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Preparation of polymeric biomaterials with the aid of radiation-chemical methods

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Abstract. The results of the application of radiation-chemical methods for the preparation of polymeric biomaterials are surveyed and treated systematically. The characteristic features of these methods and their advantages and disadvantages are indicated. The properties of polymeric biomaterials prepared using ionising radiation are examined. Particular attention is devoted to studies carried out during the last 10 – 15 years. The bibliography includes 492 references.

I. Introduction

Polymeric biomaterials are usually understood as polymeric materials and articles made from them which are used in medicine or biotechnology. Such materials are frequently prepared by the specific modification of well known polymers. The range, scale of manufacture, and importance of biomaterials have increased appreciably during recent years.

A series of reviews and monographs have been devoted to problems of their preparation, properties, and applications (see, for example, Refs 1 – 6).

Radiation-chemical technology has now become one of the effective methods for the preparation of polymeric biomaterials. The studies on the employment of radiation-chemical methods for the synthesis of polymeric biomaterials have been carried out on the following lines: radiation-induced modification of various polymers and articles made from them in order to obtain haemocompatible polymers (polymers which are in prolonged contact with blood during their employment), polymeric sorbents, prostheses for blood vessels, *etc*.; immobilisation of various biologically active substances (BAS) (enzymes, medicinal drugs, *etc*.) in polymeric matrices using radiation-induced polymerisation; radiation-chemical synthesis of polymeric carriers for medicinal preparations; radiation-induced cross-linking of polymers in order to obtain mechanically strong hydrogels (BAS carriers, dressings, eye lenses, *etc*.).

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An advantage of the radiation-chemical methods for the preparation of polymeric biomaterials compared with traditional methods is the purity of the materials (there is no need to add additional ingredients during the synthesis), the possibility of carrying out the processes at reduced temperatures, and the ease of regulation of the rate of the processes by altering the radiation dose rate. Another advantage of the radiation-chemical methods is the fact that the biomaterials can in certain cases be sterilised on the same sources of ionising radiation which were used for their preparation. It is essential to note that in the majority of cases low radiation doses, as a rule not exceeding 30 kGy, are required for the preparation of polymeric biomaterials, which makes it possible to use low-power radiation sources.

A disadvantage of radiation-chemical methods is the necessity to use, as a rule, γ-radiation sources and electron accelerators which are comparatively expensive and difficult to use.

The mechanisms of the radiation-chemical processes, the devices, the dosimetry, and the methods involving the employment of ionising radiation sources have been described in detail in a series of monographs (see, for example, Pikaev and Woods [7, 8]). In the present review, these questions are not considered.

II. Preparation of haemocompatible polymeric materials

The preparation of haemocompatible polymeric materials is an extremely complex problem. When polymers come into contact with blood, biochemical reactions inducing a change in the physiological functions of blood are initiated and the blood clotting system with subsequent thrombus formation on the surface of the polymer is 'switched on'. Reviews have been devoted to the mechanisms of thrombogenesis on the surface of polymers.[9 – 15] Important factors increasing the haemocompatibility of polymers are their properties such as minimal capacity for the adhesion and aggregation of thrombocytes, the lack of activation of blood clotting contact factors, participation in the lysis of the thrombus formed, and a selective capacity for the adsorption of blood plasma proteins, especially albumin. According to current ideas, the first stage, when the polymer comes into contact with blood, is rapid sorption of proteins from blood plasma. The nature and conformational state of the protein determine the subsequent biochemical reactions.

The problems of the sorption of proteins on various polymeric surfaces have been considered in numerous investigations (see, for example, Refs 1, 16, and 17). Unfortunately, at the present time

the level of our knowledge precludes sufficiently effective prediction of the nature and properties of the polymer surface which would fully satisfy the requirement of haemocompatibility.

It is clear from the foregoing that the surfaces of polymers must be modified in order to obtain haemocompatible materials. The following measures are taken for this purpose.

1. Polymers are created with surfaces possessing a reduced adsorption capacity in relation to protein and are close in their nature to the natural medium of the organism. In the main, these are hydrogel surfaces. It has been assumed [17] that both an approximate equality, pairwise, of the dispersion and polar components of the free surface energy of blood and materials and the closeness of the distribution of the above energy parameters, also pairwise, are needed for haemocompatible materials.

