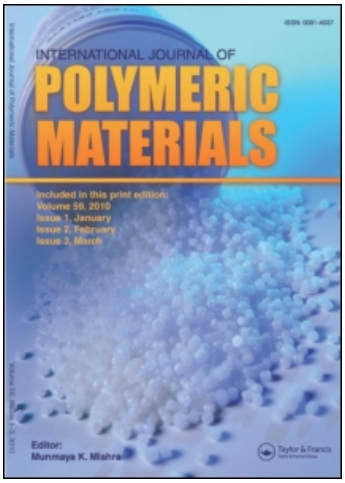

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Biodegradable Polymer-Based Controlled Release Systems: The Physicochemical Aspects. Part II. Parameters Determining Release Rate

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Parameters influencing the release rates from polymeric dosage forms are considered: geometric characteristics of the article, crystallinity, molecular weight and molecular weight distribution of biodegradable polymer, and also cross-linking degree, drug content, and so forth.

KEY WORDS Controlled release, biodegradable polymers.

Dosage forms based on biodegradable and bioerodable polymers open up basically new possibilities for the treatment of various diseases. The types of dosage forms based on such polymers and the drug release mechanisms were discussed in Part I. This part deals with the factors affecting the rate of drug release from such systems.

THE EFFECT OF DRUG DISTRIBUTION IN THE BIODEGRADABLE OR BIOERODIBLE POLYMERIC MATRIX ON THE DRUG RELEASE MECHANISM

The known dosage forms differing by type of drug distribution in a biodegradable polymeric matrix are as follows:

(I) The drug is uniformly distributed in the polymer as a solid solution.

(II) The drug is distributed in the polymer as macroscopic particles.

(III) The drug is coated with the biodegradable polymer.

(IV) The dosage form (a film, a sphere, a cylindrical capsule) is a polymer with the drug molecules (fragments) incorporated into (a) the main chain or (b) the side chain.

Type (I) dosage form is usually applied as implants. The implants are made of polylactide,[1-3] polyalkyl cyanoacrylates,[4] polyorthoethers[5] and other biodegradable polymers. In order to obtain such dosage forms the polymer and the drug are crushed, mixed and heated until the drug melts. This procedure provides for a sufficiently uniform distribution of the drug in the polymer. If the polymer used in the implant and the drug have a common solvent, the solution is prepared from these components, and the dosage form is produced through the subsequent evaporation. The latter method is mostly used for small-size implants such as films for subcutaneous application as well as to produce microcapsules, a precipitator being used in the latter case.

The consideration involves only such drug-polymer systems where the drug release rate is determined by the polymer implant resorption rate. The relevance criteria is easy to derive from the inequality obtained from the comparison of the equation of diffusion in the polymer and that of the polymer matrix resorption (6):

$$W_{\text{diff}} = -DS\frac{dc}{dl} \tag{1}$$

and

$$W_{\text{res}} = K_{\text{eff}}S \tag{2}$$

where K_{eff} is defined by the product of dl/dt and the implant surface area and the polymer density, i.e.,

$$-D\frac{dc}{dl} > K_{\text{eff}}. \tag{3}$$

Using this inequality, one can approximately estimate the drug concentration gradient as the ratio of the mean drug concentration c_0 to the boundary layer thickness taken as 10^{-4} cm according to the microscopic measurement.[7]

Given D of the order of 10^{-7} cm^2/s and the typical value of c_0 (0.1 g/cm^3), to provide for release in the kinetic region K_{eff} should be smaller than $10^{-7} \cdot 1.0/10^{-4} = 10^{-4}$ g/cm^2 s = 0, 36 g/cm$^2 \cdot$ h, which is a very considerable value and corresponds to the time of the polymer implant's operation for about 1 h. The comparison of the calculated value with the K_{eff} values given in reference 8 indicates that for polymers such as polyglycolide, release should be in the kinetic region when inequality[3] is satisfied.

