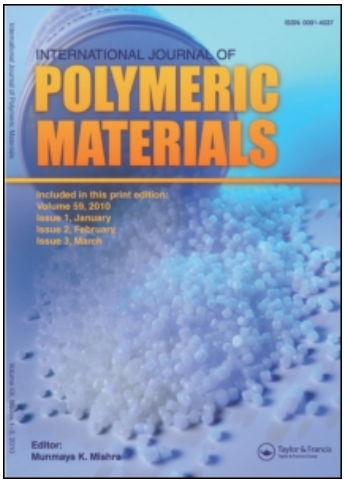

International Journal of Polymeric Materials
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713647664

Biodegradable Polymer-Based Controlled Release Systems: The Physicochemical Aspects. Part I. Systems and Mechanisms

V. S. Livshits[a]; G. E. Zaikov[ab]
[a] The All-Union Research Institute of Medical Polymers, Moscow, USSR [b] Institute of Chemical Physics, the USSR Academy of Sciences, Moscow, USSR

To cite this Article Livshits, V. S. and Zaikov, G. E.(1992) 'Biodegradable Polymer-Based Controlled Release Systems: The Physicochemical Aspects. Part I. Systems and Mechanisms', International Journal of Polymeric Materials, 16: 1, 267 — 276
To link to this Article: DOI: 10.1080/00914039208035428
URL: http://dx.doi.org/10.1080/00914039208035428

Intern. J. Polymeric Mater., 1992, Vol. 16, pp. 267–276
Reprints available directly from the publisher
Photocopying permitted by license only

Printed in the United Kingdom

Biodegradable Polymer-Based Controlled Release Systems: The Physicochemical Aspects. Part I. Systems and Mechanisms

V. S. LIVSHITS and G. E. ZAIKOV

The All-Union Research Institute of Medical Polymers, 117246 Nauchny proezd, 10 Moscow, USSR and the Institute of Chemical Physics, the USSR Academy of Sciences, 117334 Moscow, USSR

Typical systems biodegradable polymer-drugs for the treatment of different diseases are considered and also the dosage forms used therein. Biodegradable polymers are classified as to degradation mechanism, hydrolysis mechanism and solubilization mechanism. Influence of the distribution type of drug in biodegradable polymer is described in relation to release rate.

KEY WORDS Controlled-release, biodegradable polymers.

INTRODUCTION

The last decade has been a time of sustained efforts in the development of controlled release systems based on biodegradable polymers. This field has been dealt with in hundreds of papers, in several reviews[1-4] and in a special journal, Journal of Controlled Release (United States). In the USSR, the contribution to this research effort has been nearly negligible. It appears useful, therefore, to familiarize the readers with the specifics of this research trend and with the outlook for such systems in pharmacology.

Until 1973 controlled release systems were based on bioinert polymers and were almost always introduced into the organism by way of subcutaneous implantation, or were inserted under the eyelid, into the uterus or other organs. Normally, after the drug is exhausted, a repeated surgery is required in order to remove the therapeutic system from the organism. The replacement of the bioinert polymer by the biodegradable variety helps not only avoid such an operation but also changes the kinetic characteristics of release, as demonstrated in the following discussion.

The distinction between the terms "biodegradable" and "bioerodible" is discussed in review.[5] Here we will confine ourselves to the statement that polymer is called bioerodable if its degradation with the subsequent dissolution of the oligomeric products proceeds from the surface, whereas biodegradation occurs if the

external liquid medium quickly penetrates into the polymer and degradation takes place through the whole bulk. These are, indeed, the two extreme cases.

The drug-biodegradable polymer systems were first described by Yolles[6] and Yakanicz[7] in 1973. Given the general case, when the drug is evenly distributed in the polymer, the drug in such a system is released due both to the outward-directed diffusion and to the polymer's degradation.

The quantitative study of factors determining the behavior of such systems is a complex and topical physicochemical problem.