2. Polymeric materials with a definite domain structure of the surface (polyurethanes) are created.

3. Polymeric hydrocarbon materials (polyethynes) are created.

4. Polymers are created the surfaces of which model, in terms of their nature, blood anticoagulants (this is achieved by introducing sulfo- and carboxy-groups into the surface layers of polymers, by generating a negative charge on the surfaces of polymers). It is usually endeavoured to obtain a heparin-like surface, since the widely used method for the preparation of haemocompatible materials by introducing heparin suffers from a series of disadvantages due to the partial loss of activity by the heparin on covalent immobilisation and its weak anticomplement activity and biodegradation.

5. Physiologically active substances (blood anticoagulants, enzymes, *etc.*), interacting with blood components and arresting the thrombogenetic process, are introduced into the surface hydrogel layers.

In selecting the method for the modification of the polymer surface, it is essential to bear in mind the principle that the physicomechanical parameters of the initial polymer should not change significantly on modification. One of the methods for the modification of polymers is radiation-induced graft polymerisation.

A series of reviews have been devoted to various problems of the radiation-induced graft polymerisation and the methods for carrying it out.[7,18–22] Its advantages as a method for the modification of polymeric materials in order to increase their haemocompatibility are, firstly, a high universality which makes it possible to modify over a wide temperature range virtually any polymeric materials (stitches, catheters, tubes, tablets, powders, grafts, *etc.*) and secondly the possibility of creating on the polymer surface of modified layers of different thickness. The thickness of the layer depends on the conditions under which the graft polymerisation is carried out — the dose rate, the choice of the solvent for the monomer, *etc*. The modified layer is then strongly bound to the support and is not washed off on contact with the medium of the living organism.

All these features promote a fairly wide-scale employment of radiation-induced graft polymerisation for the solution of problems associated with the enhancement of the haemocompatibility of various polymeric materials and articles made from them. The principal task of such investigations is the creation of polymers with a functionalised surface, definite hydrophilic-hydrophobic properties, and a negative charge on the surface.[23–25] A large number of studies have been carried out on the modification of various polymers using highly hydrophilic monomers such as *N*-vinylpyrrolidone, 2-hydroxyethyl methacrylate, and acrylamide and its derivatives.[26–72] In a series of investigations, fairly complex copolymers have been used for modification.[73–87] Thus, polyurethanes, polyesters, and natural rubber have been mainly used for the manufacture of blood vessel prostheses.[88–118]

Table 1 presents data on the employment of the radiation-induced graft polymerisation methods for the modification of polymers. The radiation-induced graft polymerisation was carried out in most cases by the direct method from aqueous alcoholic solutions with low irradiation doses. In certain cases, especially in the grafting of acrylamide, the method involving preirradiation was used.[41]

The investigations carried out led to the preparation of a wide variety of modified polymeric materials with hydrogel surfaces. These materials are fairly strong and soft and exhibit a high swellability in water. The biomacromolecules in such materials are characterised by enhanced diffusion. The polymeric hydrogels obtained by radiation-chemical methods have been tested for haemocompatibility in experiments *in vitro* and *in vivo* on monkeys, sheep, and dogs. The tests for the haemocompatibility of the radiation-grafted polymeric hydrogels revealed the following general features: with increase in the water content from 15% to 85%, the sorption of proteins diminishes, the rate of desorption increases, and thrombogenesis takes place on the hydrogels, but the bond between the thrombus and the hydrogel surface is appreciably weakened compared with the bond between them and the unmodified polymers. The appreciable decrease in the interfacial tension between the hydrogel and the aqueous solution is very important. The hydrogel coating on the polymers should be prepared from very pure monomers. Thus a slight methacrylic acid impurity in 2-hydroxyethyl methacrylate appreciably impairs the quality of the hydrogel coating and its haemocompatible properties.[93]

Interesting results have been obtained in the study of the copolymers of 2-hydroxyethyl methacrylate (a hydrophilic monomer) with ethyl methacrylate (a hydrophobic monomer) radiation-grafted onto polyethylene (PE).[93] For a low water content ($\sim$10%), the above graft copolymers were characterised by unexpectedly low thrombocyte adsorption parameters, which was not due to the water content but to the composition of the copolymer. For a higher water content, the adsorption of thrombocytes was inversely proportional to the water content. Evidently, the composition of the copolymers and the state of water in it are important. The surface of radiation-grafted copolymers is very nonuniform (there are mounds, projections, *etc.*) and the thickness of the modified layer is as a rule 15–45 μm. Hoffman *et al*.[93] concluded that a definite combination of hydrophilic and hydrophobic sections on the surface is needed to increase the haemocompatibility.