Thus a considerable part of the drug-biodegradable polymer system ensures drug release at the rate determined by the rate of polymer biodegradation through volume or from the polymer's surface.

Type (II) dosage form (see the classification presented above) is used when the drug is insoluble in the polymer. Uniformity of the drug distribution across the polymeric matrix is determined by the technological parameters of the mix. The higher the dispersion of the drug particles incorporated in the polymer, the more uniform the release. Since in the solid phase the intermolecular interaction is

stronger, diffusion of the drug from macroscopic particles is likely to be slower than from the solid solution (Type (I) systems). Therefore, release in the kinetic region is also more probable. The importance of the aggregate state and its influence on drug release rate is discussed in more detail in reference 9.

When using dosage forms with the drug coated in a biodegradable polymer (Type (III) systems) it should be taken into account that two competing processes, viz. biodegradation of the coating, the thickness of which continuously diminished due to surface erosion, and the outward-directed diffusion of the drug through the coating, may be at work. Such dosage forms primarily include injection microcapsules.

The rates of the two processes are equal, respectively:

$$-\frac{dm}{dt} = K_{\text{eff}}S \tag{4}$$

$$\frac{dm}{dt} = -DS\frac{dc}{d\gamma} \tag{5}$$

where γ is the coating thickness.

It is easy to deduce that the degradation rate will decrease due to the reduction in the implant's surface area, even if insignificantly, while the drug diffusion rate increases due to an increase in the concentration gradient although there may appear the counteracting factor, that of the gradual drug depletion. In theory, it may be expected that under certain conditions the release rate from the microcapsule will pass an extremum. The cases of the "explosive" release in such systems have indeed been recorded, although generally it occurs in conformity with the kinetic law of the zeroth order.[10,11]

We may expect that in the case of the zeroth order we will be dealing with the polymeric matrix biodegradation, whereas in the first order we will encounter purely diffusion release. It should be born in mind that in the version above diffusion resistance of the coating to the drug flow continually diminishes and the contribution of diffusion grows so that under certain conditions release may shift from the kinetic region to the diffusion region. To give an idea of the drug flows in the systems with biodegradable coating (microcapsules) let us make the following computation.

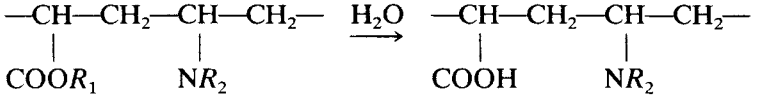
Given that the mean diameter of a microcapsule is 10 μm, its surface being ca. 3.10^{-6} cm^2, and the 10% load of the drug (by mass), it is easy to calculate that at the density of ca. 1 g/cm^3 the initial thickness of the coating is about 7.9 μm. Hence the initial value of the concentration gradient is 1,800 g/cm^4 while the diffusion flow (at $D = 1 \cdot 10^{-7}$ cm^2/s) makes up $4 \cdot 10^{-5}$ g/cm^2 day. If release proceeds uniformly at this rate and the total surface of a microcapsule is 1 cm^2, then 100 mg of the drug is released in $2.5 \cdot 10^4$ days, which fails to meet the requirements of the drug's input. We are thus led to believe that at application of biodegradable microcapsules the greater share of the drug is released as a result of biodegradation of the polymer coating shell. This is indirectly evidenced by the dynamics of reduction in the size of microcapsules coated with polylactic acid.[12] The feasibility

of this kinetic version is supported by the K_{eff} values calculated from the data on biodegradation of heterochain polymers.[8]

Type (IV) systems are mostly soluble dosage forms. Of these, systems with drug fragments in the side chain are studied best and described in detail in reference 13. At the same time, the known systems with drug fragments in the main chain are few in number. They include, for instance, heterochain polyamides based on β-aminolevulinic acid liable to degradation in model media.[14] Other insoluble systems with drug fragments in the main chain are found only among the polymers with the biocidic properties and phytoactivity.[15]

Self-degrading systems of the autolytic type first described in reference 16 are close to those under consideration and are potentially possible. Essentially, the material for such systems consists of a mixture of the heterochain polymer containing catalytically cleaved bond, the polymeric catalyst of degradation. Yet, in principle, another type of intermolecular catalysis is also possible. It can be realized through the use of water-insoluble polyalkyl acrylate splitting off the alkyl groups under the action of a catalyst of the polyvinylpyridine. The catalytic action of the latter in hydrolytic reactions of low molecular weight substrates is described in references 17 and 18.

