POLYURETHANE-BASED MACROMOLECULAR THERAPEUTIC SYSTEMS. PART 4. EFFECT OF ETHONIUM ON DIOXIDINE LIBERATION

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Due to a favorable combination of physicochemical, biological, and pharmaceutical properties, polyurethanes and related compounds have proved to be the most appropriate polymeric base for macromolecular therapeutic systems (MTS) [1 – 3]. For example, a foamed polyurethane (FPU)-based MTS, containing the immobilized drug dioxidine and certain proteolytic enzymes, is used in clinical practice for the treatment of acute bacterial infections [4].

In continuation of the systematic investigation into the synthesis and characterization of PU based MTS [5 – 7], we have studied the kinetics of dioxidine liberation from an FPU matrix and the effect of surfactants on this process.

The choice of dioxidine as a test drug is caused, on the one hand, by the broad spectrum of the antibacterial activity of this drug [8] and, on the other hand, by easy immobilization of the dioxidine molecules on the PU chain.

The selection of ethonium – N,N′-bis(2-decycloxy-2-oxoethyl)-N,N,N′,N′-tetramethyl-1,2-ethanediaminium dichloride – is related to the presence of this surfactant in almost all biological liquids and to the bactericide properties of this agent [9, 10].

Previously we have established [5] that dioxidine introduced, before the synthesis of an FPU-based MTS, into a polyol prepolymer (A) dissolves at a significant rate in the liquid phase at temperatures above 290 K. Neither the shape of the dissolution kinetics nor the effective rate constant of the dioxidine liberation from the FPU matrix depend on the dioxidine concentration in the prepolymer or on the liquid phase volume. The introduction of ethonium into the polyol prepolymer A before the MTS synthesis generally facilitates the passage of dioxidine from the high-molecular-weight phase to the aqueous phase.

The plot of Fig. 1*a* shows that, as the ethonium concentration in the polymer increases, the rate of dioxidine liberation shows an initial linear increase with the content of surfactant. Then the growth gradually slows down and the process rate becomes independent of the ethonium concentration (for $C^0_{SA} > 0.085$ M). Taking this fact into account, all the subsequent kinetic investigations were performed for the ethonium concentration in MTS equal to 0.085 M, thus providing that the effective rate constant of dioxidine liberation would be independent of the surfactant content in the polymer.

The character of variation of the rate of dioxidine liberation depending on the ethonium content (Fig. 1*a*) shows evidence that the dissolution process has the first partial order with respect to the ethonium concentration for the small initial contents of ethonium [the initial slope of the log W versus log C^0_{SA} plot (top curve in Fig. 1*a*) is close to unity] and the zero order with respect to this parameter for $C^0_{SA} >$ 0.085 M (where the process rate is independent of the surfactant concentration).

The presence of the "saturation" region in the log W versus log C^0_{SA} plot can be explained by two factors. At a relatively large surfactant content in the polymer (i) only dioxidine bound with a complex with ethonium can pass into the liquid phase and (ii) ethonium can reduce the surface tension at the polymer/liquid interface to a minimum level corresponding to the critical micelle concentration (CMC) for the given surfactant.

The kinetic curves of dioxidine liberation into water in the presence of ethonium are linearized in the coordinates of the first-order process (Fig. 1). This indicates that the process has the first order with respect to the initial drug concentration as well.

Study of the effect of the initial concentration of ethonium introduced, before the MTS synthesis, into the isocyanate prepolymer (B) showed that the kinetics of dioxidine liberation into water for this mode of surfactant immobilization is also described by a kinetic equation of the first order with respect to the dioxidine concentration in the polymer (Fig. 1*b*).

Here, the independence of the drug liberation rate (and, hence, of the effective rate constant as well) of the ethonium content is observed at approximately the same surfactant concentration in MTS as in the case of its introduction into a

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polyol prepolymer. However, the plot of log W versus log C^0_{SA} in the top of Fig. 1*b* shows that the partial order of the process with respect to the initial surfactant concentration in the polymer (determined from the slope of the initial linear region of this plot) is approximately 0.7. This result can be explained by the fact that, when dioxidine is introduced into one polymer and ethonium in the other, the drug – surfactant complexation may be hindered. Indeed, on blending of the A and B prepolymers, dioxidine will first interact with highly reactive isocyanate groups of prepolymer B, rather than enter into complexation with the surfactant. As was demonstrated previously [5], the passage into the liquid phase is hindered for dioxidine bound to the macromolecular chain.