The state of water in radiation-grafted copolymers has been investigated.[94,95] The state of water in radiation-grafted PE hydrogels with grafted polyacrylamide has been studied.[94] It has been established by differential scanning calorimetry (DSC) that the water in hydrogels does not freeze down to -50 °C and that the amount of unfrozen water per unit surface of the modified polymer which has undergone equilibrium swelling or per mole of the grafted polyacrylamide depends on the methods used to carry out the graft polymerisation. The presence of unfreezing water in radiation-grafted hydrogels with polyacrylamide chains is due to the rearrangement of the water framework in the hydrogel owing to the formation of a strong hydrogen bond between the H_2O molecule and the carbonyl group of polyacrylamide, which has been demonstrated by IR Fourier spectroscopy.[94] Data on the employment of the ESCA method for the investigation of the influence of hydration on the state of the grafted chains in a thin layer on the surfaces of polymers $\sim$50 Å thick have been published.[95] The following systems have been investigated: low-density polyethylene (LDPE) + grafted poly(2-hydroxyethyl methacrylate), LDPE + grafted polyacrylamide, silicone rubber (Silastik) + poly(2-hydroxyethyl methacrylate), and polyurethane (Tufthane) + poly(2-hydroxyethyl methacrylate). The surface was analysed by studying the C_{1s}, O_{1s}, and Si_{2p} peaks. The C/Si, O/Si, C/O, C/N, and O/N peak ratios for the hydrated and dehydrated surfaces of various radiation-grafted copolymers have been published.[95] These data make it possible to determine the location of the grafted chains in the surface layer of the polymers in the hydrated and dehydrated states. For example, in the case of the grafting of poly(2-hydroxyethyl methacrylate) on polyurethanes, the concentration of the grafted chains on the surface diminishes appreciably after dehydration. On the other hand,

Table 1. Radiation-induced graft polymerisation of monomers for the preparation of various polymers with the aim of regulating haemocompatibility.

Monomer	Conditions in radiation-induced graft polymerisarion	Remarks	Ref.
Polymer — polyethylene			
Acrylic acid	post-radiation grafting	the adsorption of antitumour preparations on adsorbents with grafted poly(acrylic acid) was studied	29
	direct grafting from aqueous phase	the hydrophilic properties of the surface were studied in detail	96, 97
	ditto	the carboxy groups were converted into acid chloride groups by treating the surface with thionyl chloride and the latter were used for the covalent binding of BAS	90
Acrylic acid chloride	direct grafting from vapour phase		23, 26
Acrylic acid, acrolein; mixture of monomers	direct grafting from liquid phase	sulfonation of graft copolymer	31
Acrylamide	grafting by the preirradiation method from aqueous and acetone solutions	the amide groups of the grafted polyacrylamide were converted into amino groups; heparin was bound to the amino groups; tests *in vivo* and *in vitro*	27
	ditto	polymer tubes were used; tests *in vivo*	28
	direct grafting from solution	the surface of the modified polymer was studied	33
	various grafting methods, including grafting from the vapour phase, were used		107
Acrylamide, *N*,*N*′-methylene-bisacrylamide	direct grafting from 10% aqueous alcoholic solution in the presence of Fe^{2+}		24
Allylamine	direct grafting in the presence of phosphoric acid	phosphoric acid increases the yield of the graft polymer	25
Diallyldimethylammonium chloride, sodium styrene sulfonate	direct grafting		35
2-Hydroxyethyl methacrylate, ethyl methacrylate; mixture of monomers	direct grafting from water–methanol mixture at low dose rates	surfaces with different hydrophilicities were obtained	30, 37
4-Vinylpyridine + 2-(*N*,*N*-diethyl-amino)ethyl methacrylate; 4-vinylpyridine + methyl methacrylate; 4-vinyl-pyridine + methacrylic acid	direct grafting of monomers from vapour phase	alkylation of graft copolymer	32
N-Vinylpyrrolidone	grafting from liquid phase by the preirradiation method		36
Methyl acrylate	direct grafting from water–acetone mixture	hydrazinolysis of graft copolymers	59
Styrene	direct grafting	introduction of sulfonate and sulfonamide groups; tests *in vitro*	48
2-Hydroxyethyl meth-acrylate, 2-hydroxyethyl methacrylate + ethyl methacrylate	direct grafting from liquid phase	the structure of the surface was investigated by electron microscopy	93
2-Hydroxyethyl meth-acrylate, *N*-vinylpyr-rolidone, acrylamide	ditto		106
Polymer — polyethylene, silicone rubber			
2-Hydroxyethyl meth-acrylate, acrylamide	direct grafting from liquid phase	the state of water was investigated by the DSC and ESCA methods	94, 95