The creation of the catalytic center incorporated into the side chain of the polymeric drug carrier is the limiting and, in the certain sense, ideal case. When dry, such a system is stable. As it swells in an aqueous medium, immobilization of the active centers is canceled and they initiate hydrolysis in the neighboring side chain according to the following scheme:



insoluble soluble

where R_1 is the drug fragment and R_2 is the radical.

As a result of hydrolysis the mixture or the individual polymer dissolves and the drug is released, the limiting condition being that the molecular weight of the dissolved products does not exceed 40,000, this being the limit determined by the permeability of tubules of the kidney. Another requirement, naturally enough, is that of the absence of acute toxicity.

The general problems of synthesis of polymers with catalytic groups performing intramolecular catalysis are discussed in reference 16. The main advantage of such systems, admitting of fast input of the drug under the extreme conditions, consists of a dramatic acceleration of hydrolysis through the formation of the intermediate ring structures. At the same time, this restricts the application of autolytic systems in long-term controlled release devices.

KINETIC LAWS OF DRUG RELEASE FROM BIODEGRADABLE POLYMERS

The general kinetic regularities of drug release from the systems of the type described are discussed in reference 19. At this point it should be emphasized that

the kinetic regularities are, to a certain extent, dependent on whether degradation occurs across the whole bulk of the drug-containing polymer or involves the surface alone (surface "erosion"). In the first case it may be expected that the kinetics will be very much like the common homogeneous (classical enzymic, in particular) kinetics whereas the surface "erosion" will proceed as the reaction of the pseudo-zeroth order.

The main types of kinetic curves for drug release from biodegradable polymers are presented in Figure 1.

The kinetics represented in Figure 1a satisfy the first-order law and is observed in the release of pyrimethamine from microcapsules made of homo- and copolymers of lactic acid,[20] caffeine[21] and methylcatechol[22] from cross-linked polyethylene oxide hydrogels, testosterone from polypropylene glycol[23] and in many other cases. In a number of cases a drop in the rate may be quantitatively explained by drug depletion. Yet such kinetic curves are frequently rectified in coordinates $M_t/M_\infty - t^{1/2}$, which correspond to the coordinates of the equation for diffusion from semi-infinite plate.[24] This is also an indication of the diffusion release mechanism in the systems described in references 21–23.

The kinetics represented in Figure 1b corresponds to the kinetic equation of the zeroth order (constant rate). Kinetics of this kind is observed in the case of such systems as film implants from polylactides containing pyrimethamine.[20] The pharmacokinetic conditions of release with reference to the first and zeroth orders are discussed in reference 25.

The most probable explanation for kinetic curves of this type is offered by assuming surface "erosion" with the simultaneous passage of some part of the drug into the solution. This assumption is confirmed for some cases by electron microscopy.[12]

The curves shown in Figure 1c are likely to be the superimposed curves of the first and zeroth orders, i.e., they testify to the existence of at least two simultaneous and independent processes occurring in the system, these being the polymeric matrix biodegradation and the outward-directed diffusion of thus released molecules or fragments of the drug.