The present paper aims at the generalization of the available literature data on drug release using biodegradable polymers and at the quantitative study of the factors determining the kinetics and absolute rates of this process.

Types of dosage forms based on biodegradable polymers and peculiarities of their applications

The rationale behind any controlled release system is to ensure a long-term effect of the drug and its steady release. In addition, the system's components should be selected so as to ensure that the polymeric matrix biodegradation is commensurable with the required duration of the drug's effect. This period may vary from several hours to several years, and depends largely on the time it takes for the polymer to resorb, which determines its biodegradability. As is known, this ability is determined by the kinetic parameters of the chain splitting or by the characteristics of various reactions resulting in solubilization of the polymer, such as, e.g., hydrolysis and cleavage of hydrophobic side groups.[1]

Microcapsules are the most widely used dosage forms based on biodegradable polymers. Usually they are in the form of microspheres 50–200 μm in diameter. The sphere contains the drug, the mass of which may reach 70–80% of the microcapsule mass. The techniques used to produce microcapsules are described in detail elsewhere.[8]

Microcapsules can be injected into the blood channel, the time of their circulation being determined by the nature of the polymer and the diameter of microcapsules. One of the first applications of biodegradable polymer microcapsules was that of "streptodecase" of dextran dialdehyde† represented by microcapsules containing the thrombolytic enzyme streptokinase.[9] Strictly speaking, this pharmaceutical was not a microcontainer as streptokinase was immobilized on the outer surface of particles. The release, therefore, began immediately upon the introduction of microparticles, which is very important in critical situations connected with the thrombus formation.

The resorbable coatings of microcapsules are made of optically active and racemic polylactic acid,[10–13] lactide copolymers,[14,15] copolycondensates of alginic acid and poly-L-lysine,[16] homo- and copolymer polyamino acids,[17] polycyanoacrylates,[18] polyorthoesters,[19] polyanhydrates,[20] and so forth.

Another method of introduction of resorbable polymer microcapsules is oral

† Partially oxidized dextran.

administration, ensuring a fast decrease in the level of the undesirable metabolite in the patient's blood.[21] Occasionally, they were administered subcutaneously.

Polymers used for controlled release should meet the same requirements as polymers that come into contact with blood and other tissues of the organism, i.e., tissue compatibility, absence of strongly acidic or strongly basic groups in order to avoid changes in the physiological pH values and absence of toxic, pyrogenic or carcinogenic action.

Intracavitary and subcutaneous implants represent the second type of dosage forms based on biodegradable and bioerodible polymers. Such implants may be quite diverse in their geometric shape and have the form of films, discs, cylinders and tubes.[22,23] The protracted application of such long-term implants is possible only when the drugs that are used are very active and their effects manifest themselves as contraceptives or insulin used in the treatment of insulin-dependent diabetes mellitus.

The treatment of cancer, especially in advanced stages, is known to be impeded by the need to use high doses of rather toxic drugs while the greater share of the active specie metabolizes before it gets to the target organ. The implantation of the drug-containing polymer into this organ provides for the directed drug transport. Such a use of biodegradable polymers is also applicable in special kinds of treatment such as, e.g., hormonal therapy, immunotherapy and enzyme therapy. The efficacy of such kinds of treatments is enhanced by special additives, surfactants for instance, and by the use of highly hydrophilic polymers. The implanted needles of polylactic acid containing the luteinizing hormone for the treatment of cancer of the prostate meet the necessary requirements, and the level of testosterone in the blood plasma is quickly normalized.[23]

Unlike bioinert polymer implants, biodegradable polymer implants involve the formation of low molecular weight products which should be physiologically harmless. Metabolism of biodegradable polymers is discussed in reviews[5,24] stating that the most widespread biodegradable polymers form nontoxic products such as lactic acid, amino acids, carbonic acids and so forth.

