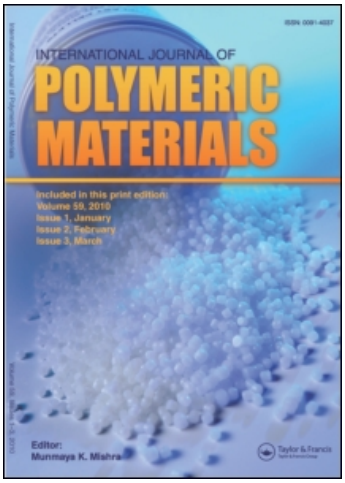


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# Biodegradation of Polymer Compounds Based on Cross-linked Dextranes

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# Biodegradation of Polymer Compounds Based on Cross-linked Dextranes

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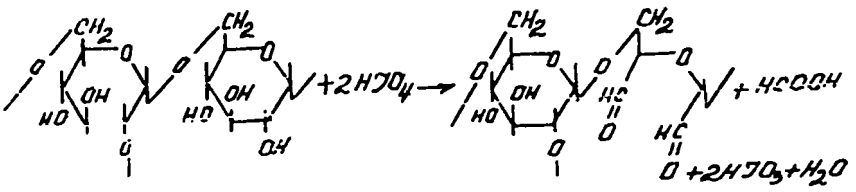
Cross-linked dextranes can be used as the basis for drug storage consisting of a physiologically active polymer and the drug grafted to the polymer matrix. The drug storage form for medical treatment of infected centers of tuberculosis has been obtained. The kinetics of drug release into model media and blood plasma has been investigated. It was found that polymeric derivatives of isonyazide and kanamycin can be used for preparation of a low rate release and long time action drug storage.

KEY WORDS Drug release, cross-linked dextranes, kinetics, tuberculosis.

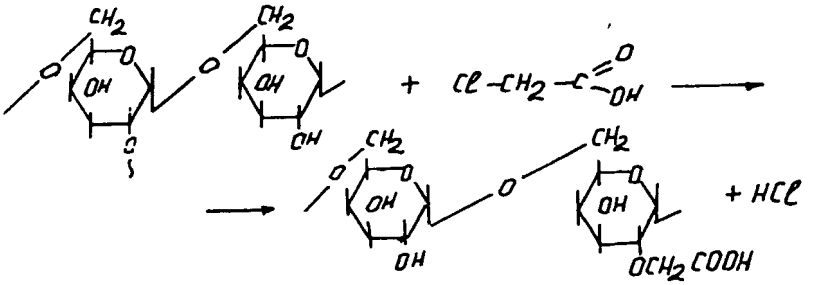


The use of new polymer drugs in medicine depends on their medical properties, the biocompatibility of polymeric drug carrier with the organism tissues, and nontoxity of products of their biodegradation. Dextran and its derivatives are biocompatible materials, susceptible to biodegradation under the influence of hydrolytic enzymes, such as dextranaza and acidic α-α-glucozidaza.[1–4] In this case the degradation products participate in organism metabolism, are nontoxic and do not cause allergic or any other ill effect. However, the quantitative data on biodegradation of medical polymers, based on cross-linked Dextranes (sefadexes) do practically nonexisting.

The scope of present investigation, was to solve a particular problem, namely, to develop a drug storage with prolonged action for treatment of infected cavities of tuberculosis. The polymeric drug forms were physiologically active polymers of "grafting" type, where the medical substances (MS) were linked to the polymer with labile chemical bonds. The role of carrier polymer was played by functional derivatives of cross-linked Dextranes in the form of hydrogels with high degree of swelling. Sefadex was chemically modified by introducing reactive functional groups into the structure. The aldehyde groups at periodate oxidation and the carboxile groups at the interaction with monochloracetic acid. The reaction scheme for obtaining aldehydesefadex (AS) is:

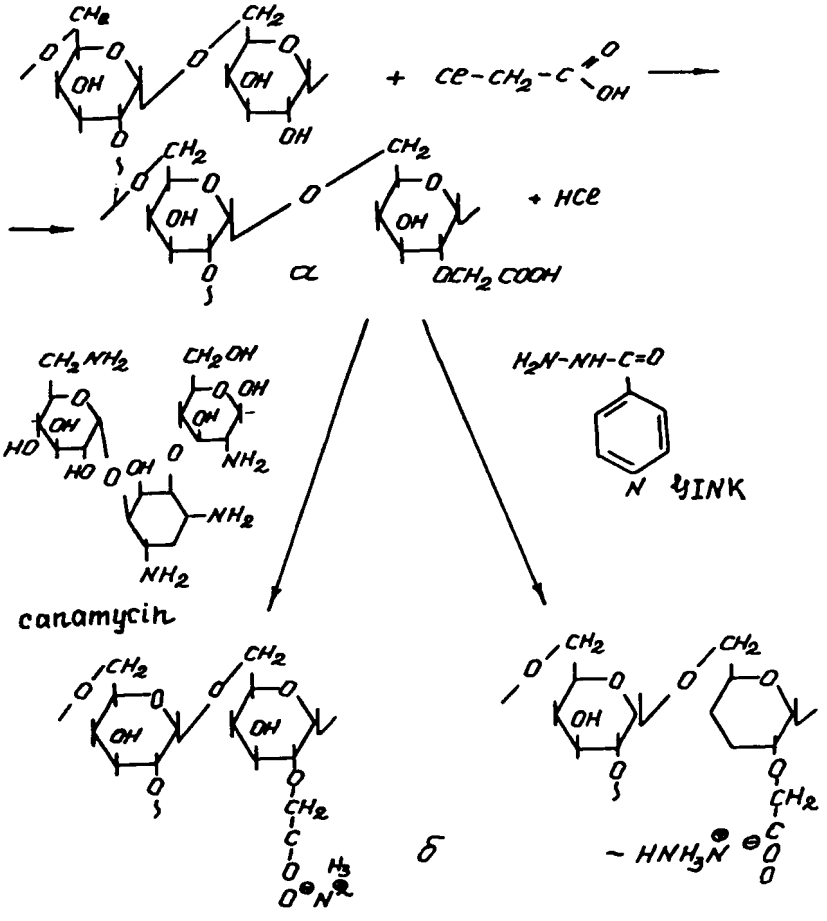


and carboximethylsefadex (CMS) is:

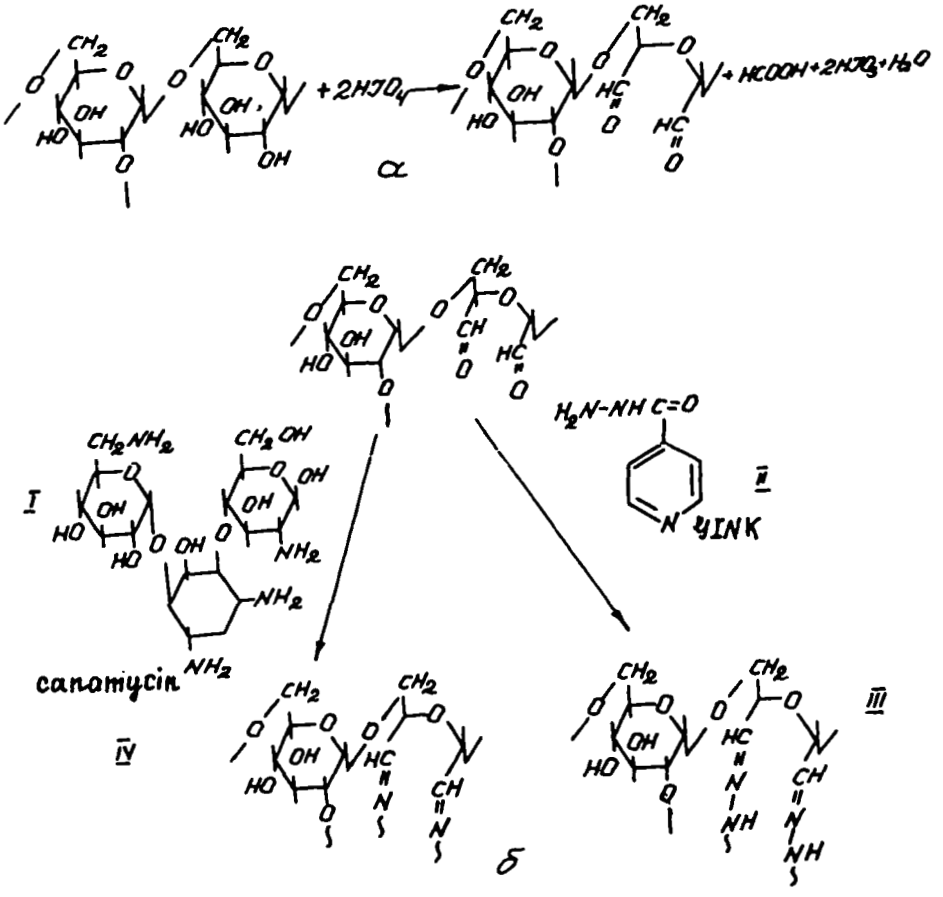


Detailed investigation of the behavior of carrier polymer and polymeric derivatives of kanamycin and isonyazide was carried out as antituberculosis medical preparations in liquid media, modeling biological ones.

The biological medium contact with polymers display activity to chemically un-




SCHEME I a) Modification of Sefadex by monoacetic acid, b) immobilisation of canamycin and isonyazide on carboximethylsefadex.




SCHEME II a) Modification of Sefadex by iodic acid, b) immobilisation of canamycin and isonyazide on aldehydesefadex.

stable bonds in these polymers.[5,6] The following simple substances display such an activity: water (45–75% of water is accumulated in intracellular tissue liquid), salts (phosphates, bicarbonates, sulfates, etc.), and enzymes.

The following substances were used as a model for biological media: for water, 0.1 M phosphate buffer solution with pH = 7.4; for salts, 0.1 M citrate-phosphate buffer solution with pH = 4.0, and for enzymes, a water solution of amilaze-enzyme and native humane blood plasma.

Polymer biodegradation was studied by measuring the weight losses of samples in time. The rate of MS hydrolytic detachment was followed by UV-spectroscopic method. It was determined, that aldehydesefadex (AS), containing 30 mole % of aldehyde groups gradually went into solution after being placed into water and buffer solution. The rate of biosolution increased with increasing pH of the medium (Figure 1). Apparently, this is stipulated by the introduction of hydrophilic aldehyde

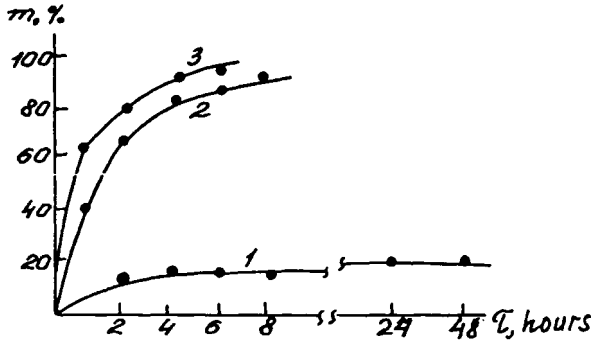
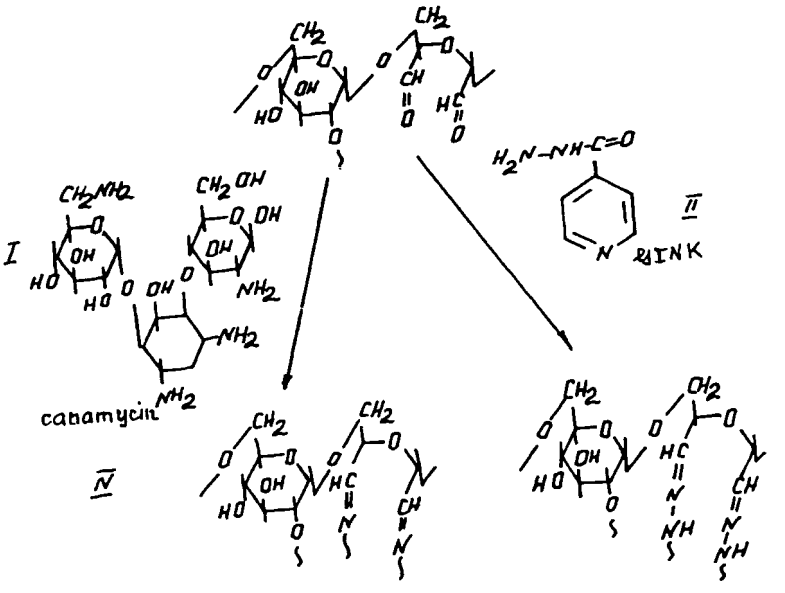



FIGURE 1 Aldehydesefadex solving in various media at 37°C: 1—water; 2—0.1 M phosphate buffer solution with pH = 7.4; 3—0.1 M phosphate buffer solution with pH = 8.2.

groups into the solution and partial destruction of cross-linking bonds during the process of sefadex oxidation.