Finally, the curves with the inflection point represented in Figure 1d obviously indicate a change of reaction region. For instance, the first stage of release of the narcotic antagonist, cyclazocin, from composites based on polylactic acid lasting

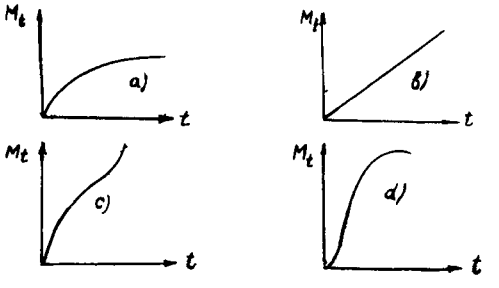


FIGURE 1 Typical kinetic curves of drug release from biodegradable polymers. (a) The first order. (b) The zeroth order. (c) Superimposed curves of the first and zeroth orders. (d) The transition from the diffusion region to the kinetic region.

for up to 10 days, proceeds with self-acceleration to be followed with the stage described by the first-order equation. It may be assumed that at the first stages the reaction is catalyzed by lactic acid formed at biodegradation, which, at later stages, is quickly washed from the implant as its size diminishes.[26]

In conclusion of this section we would like to make two remarks. First, it should be remembered that in most experiments the dynamics of drug release from the polymeric matrix is studied *in vitro*. In some cases investigation of release *in vivo* reveals somewhat different regularities but such studies are few because of the need to apply the labor-consuming radioactive tracer method.[27,28]

Of special interest is the study on the practically important case of the simultaneous release of two or more drugs from the polymeric matrix. As is shown in reference 29, in such cases it is necessary to maintain both certain concentrations of individual drugs in the blood and the very ratio of these concentrations, which, depending on values of the kinetic constants, may monotonically decrease with time, monotonically increase, or pass through an extremum, as can be seen from the equation derived in the paper cited:

$$\frac{[Dr]'}{[Dr]''} = \frac{K_i'/(K_i^{el})'\{1 - \exp(-K_{el}' \cdot t)\} + (D)_0'}{K_i''/(K_i^{el})''[1 - \exp(-K_{el}'' t)] + (D)_0''} \tag{6}$$

where the superscripts ′ and ″ refer to the first and the second drug, respectively, K_{e1}' and K_{e1}'' are the rate constants of elimination of the first and the second drug from the blood, $(D)_0'$ and $(D)_0''$ are the initial concentrations of the two drugs, respectively (in the most common case they are equal to 0) and t is the time.

THE EFFECT OF THE POLYMER'S CRYSTALLINITY ON THE DRUG RELEASE RATE

Most reactions in solid polymers are known to occur in sites of the greatest molecular mobility, i.e., in the amorphous regions. In the general case, therefore, it should be expected that biodegradation proceeding across the volume and releasing the drug will be retarded with an increase in crystallinity, and that bioerosion from the surface of a polymeric item will be independent of crystallinity. The disparate experimental findings currently available give some grounds to believe that the two cases discussed may occur.

To illustrate, in the work dealing with biodegradation of polyglycolide surgical threads[30] it was shown that the initial crystallinity was 40%, after three weeks it was 52% and on day 90 it was 23%. If degradation had occurred in the amorphous regions only the degree of crystallinity should have increased monotonically, but this was not the case. At the same time the degree of degradation on days 49, 60 and 90 was 42%, 56% and 70%, respectively, which also does not agree very well with the assumption that the reaction is confined to the amorphous regions. We agree however with the authors of reference 31 that the considerable part of the degradation in a partially crystalline polymer takes place at the boundaries of crystallites.

On the other hand, there are cases when a change in crystallinity causes a symbatic change in the release rate. The study of biodegradation in δ-polycaprolactone samples of varying degree of crystallinity indicates a decrease in biodegradability with a decrease in crystallinity.[32] These findings show that the change in the rate of drug release from biodegradable polymers caused by the change in crystallinity is not unambiguous. This is confirmed by the data presented in reference 20, where the authors found that semicrystalline polymers of lactic acid release pyrimethamine at a slower rate than amorphous copolymers containing 50%, 37% and 5% of lactic acid residues, respectively. Yet the assumption of the influence of crystallinity based on these findings should be taken with a grain of salt, since, according to these data, the obtained samples differed both in MW and MWD.

