4 (physiological) and 9 (7).

The lack of cytotoxicity by PAAC and PAAD, as well as the ability of PAAD to absorb water from solutions at different pH in a regular way, led us to test such macromolecular compounds for the release of polar and ionic drugs. In this paper we report the results of some releasing tests carried out with the following drugs: human serum albumin (HSA), vitamin B_{12} (VitB12), 5-fluorouracil (FU) and tetracycline (TCY), which were released by PAAC into Dulbecco's PBS (pH 7.3 ± 0.3).

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Experimental

Synthesis of PAAC and PAAD

The purification of the reagents and the synthesis of PAAC were carried out as already described (5). PAADs with different crosslinking degrees were obtained by heating PAAC at 200°C for different times and tested for the amidation degree, using the procedures already described (7).

Drug-releasing tests

The drug-releasing tests were carried out by the following procedure: powdered PAAC was mixed in a mortar with the solid drugs HSA, VitB12, FU and TCY, respectively, according to the percentages reported in Table 1; the resulting mixtures were sintered into tablets by compression under vacuum; the tablets were dipped in Dulbecco's PBS (pH 7.4) at 37°C; at regular time intervals the eluates were collected and replaced with fresh buffer solution. Samples of PAADs with different amidation degrees were mixed with the drugs and compressed in the same way as PAAC, as an attempt to obtain drug-containing PAAD sintered tablets.

The release of each drug was measured spectrophotometrically, at the following wavelengths: 280 nm for HSA, 361 nm for VitB12, 266 nm for FU and 355 nm for TCY. 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

The drug-releasing tests show different behaviours with the different drugs used. As regarding HSA, the experimental results (Fig. 1, point curves) indicate that its release is very rapid in the first 90-120 minutes of dipping, reaching about 80%, and then stops at this value. The release of VitB12 (Fig. 2, point curves), as well as that of FU (Fig. 3, point curves), give quite regular curves, which tend to 100% release, more rapidly in the former case. On the contrary, TCY releasing curves (Fig. 4) are neither regular nor reproducible.

The first branches of HSA release curves, as well as VitB12 and FU curves, seem to show quite regular shapes, typical of first-order kinetics. The kinetic analysis of the experimental curves (Figs 1-3, point data) was made starting from the classical first-order rate equation:

$$R_t = -(da/dt) = ka_t \qquad 1)$$

By integrating Eq 1), we have:

$$\ln(a_0/a_t) = kt \qquad 2)$$

that is:

$$a_t/a_0 = e^{-kt} \quad 3)$$

Where:
R_t = rate of release at time t
a = quantity of drug in the tablet
a_0 = initial quantity of drug in the tablet
a_t = value of a at time t
and
$a_0 - a_t$ = experimentally determined quantity of drug released at time t

By Eq 2) it is possible to obtain k as the slopes of the "logarithmic plots" of the experimental data. The so obtained values of k are listed in Table 1. By inserting such values in Eq 3), we can obtain "percentage of release vs. time calculated curves":

$$\%A_t = 100(a_0 - a_t)/a_0 = 100 \times (1 - e^{-kt}) \quad 4)$$

By means of Eq 4), we calculated the continuous curves in Figs 1-3. Fig. 1 shows that HSA has, in the first 90-120 minutes of dipping, the best fitting between experimental points and calculated curves. Figs 2 and 3 show that also the calculated curves of both VitB12 and FU fit acceptably well with the experimental points.