The formation of polymeric derivatives of isonyazide and canamycin proceeds according to the following scheme:




Isoniazide (II) and kanamycin (III), containing hydrazidic and amine groups in the structure, interact easily with AS (I), forming hydrazonic (IV) and aldimine (V) derivatives. Including the hydrolytic detachment of MS, the biodegradation of polymer matrix occurs with the disposition of these polymeric derivatives into the liquid biological medium. It is seen from Figure 2, that there is a slow degradation of medical polymer (curves $1^1$–$3^1$) and gradual detachment of MS (curves 1–3) in different media. Both these processes proceed with a decreasing rate and are completed in 2–6 days. Water has the highest activity in biodegradation of both

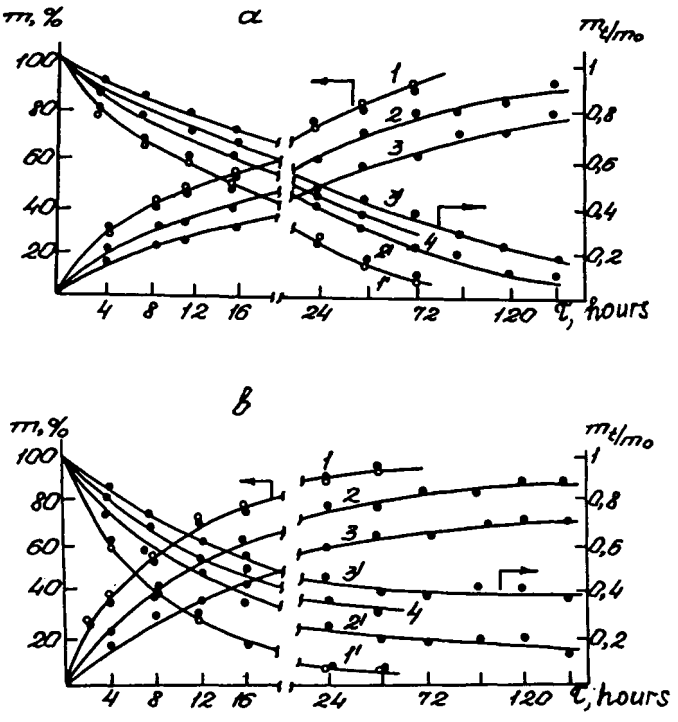



FIGURE 2 Time changes of output rate of isonyazide (a) and kanamycin (b) (curves 1, 2, 3) and relative mass of medicinal polymer AS-MS (curves $1^1$, $2^1$, $3^1$, 4) in different media at 37°C: 1, $1^1$—water, α-amylaza water solution (0.1 mg/ml); 2, $2^1$—0.1 M citrate-phosphate buffer solution with pH = 4.0; 3, $3^1$—0.1 M phosphate buffer solution with pH = 7.4; 4—blood plasma.

polymeric compounds (curves 1, $1^1$). The complete transition of the polymer and quantitative transfer of drug into the solution was observed for AS-isonyazide after 72 hours, for AS-kanamycin—after 48 hours. It should be mentioned, that on transition of medical polymers into water solution a pH = change from 6.5 to 3.4 takes place that is associated with the formation of water soluble fragments of acidic character.[7,8] It was shown, that acidic 0.1 M citrate-phosphate (pH = 4.0) and neutral 0.1 M phosphate (pH = 7.0) buffer solutions do not provide a significant catalytic influence on the degradation of medical polymers (curves $2^1$, $3^1$) we investigated.

The study of degradation of medical polymers (MP) in presence of hydrolytic enzyme α-amylaza showed, that its influence is comparable to that of water (curve $1^1$). Apparently, this is stipulated by enzyme nonspecificity with respect to dextrane matrix, which, as known, is sensitive to dextranaze enzyme.[1]

To approach the investigations to conditions in vital organism we studied MP behavior in blood plasma. In this case we found that biodegradation rate has an intermediate value between the degradation rate in water and buffer solutions (curve 4).