The discussed regularities are, above all, characteristic of release occurring in the kinetic region when the total release rate is determined by the rate of cleavage of the labile bonds in the main chain (degradation) or the side chain (solubilization). The regularities established for reactions in solid polymers[33] are fully applicable to these processes.

Release in the diffusion region, like chemical reactions, may also proceed at an appreciable rate only in the amorphous regions of polymers. With polymers of the initially high crystallinity, degradation may lead to the formation of cavities due to dissolution of the degradation products, facilitating transport of the drug outwards. The accelerated release of levongestrel at the last stages of the lactide copolymers biodegradation observed by the authors of reference 28 is likely to be associated with this effect, whose statistical nature is indisputable. The same is true of release of testosterone from subcutaneous implants based on polylactic acid.[34]

THE EFFECT OF MOLECULAR WEIGHT OF THE POLYMER ON THE RATE OF CONTROLLED RELEASE

Experimental studies on how the molecular weight of a biodegradable polymer affects the rate of drug release are not numerous. For instance, the study on the release of butambene from polylactic acid microcapsules[12] shows a regular decrease of the release rate on going from a polymer with the molecular weight of 9,100 to polymers with molecular weights of 17,000 and 25,000. The initial release rates for low molecular and high molecular weight samples differed by 3–4 times. The same authors discovered a similar effect on replacing butambene with tetracaine and dibucane. With lactic acid oligomers the effect is even more marked.[1]

The described effect may have two different explanations.

If release occurs in the diffusion region, it is possible to assume a well-known dependence of the diffusion coefficient on the molecular weight of the polymer[35]:

$$D = aM^{-1/2} \tag{7}$$

where M is the molecular weight and a is the proportionality factor. In accordance with this equation the triple increase of M should result in retardation of the rate of release by about 1.7 times, which only semiquantitatively agrees with the data presented above.

At the same time, drug release from cross-linked polyacrylamide gels is quantitatively correlated with the polymer's molecular weight and with its swelling according to the empirical equation[36]:

$$D = D_0\exp[(-d + bM)R] \tag{8}$$

where D_0, d and b are the constants for the given homologous series and R is the weight portion of the polymer in the gel.

As can be seen from this equation, in the given case we deal with a more rigid (exponential) dependence of the release rate in the diffusion region on the polymer's molecular weight. This underscores the importance of observance of the process specifications in producing polyacrylamide used for such gels.†

With release in the kinetic region, the rate of mass loss at heterogeneous degradation increases over time due to the accumulation of the share of fragments that may pass into the solution.[38] This idea was then developed in reference 39, where it was for the first time predicted that the molecular weight distribution (MWD) could affect the rate of the drug carrier resorption. Assuming that splitting of the chain occurs only by bonds of the same type at each monomer link and that molecules of a certain length are not described by the functional distribution (Z = 0, 1 or 2), it is possible to relate Z and MWD. It is also assumed that molecules containing $\leqq 1$ monomeric links may be formed as a result of both the degradation of chains of greater length and disappear due to the subsequent degradation and dissolution. The corresponding differential kinetic equations have the following form[39]:

$$N_{m-i} = \exp(-K_{bl}) \sum_{j=0}^{j=i} \frac{K_j N^0_{m-i-j}}{j} \tag{9}$$

where K_b is the rate constant for dissolving of molecules of length 1; N_{m-i} is the initial number of chains consisting of $m - i$ monomeric links. If the number of the molecule's functional ends Z with j monomeric links is constant for any j, then $KZ_j = K^I$.