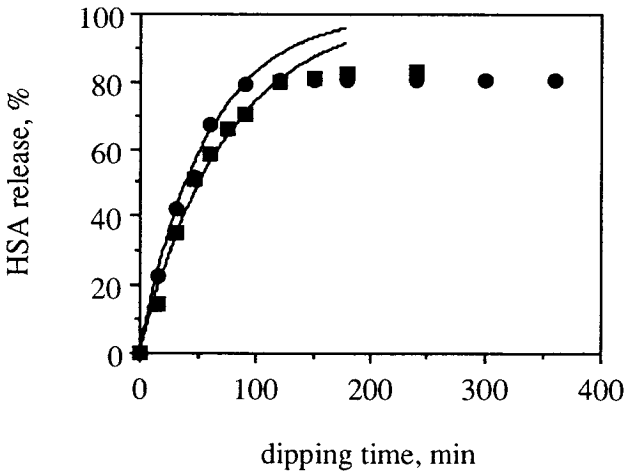


Fig. 1. Release of HSA by PAAC tablets. Point curves: experimental data of the experiments n. 1 (●) and n. 2 (■) of Table 1. Continuous curves calculated by Eq 4), using the corresponding apparent first-order constants k listed in Table 1.

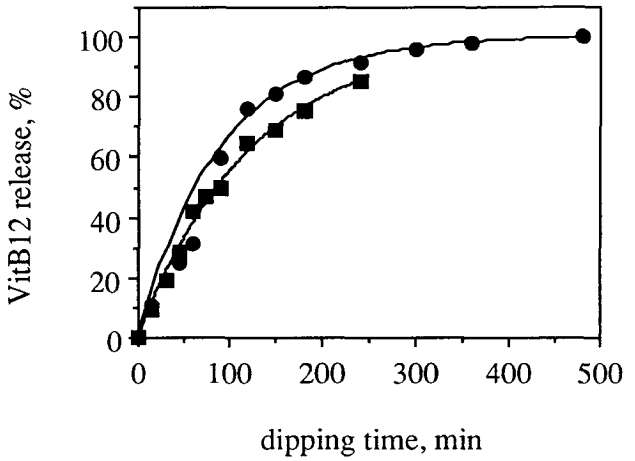


Fig. 2. Release of VitB12 by PAAC tablets. Point curves: experimental data of the experiments n. 3 (●) and n. 4 (■) of Table 1. Continuous curves calculated by Eq 4), using the corresponding apparent first-order constants k listed in Table 1.

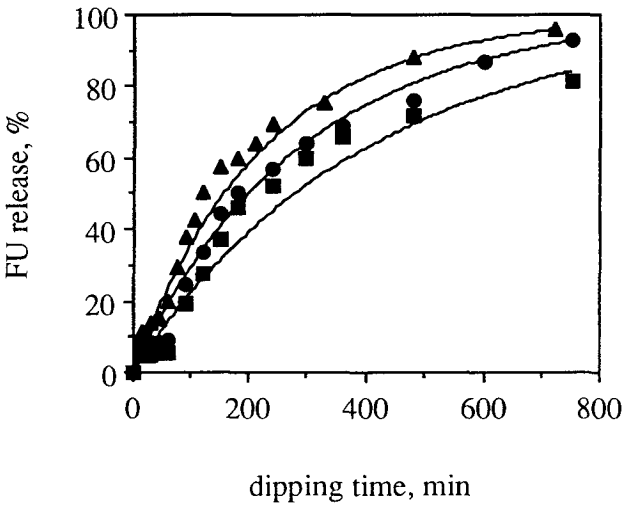


Fig. 3. Release of FU by PAAC tablets. Point curves: experimental data of the experiments n. 5 (●), n. 6 (■) and n. 7 (▲) of Table 1. Continuous curves calculated by Eq 4), using the corresponding apparent first-order constants k listed in Table 1.

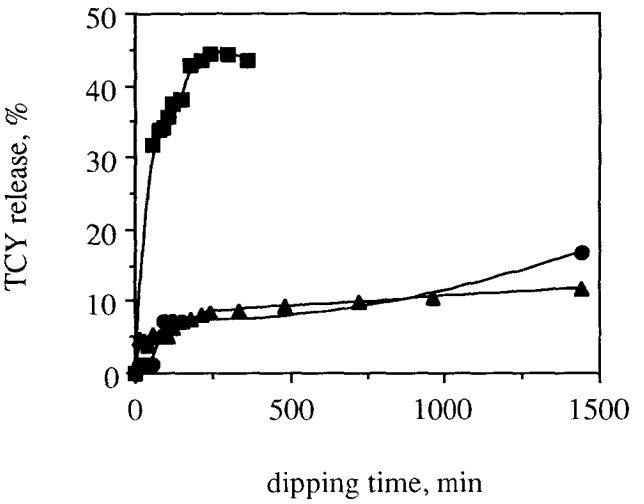


Fig. 4. Experimental data of the release of TCY by three different PAAC tablets, containing each 50 mg% of TCY mechanically mixed with preformed PAAC. No calculated curve can be evaluated from the experimental data.