Application areas for controlled release systems are generally not restricted by the type of disease. Such systems are successfully used in the treatment of cardiovascular diseases,[25] malignant tumors,[36,37] diabetes mellitus,[28] drug addiction,[29] and as contraceptives,[30] ophthalmologic remedies,[31] and so forth.

Medicinal eye films occupy a special place among the biodegradable polymer systems. These are the $5 \times 12 \times 0.5$ mm drug-containing transparent films inserted under the eyelid for the duration of the treatment course. Originally, such films were developed by the US company Alza under the trade name of Ocucert for the continuous introduction of the antiglaucoma drug pilocarpine. They served as a good substitute for eye drops that needed to be inserted 6–8 times a day, but the fact that these bioinert films need to be removed made the researchers turn to copolymers based on acrylates and metacrylates that dissolve probably due to hydrolysis in the side chains.[31]

Eye films developed to date in the USSR are based on the acrylic acid, N-vinyl pyrrolidone and ethyl acrylate copolymer, containing an antibiotic, a sulfa drug

and a hypotensive remedy. The "biodissolving" term for these copolymers is 8–14 days, the release rate of 40 μg/h and the shelf iife is 2 or 3 years.‡

The first "biodissolvable" eye films described were those based on cellulose derivatives, oxypropyl cellulose in particular, that were introduced in 1948 in British Pharmacopoeia. We failed, however, to find literature data on the successful ophthalmological application of this polymer, obviously due to fast swelling of eye films in lacrimal liquid and loss of mechanical strength. In view of this, it is likely that the most promising are the eye films based on polymers liable to surface erosion such as, e.g., polyorthoesters.

The most typical biodegradable polymer-drug systems are listed in Table I.

As can be seen from Table I, the drugs and polymers used in such systems are quite diverse. According to the classification proposed by Heller,[1] all these polymers may be categorized into three groups.

1) Polymers passing into the soluble state due to splitting of intermolecular cross bonds (e.g., in the case of cross-linked polyethylene oxide).

2) Polymers passing into the soluble state due to hydrolysis, ionization or protonation in the side chains, e.g., in the case of butyl semiester of copolymer of

TABLE I

Biodegradable polymer-drug systems

Polymer	Drug	Reference
polylactic acid (polylactide)	butambene, tetracaine, dibucan	(32)
- " -	aclacinomycin (an antibiotic)	(11)
copolymer of glycolic and lactic acids	levongestrel (a contraceptive)	(33)
polyethyl cyano acrylate	insulin (an antidiabetic drug)	(34)
polybutyric acid (polyoxybutyrate)	prednisolone, tetracaine	(35)
albumin	amphotericin B (an antimycotic drug)	(36)
copolymer of vinyl methyl ether with maleic anhydrite	hydrochlorothiazide (a diuretic)	(37)
copolymers of acrylic acids	pilocarpine nitrate (a cholinomimetic)	(31)
polyorthoester	naltrexone (a narcotic antagonist)	(38)
cross-linked polyethylene oxide	theophylline, proxyphylline (hypotensive remedies)	(39)
poly-ε-caprolactone	levongestrel (a contraceptive steroid)	(40)
copolymer of caprolactone and valerolactone	naltrexone	(41)
ethyl cellulose	monocycline (an antiparodontosis drug)	(42)
polyglutamic acid	cyclophosphamide (a cytostatic)	(43)

‡ A. E. Vasiliev and A. P. Davydon, D. I. Mendeleev Chem. Soc. J. 1985, No. 5, pp. 395–402.

vinyl methyl ether with maleic anhydride, hydrolyzed at weakly alkaline values of pH.

3) Polymers degrading on contact with the biological environment, which results in splittings of the main chain. This large group includes homo- and copolymers of lactide, polycyanoacrylates, polyorthoesters, polyphosphazenes, and so forth.

Here we do not discuss the methods used in synthesis of bioerodible and biodegradable polymers for controlled release systems. Let us state, however, that bioerodable polymers are, as a rule, prepared through polymerization and polymer analogous conversions, while biodegradable polymers are prepared through polycondensation and copolycondensation.