The mass loss rate in the given system is equal to the sum of members with the respective account of biodegradation and passage of the degradation products into the solution:

$$\frac{dP}{dt} = K^I \sum_{i=1}^{i=\max} Ni + \sum_{j=1}^{j=1} jK_jN_j \tag{10}$$

where P is the number of the removed monomeric links; the first member relates

† The effect of molecular weight on release was also found in the study on release of levongestrel steroid from lactideglycolide copolymer of the 90:10 composition.[28] On going from the copolymer with the molecular weight of 40,000 to the copolymer with the molecular weight of 165,000 the release rate was virtually unchanged and for the implantation time of 40–100 days was around 5.4 μg/day. A double drop in the release rate was ascertained at an increase in the molecular weight of the same copolymer from 150,000 to 210,000.[37]

to mass loss at biodegradation and the second denotes loss of mass due to dissolution. The theoretical curves of the dependence built in the coordinates of the latter equation are presented in Figure 2. One can see that the loss of mass in a polymer with a relatively narrow MWD is at first small and then increases sharply, as some critical degree of degradation is achieved. In a polymer with a wider MWD this transition is less dramatic, which makes it more suitable for temporary implantation for the purposes of drug introduction.

The scope of the research into the effect of MWD on controlled release is modest. The authors of reference 2, for instance, used samples of lactic acid homo- and copolymers containing pyrimethamine and having MWD from 1.6 to 2.5, the respective average molecular weights being 53,000 and 127,000. Yet we can hardly interpret the findings unambiguously since the chemical composition and the drug content varied for different samples. For instance, the rate of the pyrimethamine release from lactic acid (M_w/M_n = 2.5) was the same as in the case of the copolymer containing 92% of lactic acid residues and 8% of glycolide links (the MWD width is 1.6; the drug charge is 17% of mass). In the absence of other available experimental findings the theoretical considerations presented in the foregoing discussion prompt the conclusion that the effect of MWD on drug release does exist.

THE EFFECT OF GEOMETRIC PARAMETERS OF A POLYMER ITEM ON THE RATE OF CONTROLLED RELEASE

The geometric dimensions may affect the rate of diffusion release. As follows from the diffusion theory, rate of the diffusion processes depends on dimensional characteristics, e.g., on thickness or, more accurately, half-thickness for films and plates, or radius for spheres and cylinders.[24]

In the paper dealing with release of the caffeine from cross-linked polyethylene oxide films, it was indeed shown that there exists a linear dependence between the release halflife and the square of film thickness.[21] This dependence exactly corresponds to the known diffusion equation:

$$M_t/M_\infty = 4.0\left(\frac{Dt}{1^2}\right)^{1/2}$$

where M_t and M_∞ are the amounts of drug released by time t and at equilibrium.

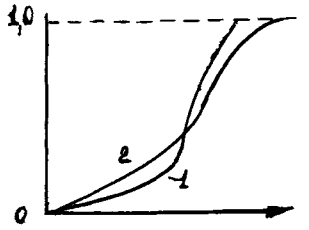


FIGURE 2 The dependence of the relative loss of mass with time for samples with different MWD. (1) Sample of a biodegradable polymer with a more narrow MWD, and (2) a Sample with a wide MWD, on the ordinate—relative loss of polymer mass due to degradation.

The effect of particle size on release rate is demonstrated in reference 41. It is found that release of naltrexone from the lactide-glycolide copolymer particles of 600 μm in 55 days amounted to 10% while the 100-μm and 200-μm particles yielded 18%, the initial release rates for samples of these two groups being 0.65% and 2.0%, respectively. In the given instance the results obviously indicate the diffusion nature of release.

THE EFFECT OF OTHER FACTORS

Other factors, the influence of which on drug release has been experimentally ascertained include:

(a) The drug charge in the polymer. The effect of this factor was ascertained in the earliest works on drug release performed in the 1970s. Of later works, the study on release of pyrimethamine from polylactic acid matrices implanted to experimental animals[20] should be mentioned. The kinetic curves of release presented in that paper show that on day 50 matrices, containing 17%, 40% and 60% of the drug, released 14%, 35% and 52%, respectively. Yet the coincidence of this dependence on the initial concentration with that predicted by the appropriate diffusion equation[24] is purely qualitative. The result, therefore, may be interpreted as release in the kinetic region.‡

(b) Cross-linking of the carrier polymer. It may be assumed *a priori* that an increase in the cross-link density retards release due to a decrease in permeability of the network (diffusion release) and a decrease in the rate of cleavage of soluble fragments from the polymeric network. This conclusion was confirmed experimentally in the study of release of caffeine and other drugs from cross-linked polymers of ethylene oxide[21] and in other works on drug release.