We believe that a key factor determining the dioxidine liberation from an FPU matrix into the liquid phase in the presence of ethonium is the drug – surfactant complexation (facilitating the dissolution), rather than the surfactant-induced decrease in the interfacial tension. It is the dioxidine fraction bound into a labile complex with surfactant that predominantly passes into the liquid phase. The complexation of the surfactant with the drug studied produces partial or complete blocking of the hydroxyl groups of dioxidine, thus hindering its chemical binding to isocyanate groups of the prepolymer B. In addition, the complexation with surfactant facilitates the passage of dioxidine into the liquid phase, thus also favoring the overall liberation process.

The temperature dependence of the experimentally determined effective rate constant k (sec^{-1}) for the process studied in the presence of ethonium introduced, before the MTS synthesis, in both polyol and isocyanate prepolymers, is satisfactorily described by the Arrhenius equation. The activation parameters of dioxidine liberation calculated from this relationship are presented in Table 1.

A comparison of the kinetic and activation parameters of the dioxidine liberation from MTS into water showed that the introduction of ethonium into polymer is accompanied by a positive kinetic effect (facilitated dioxidine passage into the liquid phase), which is most clearly manifested upon the surfactant introduction into the polyol prepolymer (the effective rate constant k of the dissolution process increases almost ten times, while the apparent activation energy E decreases by a factor of one and a half as compared to the values characterizing the drug liberation in the absence of the surfactant).

An increase in absolute value of the negative activation entropy ΔS^* in the presence of ethonium (see Table 1) is evidence of an increase in the "rigidity" of the transition state