On the mechanism of drug release from bioerodable and biodegradable polymers

Drug release from the polymeric matrix or from the hollow item made of the biodegradable polymer usually proceeds in two stages, i.e., drug diffusion in the polymer or solubilization of the polymer base. The release mechanism is realized depending on which of the two processes is limiting.

The diffusion mechanism. Diffusion in such cases is the slowest stages, i.e., the observed release rate is equal to the diffusion rate. Diffusion of low molecular weight substances is known to be described by a number of regularities,[44,45] viz.:

1) The diffusion rate is time-dependent. Some cases have been described when the rate of diffusion depends on time to the power of n, with n varying from 0.5 to 1.[46]

2) The diffusion rate depends on the initial concentration of the low molecular weight substance and other boundary conditions.

3) In semicrystalline polymers diffusion occurs as a rule in the amorphous regions only.

4) The time of drug diffusion from the polymer item depends on the shape and size of the drug molecule.

5) Change in the time-dependent drug concentration in the polymer correlates with the shape (plate, cylinder, sphere).

6) The drug diffusion coefficient depends on the diffusate molecule size, and in the homologous series it is usually correlated to the molecular mass of molecule M by the expression

$$D = KM^{-1/2}, \tag{1}$$

where K is the proportionality factor.

The expression for diffusion time τ in such systems takes the form

$$\tau = \frac{\delta^2}{aD} \tag{2}$$

where δ is the characteristic size; D is the coefficient of drug diffusion in the polymer; and a is the shape-dependent coefficient (4 for a film, 16 for a cylinder and 6 for a sphere).[47]

Let us consider the diffusion mechanism probability in controlled release systems based on the biodegradable polymer with a relatively high degradation rate in the physiological conditions.

We have shown elsewhere,[48] that reduction in the film sample linear dimension, given erosion from the surface, is described by a simple equation:

$$-\frac{dl}{dt} = (I - A)\sqrt{DK_2C_0} \tag{3}$$

where K_2 is the rate constant of hydrolysis of the biodegradable polymer low molecular analogue; C_0 is the degradant (water, metal ion, and so forth) concentration, and A is the crystallinity.

With the common values of $D = 10^{-8}$ cm^2/s, $K_2 = 0.5$ 1/mol·s and $C_0 = 0.01$ M/l, the reduction rate in the polymer item's linear dimension, according to (3), will make up $-dl/dt = 7 \cdot 10^{-6}$ cm/s. At the same time, the duration of erosion until the complete macroscopic disappearance of the polymer is, for instance, typically 100 days. Then at the initial thickness of the polymer film of 0.01 cm the erosion rate is 10^{-9} cm/s, which is three decimal orders lower than in the case of erosion in the diffusion or transitional regions (see equation (3)).

The probability of controlled release from the bioeroded polymer in the diffusion region is thus significantly higher than in the kinetic region.

When we deal with net diffusion of the drug then for the l-thick film, according to the known equation,

$$\frac{1}{2} = \frac{0.0049\ l^2}{D} \tag{4}$$

at $D = 10^{-8}$ cm^2/s and $l = 0.05$ cm 50% of the drug diffuses from the polymer in 4.5 h, i.e., in a much shorter time than is the common erosion time.

The diffusion mechanism is to a certain extent affected by drug distribution in the polymer.[49]

Case 1. The drug is uniformly distributed in the polymer as a solid solution. In order to consider this case it is necessary to account for the change over time in the linear dimension of the polymer item in the common diffusion equation.

Normally, this change can be described by a simple linear dependence $\delta = \delta_0 (1 + \beta t)$, where δ_0 is the linear characteristic size and t is the time.