(c) The composition of copolymeric drug carriers. Many physicochemical properties of polymers are known to depend on composition. More often than not, such a dependence proves to be nonlinear.[42] Thus the melting point of crystalline glycolide-ethylene oxalate copolymers is extremely dependent on the composition, the hydrolytic resistance extremum manifesting itself at the glycolide content of ca. 60 mol%.[43] Such a hydrolytic resistance dependence impedes the utilization of these systems for drug release due to the problems involved in the composition reproducibility.[44] The effect of the composition has recently been demonstrated in cis-platin release from lactide-glycolide copolymers.[45]

CONCLUSION

Microcapsules for injective administration and implants based on biodegradable and bioerodible polymers containing drugs represent a new dosage forms appli-

‡ For implants based on lactide-glycolide copolymers and containing naltrexone, the degree of loading is a very significant factor. For instance, rods containing 50, 60, 70 and 80% of haltrexone released it at the rate of 2.1, 2.8, 5.0 and 11%/day, respectively.[37] Such an effect cannot be ascribed merely to an increase in the drug concentration gradient and requires some additional studies to be explained.

cation area. The characteristic feature of these dosage forms is that, having released the drug, the polymeric matrix is completely eliminated (resorbed) under the impact of the biological environment. The rate of drug release from such systems is determined both by the chemical nature of the drug and the polymer and by the region (kinetic or diffusion) where the release occurs. The secondary factors affecting release include crystallinity, MW and MWD, the drug loading in the polymer and shape of microcapsules with biodegradable polymers or of implants based thereon.