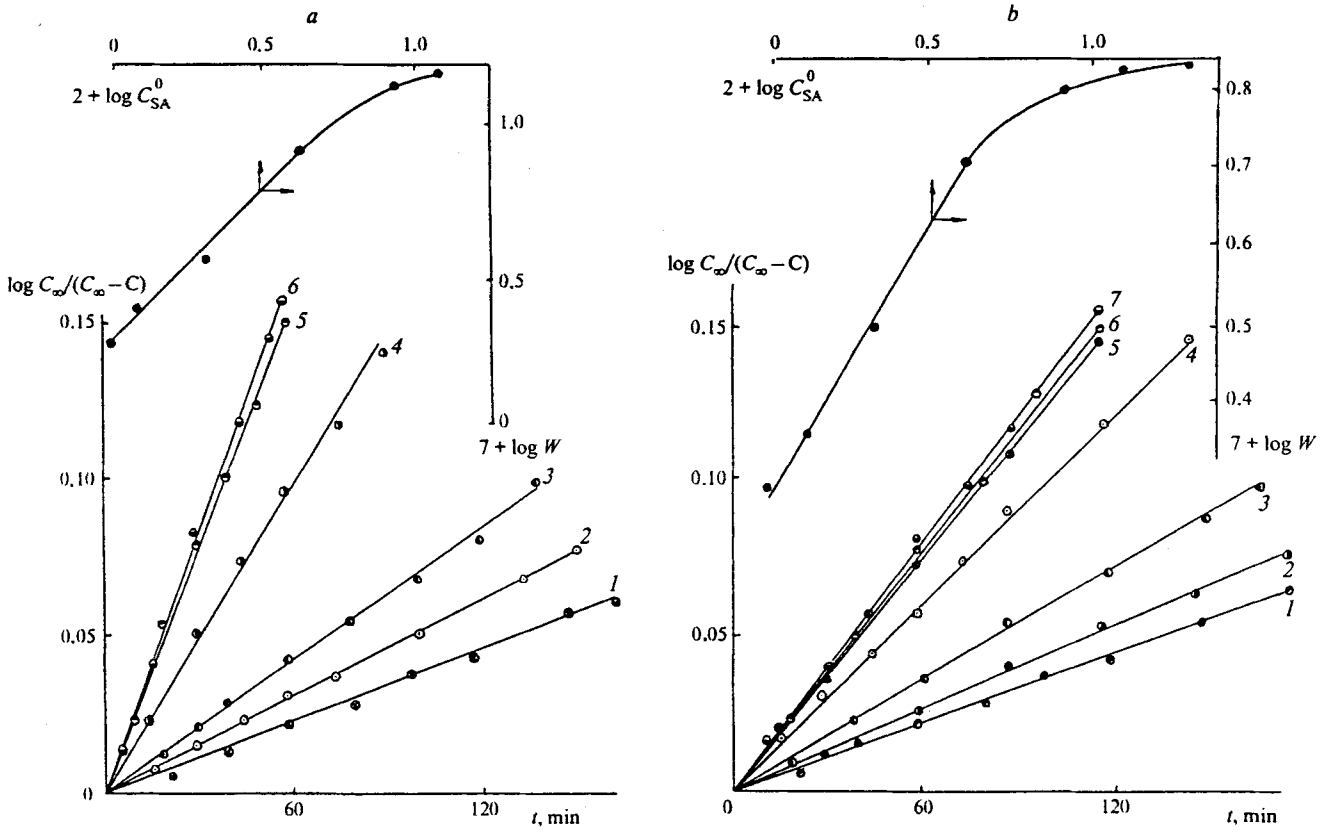

Fig. 1. Effect of the initial ethonium (surfactant, SA) concentration C^0_{SA} in an FPU based MTS on the yield of dioxidine (D) from composition into water (10 ml) at 310 K: *a*) surfactant and dioxidine introduced into prepolymer A; *b*) surfactant introduced into prepolymer B and dioxidine, into prepolymer A; $C^0_D = 0.34$ M; $C^0_{SA} = 0$ (*1*), 0.013 (*2*), 0.021 (*3*), 0.042 (*4*), 0.085(*5*), 0.128 (*6*), 0.212 M (*7*); C is the current dioxidine concentration (M), C_∞ is the value calculated assuming that all dioxidine has passed to the liquid phase (M), and W is the dioxidine liberation rate (M/sec).

upon the surfactant introduction, which is also explained by the dioxidine – ethonium complex formation.

The above notions do not disagree with the fact that the introduction of ethonium, before the MTS synthesis, into the isocyanate prepolymer leads to a less pronounced effect upon the kinetics as compared to the case of the surfactant introduction into the polyol prepolymer (see Table 1).

In order to characterize the effect of surfactant on the dioxidine liberation from a polymer matrix into the liquid phase in more detail, we have also studied the dissolution process in the presence of ethonium in the liquid phase in contact with MTS. It was established that neither the introduction of ethonium in the liquid phase nor the variation of the surfactant concentration from 0.003 to 0.034 M had significantly changed the effective rate constant of the dioxidine liberation (Table 1).

The temperature dependence of the effective rate constant of the dioxidine liberation from an FPU matrix into the aqueous solution is described by the Arrhenius equation. The activation parameters calculated from this relationship are listed in Table 1. As seen from these data, the introduction of ethonium into water has virtually no effect on the activation parameters of dioxidine liberation, which is explained by the impossibility of the complexation between drug and surfactant occurring under these conditions in different phases of the system. It should be noted that ethonium molecules occurring in the liquid phase are unable to form complexes even with the drug molecules present on the polymer surface. Indeed, the surfactant molecules are oriented at the interface so as to face the polymer surface with their hydrophobic ends not capable of forming any strong complexes with dioxidine molecules on the MTS surface.

Thus, the results described above indicate that facilitated liberation of dioxidine in the presence of ethonium is caused neither by a decrease in the surface tension at the polymer/liquid interface nor by solubilization of the drug with surfactant micelles present in the liquid phase (CMC of ethonium is 3.2×10^{-3} M at 298 K [9]). The key factor is apparently the drug – surfactant complexation occurring most likely by the hydrogen bond formation between polarized hydrogen atoms of the hydroxyl groups of dioxidine and carboxyl oxygen atoms of the ester groups of ethonium.