Table 1 (continued).

Monomer	Conditions in radiation-induced graft polymerisarion	Remarks	Ref.
Polymer — polypropylene			
2-Hydroxyethyl methacrylate	direct grafting from 20% monomer solution	a grafting maximum is observed for a dose of 5 kGy	39
	grafting by the preirradiation method	hydrophilisation of polypropylene stitch material	98
Monomer mixtures: *N*-vinylpyrrolidone + acrylic acid; vinyl acetate + crotonic acid	direct grafting	the polyacrylic acid in the modified polymer was partly neutralised with alkali	40
Acrylamide	postradiation grafting after vacuum irradiation of polymer		41
Polymers — polyethylene, polypropylene, polyesters, poly-4-methylpentene, polyvinyltrimethylsilane			
Acrylic acid, methacrylic acid, 4-vinyl-pyridine	grafting from vapour phase	the formation of polyelectrolytic complexes on the surfaces of the polymers was investigated	34
Polymers — polyethylene, polypropylene, polyamides, polyurethanes, etc.			
N-Methyl-*N*-vinylacetamide	direct grafting from liquid phase	the properties of the surfaces of the modified polymers were characterised by the critical surface tension; polymer tubes were used for modification	89
Polymers — polyethylene, polypropylene			
Vinylidene chloride	direct grafting from gas phase	dehydrochlorination of materials obtained	101 – 104
Polymer — ethylene-propylene rubber			
2-Hydroxyethyl methacrylate, *N*,*N*-dimethylacrylamide, 2-(*N*,*N*-dimethylamino)ethyl methacrylate	direct grafting from aqueous medium in the presence of Cu^{2+} ion		70
Acrylamide, *N*-vinyl-pyrrolidone, 2-hydroxy-ethyl methacrylate	direct grafting from aqueous monomer solution	the morphology of the surface and the influence of O_2 on the grafting were investigated	71
Different vinyl monomers	direct grafting from liquid phase	grafting onto a film, a tube, and a fibre was studied; the surface properties were investigated	42
Polymer — ethene – propene copolymer			
N-Vinylpyrrolidone, 2-hydroxyethyl methacrylate, acrylamide	direct grafting from liquid phase		86
Polymers — polyolefins			
Macromonomers	direct grafting	review of studies on the grafting of macromonomers; macromonomers were obtained by the acylation of the amino groups in enzymes or heparin using acrylic acid chloride	91
Polymer — polytetrafluoroethylene			
Acrylic acid chloride	direct grafting from monomer gas phase		23
N,*N*-Dimethylacrylamide	direct grafting from liquid phase	the influence of dose rate, solvent, and temperature on the grafting was investigated	45
Acrylamide	grafting by the preirradiation method	the surface of the polymer was investigated by the ESCA method and by scanning electron microscopy	46
tert-Butyl crotonate + methyl acrylate + sulfonic acid	direct grafting from liquid phase	the influence of the graft polymer on the haemocompatibility was investigated	47
Methyl methacrylate phase	direct grafting from liquid phase	modification of blood vessel prostheses	49
Styrene	ditto	the grafted chains were nitrated and the nitro groups were reduced to amino groups	43

Table 1 (continued).

