

IN VITRO STUDIES OF CAPREOMYCIN SULFATE RELEASE FROM POLYETHYLCYANOACRYLATE NANOPARTICLES

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The potential use of polyethylcyanoacrylate as a carrier for the antituberculosis agent capreomycin sulfate was demonstrated. In vitro studies addressed the release of capreomycin sulfate from polyethylcyanoacrylate nanoparticles and degradation of the polymer.

Keywords: polyethylcyanoacrylate nanoparticles, capreomycin sulfate, drug release, degradation, erosion.

There is increasing interest in the targeted delivery of drugs to target organs using nanoscale polymer encapsulation [1 – 5]. This approach addresses not only the initial objective of producing long-acting formulations, but also decreases the risk of side effects.

Polymer materials for these purposes include biocompatible and biodegradable natural and synthetic polymers widely used in medicine. These polymers include those used in the present study, i.e., polyalkylcyanoacrylates, for immobilization of the antituberculosis agent capreomycin sulfate by emulsification polymerization via an anionic mechanism [6, 7].

A not unimportant factor in the application of polymer-immobilized forms of drugs is their ability to undergo biodegradation, which has direct effects on therapeutic effects.

We present here data on the release of capreomycin sulfate from a polyethylcyanoacrylate matrix by dialysis as used by other authors [5, 8, 9].

EXPERIMENTAL SECTION

Polyethylcyanoacrylate nanoparticles immobilizing capreomycin sulfate were prepared by emulsification polymerization as described in [6].

The kinetics of capreomycin sulfate (CS) release from polyethylcyanoacrylate nanoparticles (PECA NP) were stud-

ied by dialysis in phosphate buffer solution at a temperature of 37°C as described below. NP bearing immobilized drug (at a concentration of 1 mg/ml) were dispersed in 25 ml of phosphate buffer pH 7.4 and sonicated for 30 min. The resulting dispersion was poured into a dialysis membrane (molecular weight 1000) and placed in a beaker containing 250 ml of buffer. The solution was stirred using a magnetic follower at 200 rpm. Samples were collected from the membrane and beaker at defined time points: the first sample was collected before the experiment started (the null sample), with further samples at 20 and 40 min and 1, 2, 3, 4, 5, 6, 8, 10, and 24 h, and then every other day for one week.

Samples collected from the membrane were of 1 ml, while those from beakers were of 10 ml. These volumes were selected to maintain the ratio of the internal and external volumes of phosphate buffer. As this kept the ratio unaltered, the sample volume was not replaced with fresh buffer solution.

The quantities of degraded polymer and released drug were determined using a UV spectrophotometer (HP 8453 UV-Vis spectrometer, Hewlett Packard, USA) (UV-Vis photodiode) at wavelengths of $\lambda_{\max} = 248$ and 268 nm for polymer and drug respectively.

RESULTS AND DISCUSSION

Drug release from polymer micro- and nanoparticles can occur by desorption of drug from the polymer surface and/or diffusion of drug due to erosion of the polymer matrix [10 – 12].

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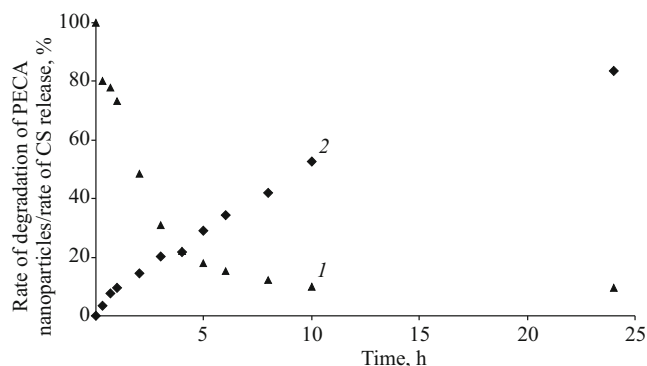


Fig. 1. Relationship between rate of PECA degradation (1) and CS release (2) and time.

We have previously described PECA NP immobilizing the antituberculosis agent CS [6] with a mean diameter of 132.3 nm, polydispersity 0.042, and polymer molecular weight of about 2000, with a binding extent of 33%. When making polymer-immobilized CS complexes, it is important to study the kinetics of drug release from the NP. The nature of drug release from the polymer matrix depends mainly on the rate and mechanism of erosion and degradation of the polymer. In the present study, the drug was located both on the surface and in the volume of the polymer, such that CS entered the surrounding medium via both of these effects.

The kinetics of drug release from PECA NP were studied in phosphate buffer pH 7.4 over a period of one day by UV spectrophotometry; the results are presented in Fig. 1.