The study of MP degradation in media with different pH (7.4, 4.0, 3.4) allowed us to calculate the kinetic parameters of this process (Figure 3, Table I). It is seen from the Table I, that the rate of degradation of kanamycin and isonyazide derivatives increases with decreasing pH of the medium and reaches the highest values at pH = 3.4.

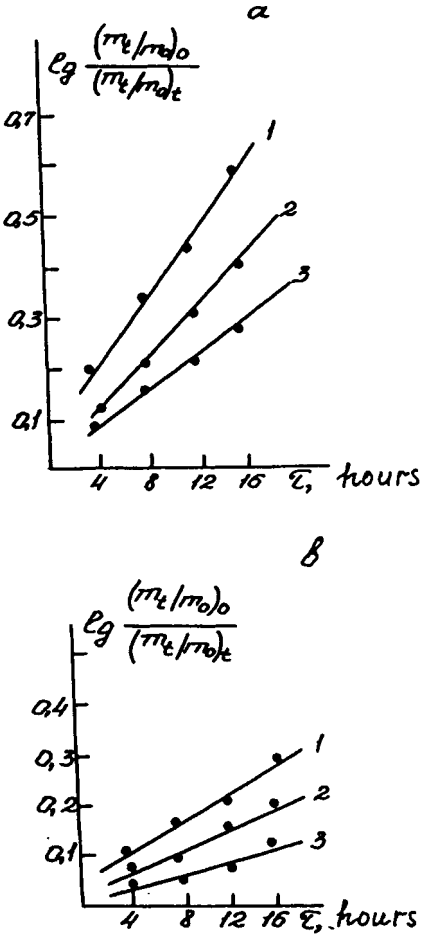



FIGURE 3 Logarythmic dependence of $(m_t/m_0)_0/(m_t/m_0)$, on time for polymer preparations degradation of kanamycin (a), isonyazide (b), based on aldehydesefadex in water solutions with different pH: 1—3.4; 2—4.0; 3—7.4.

TABLE I

Kinetic parameters of medicinal polymers degradation in water solutions with different pH

| Medium pH | Polymeric kanamycin, $K$, $10^5$ $s^{-1}$ | Polymeric isonyazide, $K$, $10^6$ $s^{-1}$ |
|---|---|---|
| 7.4 | 1.0 | 5.1 |
| 4.0 | 1.5 | 7.2 |
| 3.4 | 2.0 | 11.7 |

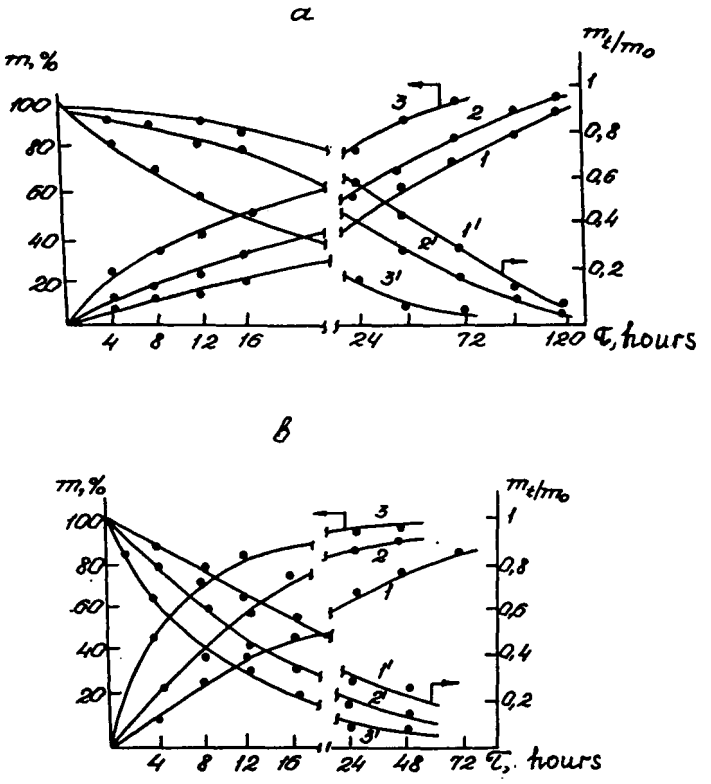



FIGURE 4 Time changes of output rate of isonyazide (a) and kanamycin (b) and relative medicinal polymer mass AS:MS (curves $1^1$, $2^1$, $3^1$) at different drug content (mg) per 1 g of aldehydesefadex (water, 37°C): 1, $1^1$—125; 2, $2^1$—250; 3, $3^1$—500.