Monomer	Conditions in radiation-induced graft polymerisarion	Remarks	Ref.
Polymers — polytetrafluoroethylene, tetrafluoroethene – ethene copolymer			
N,*N*-Dimethylacrylamide	direct grafting at different dose rates		50
Polymer — tetrafluoroethene – propene copolymer			
N,*N*-Dimethyl acrylamide	direct grafting from liquid phase	the influence of solvents on the grafiting was investigated	76
Polymer — poly(vinyl fluoride)			
2-Hydroxyethyl methacrylate, vinyl acetate, acrylic acid, *N*-vinylpyrrolidone, 4-vinylpyridine, acrylamide, vinylene carbonate	grafting by the preirradiation method from the liquid phase of the monomer; irradiation by electron accelerator	the kinetics of graft polymerisation were investigated	51
Polymer — poly(vinylidene fluoride – hexafluoropropene)			
Styrene	grafting by the preirradiation method; irradiation by accelerated heavy ions	functionalisation of grafted chains; modification of blood vessel prostheses	62
Polymers — poly(vinylidene fluoride), hexafluoropropene – vinylidene difluoride copolymer			
Styrene	grafting by the preirradiation method; irradiation with accelerated heavy ions	introduction of sulfo groups; formation of a heparin-like surface	87
Organosilicon polymers			
N-Vinylpyrrolidone	direct grafting from monomer solution in methanol or toluene	grafting on silicone rubber tubes	52, 58
	direct grafting from liquid phase	review of studies on radiation-induced grafting of *N*-vinylpyrrolidone	60
N-Vinylpyrrolidone, 2-hydroxyethyl methacrylate; mixture of monomers	direct grafting from aqueous monomer solution	the influence of Cu^{2+} on the distribution of grafted layer and the degree of grafting in the presence of Cu^{2+} ions was investigated	57 the
	direct grafting from 20% aqueous solution	the influence of the irradiation dose on the grafting and the swelling of the modified polymers in water was investigated	53
N-Vinylpyrrolidone mixture of *N*-vinyl-pyrrolidone and 2-hydroxyethyl methacrylate	direct grafting from aqueous solution of monomers		63
2-Hydroxyethyl methacrylate	direct grafting		64
Different hydrophilic monomers	grafting from aqueous solution		67
2-Hydroxyethyl meth-acrylate, ethyl acrylate; mixture of monomers	direct grafting from water – methanol mixture	the rate of grafting depends significantly on the water : monomer ratio	54
2-Hydroxyethyl meth-acrylate, ethyl meth-acrylate; mixture of monomers	direct grafting from aqueous phase	separate grafting of each monomer and of the mixture of monomers; the surface of polymers was investigated by scanning electron microscopy	56
Acrylamide	direct grafting from liquid phase in the presence of Cu^{2+} ions		55
Polymers — polyurethane, silicon rubber			
Acrylamide	direct grafting from liquid phase	sections through films and the swelling of the polymers in water were investigated	38
N-Vinylpyrrolidone	ditto	grafting onto polymer tubes; tests for haemocompatibility *in vivo*	69

Table 1 (continued).