To describe "bioerosion" some authors[50,51] use the expression

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{K_0 t}{c_0 a}\right)^n, \tag{5}$$

where M_t and M_∞ are the amounts of drug diffused over time t and ∞, K_0 is the shape-dependent coefficient ($K = 1$ for a film, $K = 2$ for a cylinder and $K = 3$ for a sphere), K_0 is the rate constant, t is the time, c_0 is the drug concentration in the polymer, $a = (1/2)$ for a plate, $a = r$ for a cylinder and a sphere, r being the radius.

In (5) it is shown, however, that equation (5) is in correa and that the drug release dynamics is described in this case by the following equation:

$$\frac{M_t}{M\infty} = 1 - \left(\frac{K_0 t}{c_0 a}\right)^n. \tag{6}$$

According to this equation, the diffusion release rate changes less sharply with time than in the case of equation (5), which is in better agreement with the available experimental data.

Release determined by biodegradation rate. Release is said to proceed in the kinetic region if the observed rate is determined by the biodegradation rate of the polymer in which the drug is distributed. The concept of kinetic, diffusional and transitional regions has been elaborated on in detail by Frank-Kamenetsky.[53] While in diffusion release the rate of the process may be controlled by, e.g., loosening of the polymer structure or by reducing the number of cross-links, the rate of release in the kinetic region is largely determined by the nature of the biodegradable polymer. Quite telling in this respect are the experimental data on the time of complete or partial resorption for various polymers summed up in the author's review[24] (Table II).

As can be seen from Table II, the heterochain polymers of the aliphatic series show the least biodegradation rate. The introduction of lactide units (lactic acid residues) into the polyglycolide chain leads to retardation of biodegradation (this effect will be discussed in more detail in the last section).

It has been demonstrated in reference [24] that in most cases biodegradation may be associated with hydrolytic cleavage of the chain in heteroatom sites, i.e., hy-

TABLE II

Resorption of various polymers in the organisms of man and animals

Implanted polymer*	Implant shape	Animal	Resorption time	Reference
polyethylene terephthalate	net	dog	30±7 years	(54)
- " -	net	man	30±7 years	(54)
- " -	net	rabbit	20±7 years	(55)
polydodecamide (polyamide 12)	thread	rabbit	8% in 130 days	(56)
polylactide	thread	rat	13% in 2 months	(57)
polycaproamide	fiber, tissue	rabbit	240 days	(58)
polydioxanone	thread	man	180 days	(59)
glycolide-lactide copolymer	thread	rat	70 days	(60)
carboxymethyl cellulose (low-substituted)	thread	rat	over 15 days	(61)
oxidized cellulose	thread	man	10 days	(62)
alginate (cross-linked)	sponge	man	10–14 days	(63)

* In all cases except alginate polymers were implanted subcutaneously.

drolytically the most labile parts of the chain. Such cleavage is connected with the action of hydrolytic enzymes (hydrolases) in the organism. At the same time, it was shown in reference 48 that in the number of cases hydrolytic resistance of polymers, polyesters among them, may be quantitatively predicted based on the common analogy to low molecular weight analogues with the account of the hydrolytic agent diffusion in the polymer and the polymer crystallinity A. The rate of change in the biodegradable polymer item's shape as derived in reference 48 is expressed in the following way:

$$K_{\text{eff}} = \rho\delta\ (I - A)\ \sqrt{DK_2C_0}, \tag{7}$$

where ρ is the polymer density and δ is the probability of cleavage of soluble fragments.[64]

As to the dependence of hydrolytic resistance and biodegradability on the polymer composition, it has been demonstrated in a number of papers[65-67] (see Part II).

The experimental findings on mean biodegradation rates are summed up and compared in reference 49. These rates fluctuate over a broad range of from 0.00026 to 0.010 day^{-1} for polyesters of the aromatic and aliphatic series. The reason for these differences lies not only in different hydrolytic resistance of the ester bond in the presence of various substitutes but also in the different affinity of such proteolytic and esterolytic enzymes as chymotrypsin to the aliphatic and aromatic substrates.[68] A broad range of polyester implant resorption rates make it possible to ensure drug release from these polymers with the controlled therapeutic course duration of 100 days and more.