The study of the influence of ethonium on the dioxidine liberation into the physiological solution also showed an additional positive kinetic compensation effect. However, this effect is less pronounced that that observed for the drug liberation into water under the same experimental conditions (see Table 1). This difference is consistent with the data reported in [11]

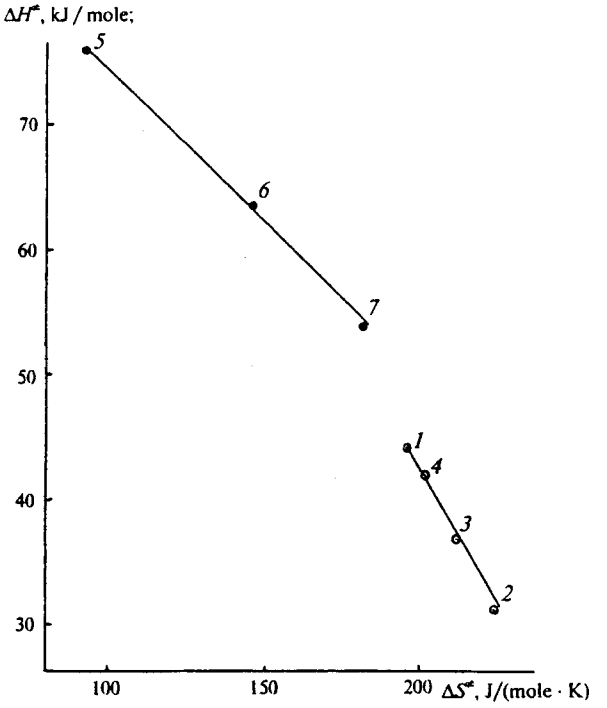

Fig. 2. The plot of enthalpy $\Delta H^{\neq}$ versus entropy $\Delta S^{\neq}$ for activation of the process of dioxidine (D) liberation from an FPU based MTS (0.4 g) into a liquid phase (10 ml) in the presence of ethonium (surfactant, SA); C_D^0 = 0.34 M; C_{SA}^0 = 0.085 M; $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values are reduced to 298 K; the numbers at the points correspond to those in Table 1.

where it was demonstrated that adding inorganic salts decreases the desorption of organic substances from FPU-based compositions.

In the course of dioxidine liberation into the liquid phase in the presence of ethonium, the kinetic compensation effect (Fig. 2) is manifested differently for the dioxidine evolving

TABLE 1. Activation Parameters for the Liberation of Dioxidine (D), Immobilized on a Polyol Prepolymer (A), from FPU (0.4 g) into a Liquid Phase (10 ml) in the Presence of Surfactant (Ethonium) at Temperatures Ranging from 297 to 319 K (C_D^0 = 0.34 M; C_{SA}^0 = 0.085 M)

No.	Liquid phase	Surfactant introduced into prepolymer	E, kJ / mole	log k_0	$\Delta H^{\neq}$, J/(mole · K)	$-\Delta S^{\neq}$, kJ / mole	$\Delta G^{\neq}$, kJ / mole
1	Water	–	46.2	3.1	43.7	194.4	101.6
2	Water	A	33.5	1.6	31.0	223.0	97.5
3	Water	B	39.0	2.3	36.5	210.5	99.3
4	Aqueous ethonium (3.4×10^{-3} M)	–	44.1	2.7	41.6	201.8	101.7
5	Physiological solution	–	78.8	8.4	76.3	92.6	103.9
6	Physiological solution	A	55.9	3.8	53.4	180.8	107.3
7	Physiological solution	B	65.9	6.7	63.5	146.2	107.0

Notes. The values of log k_0 and E were calculated by the least squares procedure (the rms errors do not exceed ± 0.3 and ± 6.5 kJ / mole, respectively); the values of enthalpy, entropy, and Gibbs energy for the process activation are reduced to 298 K.

into water and into the physiological solution. The quantitative relationship determined by mathematical methods is expressed by equations (1) and (2) for water and physiological solution, respectively:

$$\Delta H^{\neq} = 128.75 + 0.437\Delta S^{\neq}, \quad (1)$$

$$\Delta H^{\neq} = 100.49 + 0.258\Delta S^{\neq}, \quad (2)$$

The pairwise correlation coefficients in equations (1) and (2) are 0.989 and 0.992, respectively; the values of the enthalpy and entropy for the process activation are reduced to 298 K and expressed in kJ / mole and J/(mole · K), respectively.