Monomer	Conditions in radiation-induced graft polymerisarion	Remarks	Ref.
Polymer — segmented polyurethane			
N-Vinylpyrrolidone	direct grafting from monomer solution in water	the influence of the degree of swelling and of the irradiation dose on the grafting was investigated	75
2-Hydroxyethyl methacrylate	direct grafting in swollen state	the influence of the degree of swelling and temperature on the grafting was investigated	74
Polymer — polyesterurethane			
2-Hydroxyethyl methacrylate	direct grafting from water – ethanol mixture	modified blood vessel prostheses were obtained; the swelling of the modified polymers was investigated	72
Polymer — polyurethanepolyester (Upjohn)			
N-Vinylpyrrolidone	direct grafting from monomer solution in water, benzene, toluene, and Freon	the influence of temperature on the grafting and the cross-sectional distribution of the grafted polymer was investigated; the grafting was carried out on tubes	77
Polymer — polyurethane			
2,3-Epoxypropyl methacrylate, acrylamide, 2-hydroxyethyl methacrylate	direct grafting from liquid phase	the influence of solvents on the grafting was investigated; the best solvent is acetone	73
Monomers with sulfonate groups	ditto	the haemocompatibility was investigated *in vivo*	105
Polymer – polyamide 6			
Various monomers	direct grafting from liquid phase	the grafting was carried out from solvents with a specific solubility parameter; modification of polyamide beads; preparation of new adsorbents	61
2-Hydroxyethyl methacrylate, glycidyl methacrylate	ditto	grafting onto polymer beads; the modified beads obtained were used as carriers for affinity chromatography	84
Polymer — poly[bis(trifluoroethoxyphosphazene)]			
N-Vinylpyrrolidone	direct grafting from aqueous monomer solution		67
Polymers — polyphosphazenes			
N-Vinylpyrrolidone	direct grafting from aqueous monomer solution	heparinisation; tests *in vivo*	68
Polymer — natural rubber			
N,*N*-Dimethyl acrylamide	direct grafting from monomer solution in CCl_4		99
	grafting by the preirradiation method as a result of the decomposition of hydroperoxy groups	the haemocompatibility was investigated	108
2-(*N*,*N*-Dimethylamino)-ethyl methacrylate	direct grafting from monomer solution in CCl_4 tubes	grafting onto polymer tubes	92
Polymer — natural leather			
Butyl methacrylate, styrene, methyl methacrylate	direct grafting		81
Polymers — poly(vinyl alcohol), polyamide 6			
Acrylamide, *N*-vinylpyrrolidone, 2-hydroxyethyl methacrylate, 2-(*N*,*N*-dimethylamino)ethyl methacrylate	direct grafting from aqueous solution in the presence of added formamide and tetrahydrofuran	adsorbents for affinity chromatography	44
Polymer — poly(ethylene glycol dimethacrylate)			
2-Hydroxyhexyl methacrylate	direct grafting	the adsorption of γ-globulin on the polymers obtained was investigated	66

Table 1 (continued).

Monomer	Conditions in radiation-induced graft polymerisarion	Remarks	Ref.
Polymers — polystyrene, polyester			
N-Vinylpyrrolidone, 2-hydroxyethyl phase methacrylate	direct grafting from liquid phase	hydrophilisation of polystyrene articles for immunodiagnostics; modification of polyester blood vessel prostheses in order to increase haemocompatibility	78
Polymer — polystyrene			
N-Isopropylacrylamide	direct grafting	transition from a hydrophilic to a hydrophobic surface with the increase in temperature; the study of the adhesion of endothelial cells	79
Polymer — polycarbonatepolysiloxane			
Acrylic acid	grafting by the preirradiation method; irradiation by electron accelerator		82
Polymer — triblock copolymer (styrene–butadiene–styrene)			
2-Hydroxyethyl methacrylate	direct grafting from aqueous monomer solution	the modified specimens were investigated by electron microscopy and IR spectroscopy; the wetting angles were measured	83
Polymer — poly(vinyl chloride)			
2-(*N*,*N*-Dimethylamino)-ethyl methacrylate	grafting by the preirradiation method	grafting on polymer powder; preparation of immunoadsorbents	85
Polymer — poly(ethylene terephthalate)			
Acrylamide	direct grafting	modification of blood vessel prostheses	80
Polymer — poly(methyl methacrylate)			
Acrylic acid	direct grafting	binding of enzymes to the polymer surface	88

when poly(2-hydroxyethyl methacrylate) is grafted on the LDPE surface, dehydration does not affect the concentration of the grafted chains in the surface layer while the concentration of polyacrylamide grafted on polyurethanes does not change on the surface after dehydration.

In the case of organosilicon rubbers, the number of grafted chains on the surface diminishes as dehydration proceeds and the grafted chains are gradually immersed in the film. The second process occurring on dehydration is the formation of clusters by the grafted chains. The clusters are formed from several macromolecules. The disposition of the clusters on the surface depends on the degree of dehydration. Hydration significantly increases the concentration of the grafted chains on the polymer surfaces. This is particularly notable in the case of radiation-grafted silicone rubbers. Such data are important for the biomedical employment of the hydrogels obtained by radiation-induced graft polymerisation, since it is essential to take into account the change in the state of the grafted chains in the hydrogels on contact with blood or other biological liquids.