Self-regulated drug release systems

The development of standard controlled release systems involves determination of the release rate prescribed by the nature of the drug and the polymeric matrix as well as by the drug distribution in the polymer. In some cases, especially when the course of the disease in unpredictable or fitlike, this may be a disadvantage because the organism will receive much more or considerably less of the drug than in the biological demand of the moment. This consideration has prompted the researchers in the past 6 or 7 years to develop guidelines for self-regulated drug release systems where the drug input rate depends on the current concentration of the corresponding metabolite such as, e.g., glucose or urea.[69-72]

Controlled feedback may be achieved in several ways, i.e., (a) through the use of a polymer whose solubilization is linearly correlated with pH (this version is applicable to metabolitic reactions accompanied with changes in pH, e.g., to destruction of urea by urease); (b) through the use of redox polymers, reversibly changing their electronic state; (c) through the use of systems "triggered" only upon the input of an undesirable agent such as a narcotic or alcohol into the organism.

To this end, along with bioinert polymers, the use is made of biodegradable and bioerodable polymers such as glycolide-lactide copolymers and the copolymer of vinyl methyl ether with maleic anhydride (in the form of semiester). The listed

kinds of self-regulated systems should be classed as the 4th generation dosage forms, the 1st generation being represented by common drugs, the 2nd by prolonged-release drugs and the 3rd by constant-rate-release drugs.