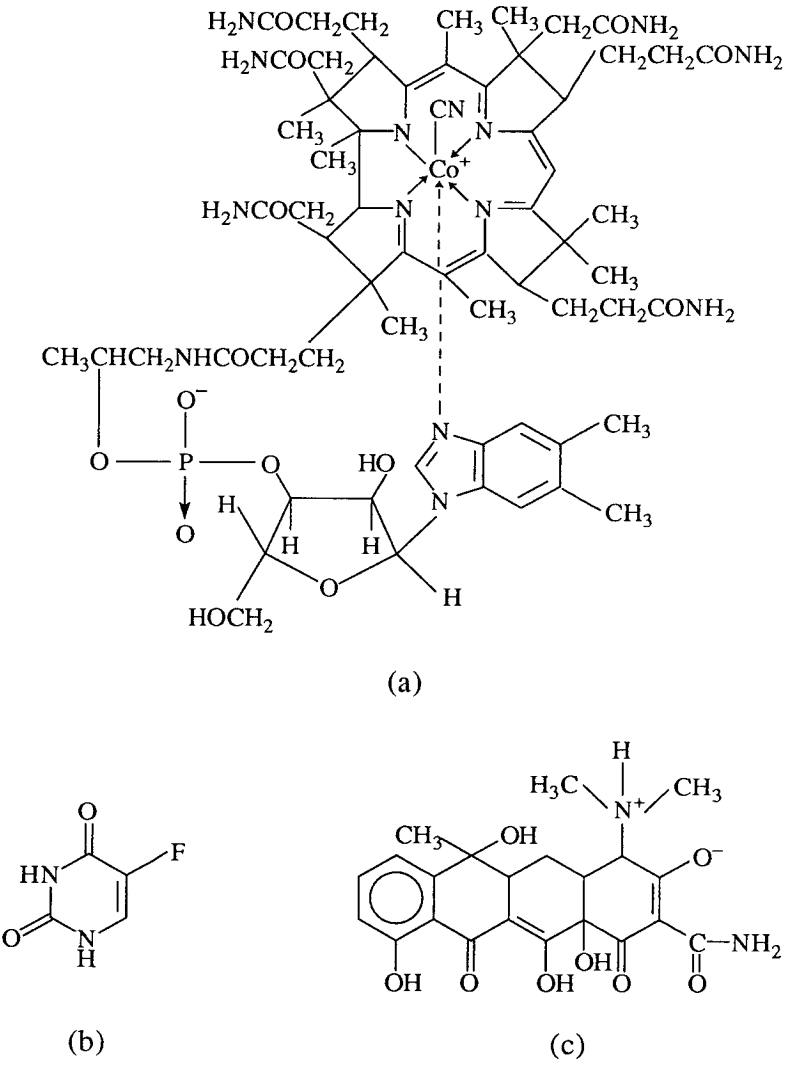
Table 1. Drug amounts and apparent first-order kinetic constants k for drug release from PAAC tablets at pH 7.3

Experiment n.	Drug	Amount (weight %)	$k \times 10^3$ (min^{-1})
1	HSA	20.7	17.60
2	HSA	20.7	13.57
3	VitB12	2	10.98
4	VitB12	2	7.93
5	FU	0.06	3.42
6	FU	0.1	2.45
7	FU	0.1	4.34

However, the values of k listed in Table 1, which are very different for the different experiments made with the same drug, show that the release of these three drugs is not perfectly reproducible. So, these k values, found at pH 7.3, must be regarded only as apparent first-order kinetic constants.