References

1. R. Wada, S.-H. Hyon and Y. Ikada, *J. Bioactive Compat. Polymers*, **3,** 126 (1988).
2. M. Tsahata, J. Willard and M. Roland, *J. Controlled Release*, **5,** 233 (1988).
3. M. Vert, J. P. Renoit and G. Splenlehauer, *J. Controlled Release*, **7,** 217 (1988).
4. C. Damgé, C. Michel and M. Aprahamian, *Diabetes*, **37,** 246 (1988).
5. J. Heller, *J. Bioactive Compat. Polymers*, **3,** 87 (1988).
6. Yu. V. Moiseev and G. E. Zaikov, *Chemical Resistance of Polymers in Aggressive Media*, Khimiya, Moscow, 1979.
7. *Diffusion in Polymers* (J. Crank and C. G. Park, eds.), Plenum Press, London, 1968.
8. Yu. V. Moiseev, T. T. Daurova and O. S. Voronkova, *J. Pol. Sci., Polymer. Symp.*, **66,** 269 (1979).
9. E. F. Vainshtein and V. S. Livshits, *Khim-Farm. Zh.*, **11,** 1300 (1987).
10. N. Wakayama, K. Juni and M. Nakano, *Chem. Pharm. Bull.*, **29,** 3363 (1981).
11. J. Heller, *CRC Critical Reviews in Therapeutics and Drug Systems* (J. Heller, ed.), CRC Press, Boca Raton, Florida, **1,** 39 (1984).
12. N. Wakiyama, K. Juni and N. Nakano, *Chem. Pharm. Bull.*, **30,** 2621 (1982).
13. N. A. Platé and A. E. Vasil'ev, *Physiologically Active Polymers*, Khimiya, Moscow, 1986.
14. V. S. Livshits, A. V. Zakirov and V. A. Savin, *Symposium on Physiologically Active Synthetic Polymers* (N. A. Platé, ed.), Riga, Zinatne, 1971, p. 52.
15. M. I. Shtil'man, Advances in Science and Technology, ser. Chemistry and Technology of High-molecular Compounds (V. V. Korahak, ed.) **20,** 252 (1986).
16. G. E. Zaikov and V. S. Livshits, *Khim-Farm. Zh.*, **4,** 416 (1984).
17. V. A. Kabanov, *Uspekhi khimii*, **36,** 217 (1967).
18. V. S. Livshits and E. I. Klabunovsky, Vysokomolekulijarnye Svedineniya, **12B,** 348 (1970).
19. V. S. Livshits, E. F. Vainshtein and G. E. Zaikov, *Polymer Yearbook* (R. A. Pethrick, ed.), 7 (1990) in press.
20. M. Tsahata, J. Willard and M. Roland, *J. Controlled Release*, **5,** 233 (1990).
21. N. B. Graham, M. Zulfugar and B. B. McDonald, *J. Controlled Release*, **5,** 243 (1988).
22. B. Gander, R. Gurny and E. Doelker, *J. Controlled Release*, **5,** 272 (1988).
23. G. Contrath, R. Y. Folson and M. Beehar, *J. Controlled Release*, **5,** 285 (1988).
24. J. Crank, *The Mathematics of Diffusion*, Clarendon Press, Oxford, 1975.
25. W. K. Cheung, A. Yacobi and B. M. Silber, *J. Controlled Release*, **5,** 263 (1988).
26. J. H. R. Woodland, S. Yolles and D. A. Blake, *J. Med. Chem.*, **16,** 897 (1973).
27. S. Z. Roginsky and S. E. Shnol', *Isotopes in Biochemistry*, Academy of Sciences Publishers, Moscow, 1963.
28. A. C. Sharon, D. L. Wise and J. F. Howes, *Biopolymeric Controlled Release Systems* (D. L. Wise, ed.) **2,** 3 (1984).
29. V. S. Livshits and E. F. Vainshtein, *J. Chem. Biol. Kinetics*, 1 (1991), in press.
30. C. C. Chu, *J. Biomed. Mater. Res.*, **15,** 19 (1981).
31. Yu. V. Moiseev and G. E. Zaikov, *Chemical Resistance of Polymers in Reactive Media*, Plenum Press, London, 1986.
32. C. G. Pitt and A. Shindler, Biodegradables and Delivery Systems for Contraception (E. S. Hafez and W. A. van Os, eds.), Hall Medical Publishers, Boston, 1980, p. 17.
33. *Chemical Reaction of Polymers* (Z. A. Rogovin, ed.), Khimiya, Moscow, Vols. 1, 2 (1967).
34. J. Kaetsu, *J. Bioactive Compat. Polymers*, **3,** 164 (1988).
35. *Immobilized Enzymes* (I. V. Berezin and K. Martinek, eds.), Moscow State University Publ., Moscow, 1976.

36. B. K. Davis, *Proc. Roy. Natl. Acad. Sci. U.S.A.*, **71,** 3120 (1973).
37. D. Gresserj and J. E. Sanderson, *Biopolymeric Controlled Release Systems* (D. L. Wise, ed.) CRC Press, Boca Raton, Florida, **1,** 127 (1984).
38. V. S. Livshits, L. F. Krivirotova and I. A. Tsirule, Vysokomolekulyarnye/Svedineniya, **18B,** 336 (1976).
39. E. F. Vainshtein and V. S. Livshits, *Khim.-Farm. Zh.*, **3,** 332 (1989).
40. I. I. Bronshtein and K. A. Semendyaev, *Handbook on Mathematics*, Vysshay Shkola, Moscow, 1955, p. 455.
41. S. Yolles and M. F. Sartori, *Drug Delivery Systems* (R. L. Juliano, ed.) Oxford University Press, Oxford, 1980, p. 93.
42. P. Flory, *Principles of Polymer Chemistry*, Cornwell University Press, Ithaca, 1953.
43. G. E. Zaikov and V. S. Livshits, *Polymer Degrad. Stab.*, **17,** 65 (1987).
44. A. L. Iordansky, T. E. Rudakova and G. E. Zaikov, *Interaction between Polymers and Biological Media. Diffusion and Chemical Reactions*, Nauka, Moscow, 1991.