The hydrophilic properties of LDPE with grafted poly(acrylic acid) have been investigated.[96,97] It was established that the hydrophilic properties are stabilised after a 15%–17% graft (complete surface coverage). The polar component of the free surface energy then increases appreciably and the molecules of poly(acrylic acid) are reorganised under the influence of water.

The preparation of a hydrophilic stitch material by the radiation-induced grafting of 2-hydroxyethyl methacrylate on a single polypropylene fibre has been described.[98] The influence of solvents and irradiation conditions on the graft has been investigated. Hydrophilic polypropylene filaments were obtained as a result.

The view has been expressed in certain investigations that the modified layer must be of definite thickness for the successful increase in haemocompatibility. In a study of the radiation-induced graft polymerisation of 2-hydroxyethyl methacrylate and acrylamide on polyolefin films and blood vessel prostheses, it has been established [72] that the adsorption of proteins is reduced if the amount grafted does not exceed 10%. On the other hand, an appreciable decrease in interfacial tension and in the adsorption of thrombocytes is observed only after the attainment of a 20%–30% graft. The adhesion of thrombocytes diminishes significantly after the film has been coated with albumin. Haemocompatibility (investigated *in vivo* on sheep) as a rule increases significantly only for comparatively high amounts grafted (exceeding 30%).[33,72,75] The study of the haemocompatibility of high density polyethylene (HDPE) modified by the radiation-induced grafting of polyacrylamide (the tests were carried out *in vivo*) showed [33] that after modification the thromboresistance of the polymer increases several fold. The haemocompatibility of segmented polyurethane after the radiation-induced grafting of *N*-vinylpyrrolidone has been investigated by Hongfei *et al.*[75] The influence of pH on the radiation-induced grafting of *N*-vinylpyrrolidone has been studied. The surface of the modified polymer is rough and its swelling in water increases exponentially with the amount grafted. An appreciable increase in thromboresistance is achieved in tests *in vivo* after the attainment of a 20% graft.

The haemocompatibility of modified silicone tubes (*in vivo* tests) has been investigated by Chapiro *et al.*[52] The modification was carried out by the radiation-induced grafting of N-vinylpyrrolidone from a solution of the monomer in methanol or toluene. It was established that the haemocompatibility increases significantly after a 33% graft. On the other hand, the adsorption parameters of the proteins have a minimum at a certain thickness of the grafted layer. For example, in a study of the radiation-induced grafting of methoxypoly(ethylene glycol methacrylate) with 2-hydroxyethyl methacrylate by the direct method onto silicone rubber (Silastik), it was observed that the adsorption of fibrinogen has a minimum for an 8% graft.

The texture of the surface also influences the haemocompatibility. The radiation-induced graft polymerisation of *N*,*N*-dimethylacrylamide on polytetrafluoroethylene and the tetrafluoroethene–ethene copolymer (Aflon) has been investigated.[27, 50] The influence of the monomer concentration and the dose rate on the haemocompatibility of the modified polymers obtained was studied. It was established that a decrease in dose rate from 1 to 0.1 kGy h^{-1} increases the haemocompatibility (*in vivo* tests), which is associated with the increase in the smoothness of the surface. Collin *et al*.[85] studied the adhesion of red blood cells on polycationic carriers, which were prepared by modifying poly(vinyl chloride) grains by means of radiation-induced graft polymerisation of dimethylaminoethyl methacrylate; electron micrographs of the system with adhering cells have been published.