Since the marked water-solubility of PAAC at low and high pH values does not permit to carry out the tests at pH 2 and 9, we attempted to use the crosslinked material

PAAD as a drug release system, but we found some experimental difficulties. The PAAD powder could not be sintered, so that no drug release test was possible, at least in the experimental conditions used with PAAC. We tried thus to crosslink PAAC tablets, containing FU or TCY, by heating them at 200° C for only 2.5 min: the results of the drug release tests were not substantially different from those obtained with the non-crosslinked material. In addition, attempts to evaluate the amidation degree by acid-base titration of the free amino groups showed that not all the macromolecules were crosslinked after a so short heating time.



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

The poor reproducibility of the results, obtained with unmodified PAAC, may be attributed to the procedure used to form the drug-containing tablets: the mechanical mixing of the two powders, notwithstanding the thorough grinding, cannot give a uniform distribution of the drug in the tablet. In addition, the eluting buffer solution needs one to two hours to reach a complete saturation of the tablet (7), which is the necessary condition for all the drug to come in intimate contact with the polyelectrolyte complex.

As regarding the different behaviours of the drugs, HSA is a globular protein with a molecular mass of about 69000, having many ionic or ionizable groups along the macromolecular chain. These groups are chemically able to undergo strong interactions with the ionic sites of PAAC; but the great tightness of such a polyelectolyte complex (5), as well as the big size of HSA molecule, makes the ionic drug-matrix interactions very difficult, before the complete saturation of the tablet. So, during the saturation time, about 80% HSA undergoes a "regular" (Fig. 1), but not very reproducible (Table 1) release, which stops quite completely when the hydration of the tablet allows an intimate contact between HSA and PAAC. As concerning VitB12, it is a "middle" molecule (molecular mass = 1355), having the dipolar ion structure shown in Scheme 1a. The two releasing curves in Fig. 2 show a quite irregular release in the first branches of the curves, approximately corresponding to the saturation time of the tablets (7); afterwards, an apparent first order release is present, although not reproducible (see also Table 1). Both the positive Co^+ charge and the negative diesterphosphate one are very localized in the molecular structure; moreover, the former is quite "masked" by the surrounding porphyrin-like structure. So, it is unlikely that they can easily come into intimate contact with the corresponding charge of the polyelectrolyte complex, both before and after the complete hydration of the tablet. Then, the drug is linked to PAAC mostly by hydrogen bonds, quite easily broken by the eluting solution. Similar considerations seem also valid for the release of FU (Fig. 3), which is a small molecule (molecular mass = 130.8), having a weakly acidic hydrogen, with an apparent pK_a of 7.98 (8), linked to the imide nitrogen 3 of the pyrimidine ring (see Scheme 1b). Non-salified FU exists, in the solid state, only in the non-dissociated form, whereas it is partially dissociated ($\alpha = 0.2$) in a pH 7.3 buffer solution. As the hydration of the tablet by the buffer goes on, a series of acid-base equilibria occurs, both within the tablet and in the surrounding solution, to which the non-dissociated FU, linked to PAAC only by hydrogen bonds, migrates more easily than the FU anion, which can link ionically to the polyelectrolyte complex. This fact can explain why FU release, notwithstanding its smaller dimensions, is more slow, less regular and less reproducible than that of VitB12 (see Fig. 2, Fig. 3 and Table 1). Finally, TCY is the quite small (molecular mass = 444.44) dipolar ion shown in Scheme 1c (9,10). It is very likely that the possibility of ionic interactions between such a "zwitterion" and the polyelectrolyte complex must be strongly dependent on its distribution in the tablet, at any hydration degree. So, its release (Fig. 4) is very irregular and not reproducible independently of the dipping time.

These results lead to suppose that the hydration of such an irregular drug-complex mixture and the drug release may be concurrent processes, so that the release seems to occur in conditions very difficult to be controlled. An attempt to obtain a more uniform distribution of the drugs in the polysalt matrix will be object of the subsequent paper.

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