We also studied the influence of other factors such as; MS content in polymer and temperature on MP degradation rate.

The change of MS content in AS caused the change of polymer degradation rate and MS detachment (Figure 4a,b). Thus, for polymeric isoniazade, containing 125 mg of MS per 1 g of carrier, degradation was completed by 55% after 24 hours, and for derivative kanamycin—by 75% (Figure 4, curves 1, $1^1$). The rates of degradation and MS detachment increase with increasing MS content in the polymer (curves 2, $2^1$, 3, $3^1$). This allows us to regulate the release rate of physiologically active component into organism by controlling the amount of MS linked with polymer-carrier.

Polymer samples were thermostated in water at temperatures of 25, 37, 40°C (Figure 5a,b) to eliminate the temperature influence on the rate of MP degradation and MS detachment. It is seen from the figure, that the rates of MP degradation (curves $1^1$–$3^1$) and MS detachment (curves 1–3) increase with increasing temperature. The study of temperature dependence of hydrolytic detachment of drugs from polymeric matrix allowed us to calculate the kinetic parameters of this process (Figures 6–9, Table II).

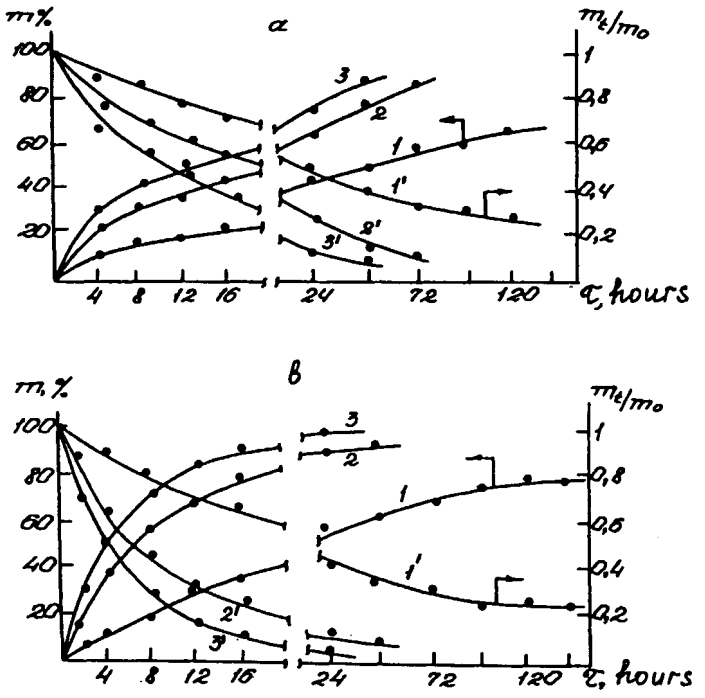



FIGURE 5 Time change of output rate of isonyazide (a) and kanamycin (b) (curves 1, 2, 3) and relative medicinal polymer mass AS:MS (curves $1^1$, $2^1$, $3^1$) at different temperature in water: 1, $1^1$—25°C; 2, $2^1$—37°C; 3, $3^1$—40°C.

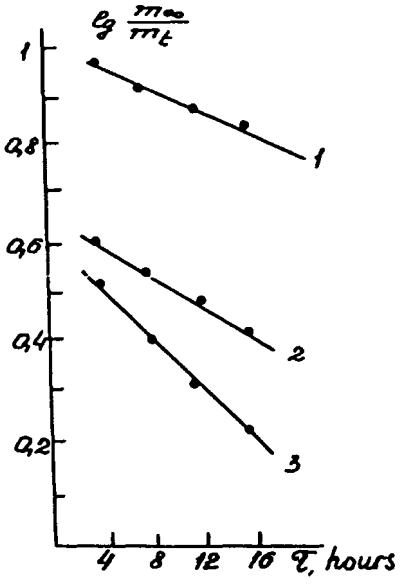



FIGURE 6 Logarythmic dependence of $(m_\infty/m_t)_0$ on time for isonyazide extraction from aldehyde-sefadex at different temperatures: 1—25°C; 2—37°C; 3—40°C.