References

1. J. Heller, *CRC Critical Rev. in Therapeutics and Drug Carrier Systems*, **1**, 39 (1984).
2. J. Feijen, *NATO ASI ser. (Polymer Biomaterials)*, **106**, 62 (1986).
3. D. L. Wise (ed.), *Biopolymeric Controlled Release Systems*, **2**, **3**, 127 (1984).
4. N. B. Graham and D. A. Wood, *Polymer News*, **8**, 230 (1982).
5. G. E. Zaikov and V. S. Livshits, *Polymer Yearbook*, Eds. R. A. Pethrick and G. E. Zaikov, **4**, 177 (1987).
6. S. Yolles, S. Woodland and D. Blake, *J. Med. Chem.*, **8**, 227 (1973).
7. T. M. Yakanicz, H. A. Nash and D. L. Wise, *Contraception*, **8**, 227 (1973).
8. V. D. Solodovnik, *Microcapsulation*, Nauka, Moscow, 1980. (In Russian.)
9. V. P. Torchilin, E. F. Tishchenko and V. N. Smirnov, *J. Biomed. Mater. Res.*, **11**, 223 (1977).
10. N. Wakayama, H. Juni and M. Nakano, *Chem. Pharm. Bull.*, **30**, 2621 (1982).
11. R. Wada, S. H. Hyon and Y. Ikada, *J. Bioactive Compat. Polymers*, **3**, 126 (1988).
12. M. Tsachata, J. Willard and M. Roland, *J. Controlled Release*, **7**, 233 (1988).
13. M. Vert, J. P. Benoit and G. Splenlehauer, *J. Controlled Release*, **7**, 217 (1988).
14. G. E. Vischar, J. E. Pearson and J. W. Fong, *J. Biomed. Mater. Res.*, **22**, 733 (1988).
15. Y. Ogawa, M. Yamanita and S. Takada, *Chem. Pharm. Bull.*, **36**, 1502 (1988).
16. A. M. Sun, *Methods in Enzymol.*, **137**, 575 (1988).
17. K. R. Sidman, W. D. Steber and A. D. Schwope, *Biopolymers*, **22**, 547 (1983).
18. C. Damgé, C. Michel and M. Aprahamian, *Diabetes*, **37**, 246 (1988).
19. J. Heller, *J. Bioactive and Compat. Polymers*, **3**, 97 (1988).
20. R. J. Tamarlo, *J. Biomed. Mater. Res.*, **23**, 253 (1989).
21. M. Aprahamian, C. Michel and W. Humbert, *Biology of Cell.*, **61**, 69 (1987).
22. A. R. Fassini, *J. Pharmacy and Pharmacol. 40-Supplement*, 32P (1988).
23. I. Kaetsu, *J. Bioactive Compat. Polymers*, **3**, 164 (1988).
24. G. E. Zaikov and V. S. Livshits, *Khim. Farm. Zh.*, **4**, 416 (1984).
25. J. Glynn-Barnhart, *Drugs*, **5**, 711 (1988).
26. K. C. Wright, S. Wallace and B. Mosier, *J. Microcapsulation*, **5**, 13 (1988).
27. Y. Chen, N. Willmott and J. Anderson, *J. Controlled Release*, **8**, 93 (1988).
28. S.-Y. Lin, *Biomat. Artif. Cells, Artif. Organs*, **161**, 825 (1988).
29. A. D. Schwope, D. L. Wise and J. F. Howes, *Life Sci.*, 1877 (1975).
30. C. G. Pitt, M. M. Cratzl and A. Jeddcoat, *J. Pharm. Sci.*, **68**, 1534 (1979).
31. E. Chiellini and M. F. Saettone, *J. Bioactive Compat. Polymers*, **3**, 86 (1988).
32. N. Wakayama, H. Juni and M. Nakano, *Chem. Pharm. Bull.*, **29**, 3363 (1981).
33. A. C. Sharon, D. L. Wise and J. F. Howes, in *Biopolymeric Controlled Release*, Ed. D. L. Wise, Boca Raton, Florida, **2**, 3 (1984).
34. C. Damgé, C. Michel and M. Aprahamian in *Biomaterials and Clinical Applications*, Eds. A. Pizzaferrato, P. C. Marchetti, A. Ravaglioli and A. J. C. Lee, Elsevier, Amsterdam, 643 (1987).
35. S. Akhar and C. W. Ponton, *J. Pharmacy and Pharmacol. 40-Supplement*, 118P (1988).
36. J. A. Weyon and J. E. Brown, *J. Pharmacy Pharmacol. 40-Supplement*, 58P (1988).
37. S. A. Mortada, M. A. E. Egaky and A. M. Motavi, *J. Microcapsulation*, **5**, 203 (1988).
38. R. C. Capozza, B. Sendelbeck and W. J. Balkenhol, in *Polymeric Delivery Systems*, Ed. R. J. Kostelnik, Gordon and Breach, New York, Chap. 3 (1978).
39. B. Gander, R. Gurny and E. Doelker, *J. Controlled Release*, **5**, 271 (1988).
40. C. G. Pitt, T. A. Marks and A. Schindler, in *Controlled Release of Bioactive Materials*, Ed. R. W. Baker, Academic Press, New York, 36 (1980).
41. C. C. Pitt and A. Schindler, *Biodegradable and Delivery Systems for Contraception*, Eds. E. S. E. Hafez and W. A. van Os, Hall Medical Publishers, Boston, (1980), p. 17.
42. R. Elkayan, M. Friedman and A. Stobholz, *J. Controlled Release*, **7**, 231 (1988).
43. T. Hirano, W. Klesse and H. Ringsdorf, *Makromol. Chem.*, **180**, 1125 (1979).
44. *Diffusion of Polymers*, Eds. J. Crank and C. G. Parks, Plenum Press, London (1968).
45. J. S. Vrentas and J. L. Duda, *Encyclopedia of Polymer Science and Technology*, 2nd ed., Academic Press, New York, **5**, 36 (1986).