The presence of the kinetic compensation effect indicates that the introduction of ethonium in the system does not significantly modify the mechanism of the limiting stage of the process of dioxidine liberation from an FPU matrix into the liquid phase.

Data obtained in this work suggest that the presence of surfactants in various concentrations in the liquid phase contacting with the FPU-based MTS has no significant effect on the laws of dioxidine liberation from the composition. This fact allows us to believe that all the laws established previously for the process of dioxidine liberation in the absence of surfactants [5 – 7] will be also generally valid for any real process with similar FPU-based drug compositions involved, for example, in the treatment of purulent wounds.

The yield of dioxidine into the wound fluid from an FPU-based drug composition can be controlled, if necessary, by introducing certain surfactants immediately into the high-molecular-weight base. The yield will be increased by surfactants capable, like ethonium, of forming labile adducts with the drug, that is, containing atomic groups susceptible to the surfactant – drug complex formation. Note that the surfactant must not contain any groups capable of interacting with highly reactive isocyanate groups of a prepolymer used for the FPU-based MTS preparation. The presence of such groups in the surfactant may reduce the rate of drug liberation into the liquid phase. On the other hand, this would provide (for a constant drug content in the composition) prolonged therapeutic action of MTS.

EXPERIMENTAL PART

A polyol prepolymer (A) was obtained by mixing 94 g (1.9×10^{-2} mole) of laprol 5003-26-10, 31 g (7.8×10^{-3} mole) of laprol 402-2-100, 7.2 g (6.4×10^{-2} mole) of 1,4-diazabicyclo[2.2.2]octane, and 3.0 g (0.167 mole) of water. The content of hydroxyl groups in prepolymer A was 1.1 wt.%. The isocyanate prepolymer (B) according to the technological conditions TU-113-03-29-12-83 was obtained by copolymerization of 5 g (2.5×10^{-2} mole) of laprol-202 and 35.2 g (0.133 mole) of 4,4′-diphenylmethanediisocyanate. The content of isocyanate groups in prepolymer B was 22.7 wt.%.

The PU composition was prepared immediately before experiments in a cylindrical pyrex glass setup specially designed for the study of the dioxidine liberation. The setup was charged with 0.3 g of prepolymer A, an aliquote (30 mg) of dioxidine, and (in the case when the surfactant is introduced into A) a weighted amount of ethonium. The mixture was thoroughly stirred manually to a homogeneous mass. To this mass was added 0.1 g of isocyanate prepolymer (B) or (in the case when the surfactant is introduced into B) a preliminarily prepared suspension of the surfactant in prepolymer B. The mixture was thoroughly stirred for 60 sec and allowed to equilibrate for 12 h. Then 10 ml of a liquid was placed over the polymer-based composition and the system was placed in a thermostat. This moment was considered to be the onset of the drug liberation process.

The experiments were performed with dioxidine according to the State Pharmacopeial Issue FS 42-1232-79. The drug was additionally purified by multiple recrystallization from absolute ethanol and dried for not less than 6 h at 323 K in a vacuum of 2.5×10^{-2} Torr to provide for the main substance content of not less than 99.8% (according to data of IR spectroscopy and chromatography). Ethonium (reagent grade) was used without additional purification.

The kinetics of dioxidine liberation from an FPU based composition was studied by a spectrophotometric technique using a KFK-3 instrument and measuring the peak of absorption at a wavelength of 409 nm. A reference cell was filled with a solution used as the liquid phase in a given experiment. Preliminary measurements showed that the ethonium solution is virtually transparent in this spectral region. The error of the dioxidine concentration in the liquid phase in all experiments did not exceed 1×10^{-4} M.

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