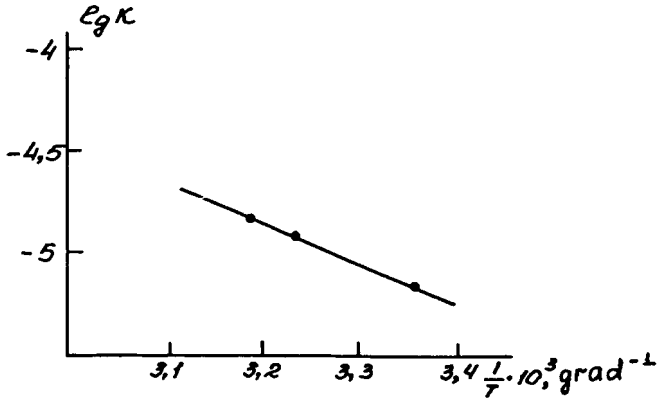



FIGURE 7 Arrhenius dependence for rate constants of isonyazide extraction from aldehydesefadex.

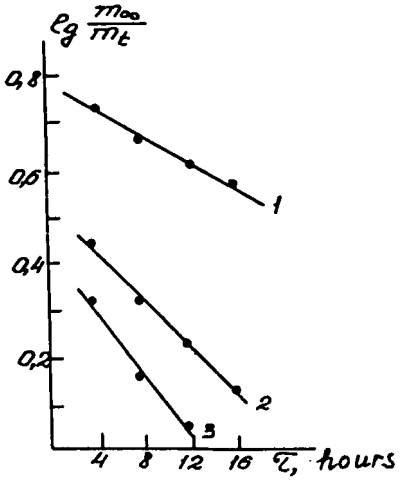



FIGURE 8 Logarythmic dependence of $(m_\infty/m_t)_0$ on time for kanamycin extraction from aldehydesefadex at different temperatures: 1—25°C; 2—37°C; 3—40°C.

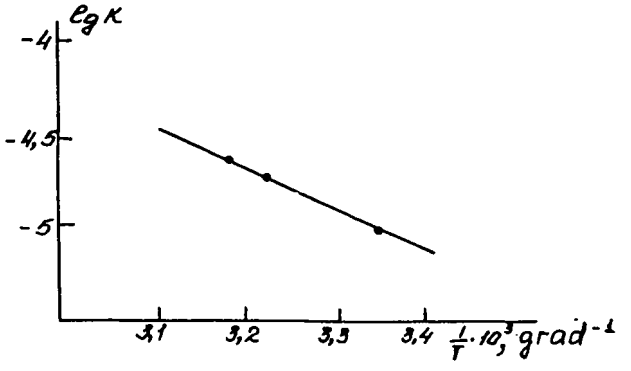



FIGURE 9 Arrhenius dependence for rate constants of kanamycin extraction from aldehydesefadex.

TABLE II

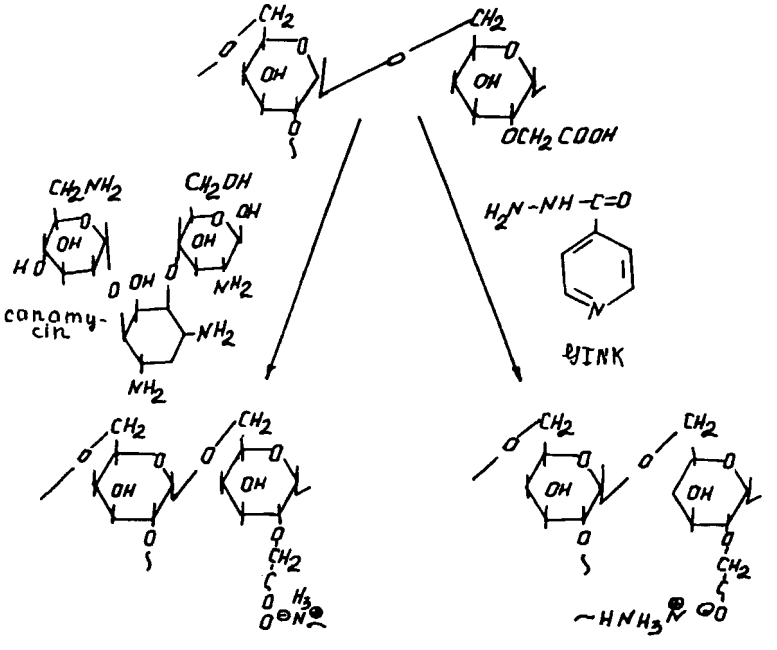
Kinetic parameters of the detachment of kanamycin and isonyazide from polymeric matrix