46. G. Illinger and N. Schneider, *Water in Polymers*, Eds. S. Rouland and G. E. Zaikov, Mir, Moscow (1984), p. 528. (In Russian.)
47. J. Crank, *Mathematics of Diffusion*, Oxford, Claredon Press (1979).
48. G. E. Zaikov and V. S. Livshits, *Polymer Degrad. and Stability*, **9**, 41 (1984).
49. G. E. Zaikov and V. S. Livshits, *Khim.-Farm. Zh.*, **5**, 537 (1984).
50. H. B. Hopfenberg, *Controlled Release Polymeric Formulations*, Eds. D. R. Paul and F. W. Harris, Washington, D.C., Amer. Chem. Soc. (1976), p. 26.
51. N. B. Graham and D. A. Wood, *Macromolecular Biomaterials*, Eds. G. G. Hastings and P. Ducheyne, Boca Raton, Florida (1984), p. 181.
52. G. E. Zaikov, A. L. Iordansky and V. S. Livshits, *Polymer. Degrad. Stab.*, **15**, 327 (1986).
53. D. A. Frank-Kamenetsky, *Diffusion and Heat-Transfer in Chemical Kinetics*, Khimiya, Moscow (1967).
54. T. T. Daurova, O. S. Voronkova and S. D. Andreev, *Doklady Akad. Nauk SSSR*, **231**, 219 (1976).
55. T. E. Rudakova, G. E. Zaikov and O. S. Voronkova, *J. Pol. Sci., Pol. Symp.*, **66**, 277 (1979).
56. G. E. Titova, O. S. Voronkova and M. S. Akutin, *17th Microsymp. on Macromolecules*, Prague (1977), p. 34.
57. R. K. Kulkarni, K. C. Pani and B. S. Neuman, *Arch. Surg.*, **92**, 839 (1966).
58. A. N. Rogova, T. V. Bazhbeuk-Melikova and T. T. Daurova, *Vysokomolekulyarnye Soedineniya*, **19A**, 2120 (1977).
59. R. S. Bartholomew, *Ophthalmologica* (Basel), **182**, 81 (1981).
60. P. H. Craig, *Surg. Gynec. Obstet*, **140** (1975).
61. A. A. Saramsykov, U. E. Begaliev and Sh. Nadzhamutdinov, *Synthetic Polymers for Medical Purposes*, Ed. N. A. Platé, Riga, Zinatne (1981), p. 210.
62. B. G. Yasnitsky, A. P. Bezuglaya and E. D. Dol'berg, *Synthetic Polymers for Medical Purposes*, Ed. N. A. Platé, Dzerzhinsk, Nauka (1979), p. 195.
63. M. I. Kuzin, V. K. Sologub and V. V. Yudenich, *Khirurgiya*, **8**, 86 (1979).
64. V. S. Livshits, L. F. Krivorotova and I. A. Tsirule, *Vysokomolekulyarnye Soedineniya*, **18B**, 336 (1976).
65. R. A. Miller, J. M. Brady and D. E. Cutright, *J. Biomed. Mater. Res.*, **11**, 711 (1977).
66. J. D. Gresser and J. E. Sanderson, *Biopolymeric Controlled Release Systems*, Ed. D. L. Wise, Boca Raton, Florida (1984), p. 127.
67. G. E. Zaikov and V. S. Livshits, *Polym. Degrad. Stab.*, **17**, 65 (1987).
68. M. Dixon and E. Webb, *Enzymes*, Mir, Moscow (1966).
69. J. Heller, S. H. Pangburn and D. W. H. Penhale, *Controlled Release Technology, Pharmaceutical Applications*, Eds. P. I. Lee and W. R. Good, Washington, D. C., Amer. Chem. Soc. Ser., **348**, 172 (1987).
70. J. Heller, *J. Controlled Release*, **8**, 111 (1988).
71. V. S. Livshits and B. I. Kurganov, *Khim.-Farm. Zh.*, **2**, 154 (1990).
72. G. E. Zaikov, *Degradation and Stabilization of Polymers*, Eds. H. H. G. Jellinek and H. Kachi, Elsevier, Amsterdam, **2**, 433 (1989).