Figure 1 shows that the rate of drug release was quite high at the beginning of the process: 10% of the CS was released in the first hour, 20% of immobilized drug was released in 3 h, and about 50% of drug was released from polymer NP by 8 h; the remainder was released by 24 h. It is important to note that the elimination half-life of CS is about 3–6 h. Thus, immobilization of CS in PECA NP should triple the elimination half-life of capreomycin sulfate, decreasing or avoiding the need for frequent dosage. Published data indicate that the drug elimination time can be prolonged by increasing the molecular weight of the polymer and/or using a monomer with longer side chains (butyl, hexylcyanoacrylate) [10–12], which is associated with slower erosion of the polymer matrix and degradation, which will be the subject of future studies.

The quite rapid release of CS from polymer NP can initially be explained in terms of the ability of some quantity of drug to desorb from the surfaces of PECA NP.

Investigations were continued by studying the processes of erosion of polymer matrices and degradation of both empty and drug-immobilizing particles. Figure 2 shows data on the kinetics of erosion and degradation of empty PECA studied by UV spectrophotometry.

The plots show that about 50% of drug-free NP underwent degradation in 3 h, 19.4% of polymer persisting at 10 h. The degradation of NP containing biologically active sub-

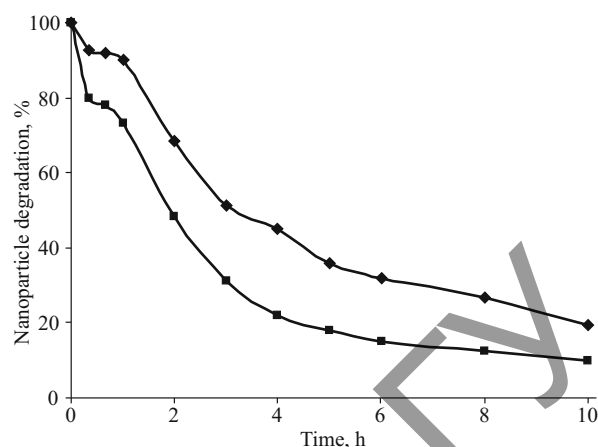


Fig. 2. Relationship between degradation of empty (1) and CS-immobilizing (2) nanoparticles and time.

stance was then studied (Fig. 2). This shows that degradation of CS-containing NP PECA occurred somewhat more quickly. At the first level, about 70% of PECA was degraded in 3 h, probably linked with a higher rate of erosion of the polymer surface and degradation of PECA blocks.

The experimental data showed that CS-immobilizing polymer degraded more quickly than drug-free PECA. Thus, these results provide grounds for the view that the presence of drug in the polymer matrix leads to some increase in the rate of NP degradation processes.

In biological conditions, polymers undergo destruction with or without changes to their chemical structure, or they may undergo chemical degradation; both processes can occur. There are two generally recognized mechanisms of degradation of polyalkylcyanoacrylates [10–12].

1) Degradation of the main polymer chain to form formaldehyde.

2) Cleavage of the ester group, leading to formation of soluble polyalkylcyanoacrylic acid.

The first means of degradation is the reverse of the Knoevenagel condensation reaction, though destruction of polyalkylcyanoacrylates by this pathway occurs much more slowly. In degradation by the second pathway, the main polymer chain remains unaltered, though the hydrophobic chain becomes increasingly hydrophilic until it is completely water-soluble, and the low molecular weight products formed by the degradation process are eliminated from the body over short periods of time. There are increasing numbers of studies indicating a predominance of degradation of polyalkylcyanoacrylates by the second pathway over the first [10–12].

The scheme of the chemical degradation of polyalkylcyanoacrylates by hydrolysis of the ester group, leading to forming of alcohol and polyalkylcyanoacrylic acid, is shown below (Fig. 3).

Polyalkylcyanoacrylates are rapidly-degrading polymers, so they can leave the body over a period of a few days [11]. The rate of degradation of polyalkylcyanoacrylates de-

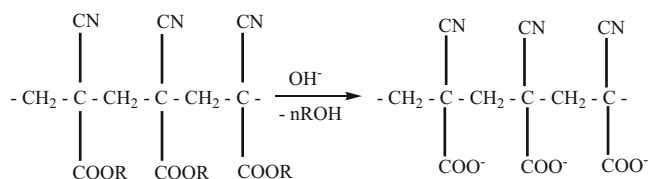


Fig. 3. Degradation of polyalkylcyanoacrylates.

depends on the length of the side chain: the longer the chain, the slower the degradation process (i.e., polymethyl- and polyethylcyanoacrylates are degraded very rapidly) [12]. This may also explain the relatively rapid biodegradation of PECA. In addition, the low molecular weight of the polymer (about 2000) may also be a cause of its rapid degradation. Release of ethanol into the medium due to destruction, as shown in the scheme, provides evidence of the degradation of PECA by the second pathway. Thus, gas chromatography studies showed that the ethanol content in the medium was 6.8%. These observations lead to the conclusion that only a small proportion (about 7%) of drug-immobilizing PECA is degraded by hydrolysis of the ether group.

Thus, these studies showed that erosion-mediated release from NP surfaces is predominant over processes of degradation of the macromolecules of the polymer matrix.

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