| | Kanamycin | | Isonyazide | |
|---|---|---|---|---|
| $T$°C | $K$, $10^5$ $s^{-1}$ | $E$, kJ/mole | $K$, $10^5$ $s^{-1}$ | $E$, kJ/mole |
| 25 | 0.9 | | 0.7 | |
| 37 | 1.9 | 34.4 | 1.2 | 47.6 |
| 40 | 2.6 | | 1.6 | |

The values of rate constants and activation energies, presented in Table II, show that energy of hydrozonic bond break is higher, than that of aldymine bond. The same difference is observed in all the tests. Under various conditions the rate of kanamycin detachment is higher, than that of isonyazide. In this case, as it is mentioned in a series of articles,[9] MS can transit into the surroundings linked with fragments of carrier polymer resulting from MP decomposition.

This study of behavior of MP based on AS in media similar to physiological ones, showed that MS detachment proceeds concurrently with polymeric matrix decomposition. These two processes proceed with a decreasing rate and are 80–90% completed after 2–6 days. The detachment of the active component into the model medium depends on the nature of chemical bond between polymer and MS and the rate of polymeric matrix decomposition.

Carboximethylsefadex (CMS) was used as ionogenic polymer carrier. The immobilisation of MS occurs through electrovalent interaction of polymer functional groups and MS and leads to the formation of polymer complexes:



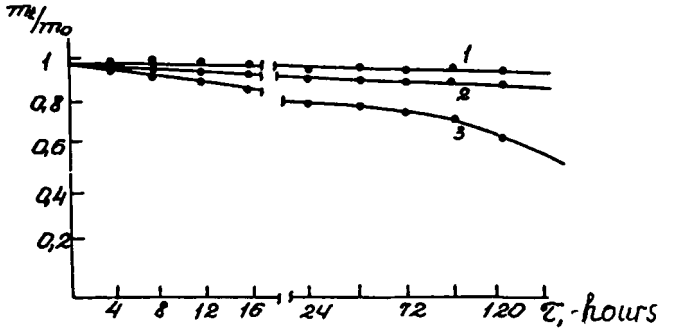



FIGURE 10 Time change of carboxymethylsefadex relative mass in various media, 37°C: 1—0.1 M phosphate buffer solution with pH = 7.4; 2—Ringer-Lock solution with pH = 6.5; 3—blood plasma.

As some authors point out, MS interaction with polyelectrolytes leads to changes in their performance characteristics. The degradation resistance increases, toxicity decreases.[10] In biological medium such polymeric complexes dissociate to initial polymer (if it does not biodegrade) and MS, resulting in the interaction of competitive or newly formed counterions.

The investigation of biodegradation of CMS and polymer complexes, based on it, in media, similar to biological ones, displayed some features of these polymers behavior. Unlike AS, CMS did not biodegrade in phosphate buffer solution with pH = 7.4 and in Ringer-Lock solution with pH = 6.5 (Figure 10, curves 1, 2). This is attributed to the fact, that there is no decomposition of carbohydrate skeleton and cross-linkages during sefadex chemical modification at carboxiderivative formation. This is contrary as to what occurred at AS formation. Slow decomposition of CMS was observed in blood plasma (curve 3). Probably, there are biologically active substances in blood plasma, which split polymer chain of CMS, yielding bioresolvable fragments.

Thus, it is found, that CMS polymer complexes with kanamycin and isonyazide detach MS gradually without degradation of the initial polymer carrier structure. The biodegradation of polymeric matrix occurs only in blood plasma.

Consequently, we expect that polymeric derivatives of isonyazide and kanamycin will be used as storage with slow detachment of MS during long time in vital organism.

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