The radiation-induced graft polymerisation of acrylamide on polypropylene (PP) films by the post-effect method in order to render them hydrophilic is also promising.[100]

Another method for the preparation of haemocompatible polymeric material involves the creation of hydrocarbon polymers (polyethynes). For this purpose, vinylidene chloride was radiation-grafted from the gas phase onto polymeric materials with subsequent dehydrochlorination of the modified polymers obtained. These materials are used in endosurgery.[101–104]

One of the methods of increasing haemocompatibility involves the use of radiation-induced graft polymerisation in order to obtain negatively charged surfaces of polymers containing carboxy, hydroxy and sulfo groups in the surface layers. The communication of Stever *et al*.[105] is devoted to the study of polyurethanes modified by the grafting of propanesulfonate functional groups. It was established in experiments *in vivo* that the haemocompatibility of such polyurethanes increases, the adhesion of blood cells to the surface is low, and the adhering cells do not undergo marked changes. The conversion of the adsorbed fibrinogen into fibrin is blocked and inhibited, *i.e*. the surface modification acts in approximately the same way as heparin — a blood anticoagulant. The radiation-induced grafting of the bisulfite derivative of acrolein mixed with acrylic acid followed by the sulfonation of the grafted layer with sulfurous acid and neutralisation of the sulfo and carboxy groups has been investigated.[31] Modified materials with a thromboresistant effect were created.

Ratner *et al*.[106] described a study of the influence of the nature of the monomer used for radiation-induced graft polymerisation on the antithrombogenic properties of the modified materials. The authors studied the thrombogenic properties (*in vivo*) of the hydrogels obtained by the radiation-induced grafting of 2-hydroxyethyl methacrylate, acrylamide, a mixture of 2-hydroxyethyl methacrylate and ethyl methacrylate, and a mixture of 2-hydroxyethyl methacrylate and *N*-vinylpyrrolidone on LDPE. The influence of the composition of the copolymer and the water content on the deposition of thrombi is described in detail. It has been noted that the use of radiation-modified polyphosphazenes as haemocompatible materials is promising.[70] It has been shown [72] that the number of attached thrombocytes diminishes with decrease in the interfacial free energy (*in vivo* tests in the canine carotid arteries of polyurethane tubes modified by the grafting of 2-hydroxyethyl methacrylate). The interfacial free energy decreases significantly after the grafting of 30% of 2-hydroxyethyl methacrylate. The coating of the graft polymer with albumin or γ-globulin decreases the adhesion of thrombocytes. In a study of the influence of the radiation-induced grafting of acrylamide on LDPE and PP tubes on the antithrombogenic properties, it was efitablished that the best antithrombogenic properties are attained for a 30% graft (the wetting angle is $< 28\ ^{\circ}$).[27, 28, 41] The influence of the conditions in the graft polymerisation on the antithrombogenic properties has been demonstrated. When *N*-vinylpyrrolidone is grafted on polyurethane; the best antithrombogenic properties are also attained for a 30%–35% graft (experiments on the blood circulatory system of sheep).[69] The study of the radiation-induced grafting of acrylamide and acrylic acid on LDPE and HDPE showed that the radiation-induced graft polymerisation of acrylamide takes place most effectively in the case of HDPE.[24, 33, 107] The modified PE polymers with grafted polyacrylamide have a low wetting angle and exhibit enhanced antithrombogenic properties in tests *in vivo* in the carotid arteries of rats. The thrombus formation time increases several fold compared with pure PE.[33] The cross-linking of the polyacrylamide chains in the radiation-induced grafting of acrylamide together with the *N*,*N*′-methylenebisacrylamide cross-linking agent leads to a decrease in thromboresistance.[28]

The radiation-induced graft polymerisation of *N*,*N*-dimethylacrylamide on natural rubber tubes has been studied in detail.[92, 108] It was established that the best solvent for grafting is CCl_4 and that satisfactory haemocompatibility is manifested for a 30% graft.

The presence on the polymer surface of uniformly distributed negatively charged functional groups is important for increasing haemocompatibility.[47]

Studies on the use of radiation-induced graft polymerisation for the modification of blood vessel prostheses made from polyester materials have been carried out in Poland (Institute of Applied Radiation Chemistry, Lodz). Acrylamide was used for the radiation-induced graft polymerisation. The influence of the dose and the monomer concentration on the process was investigated. Grafting results and an increase in hydrophilicity and a decrease in the gas-permeability of the prostheses. Tests on the prostheses demonstrated their fairly satisfactory biocompatibility. Thus acrylamide and its derivatives are promising monomers for increasing the hydrophilicity and biocompatibility of various polymeric materials. Another monomer which being vigorously employed for increasing biocompatibility is the highly hydrophilic monomer *N*-vinylpyrrolidone.[48, 52, 58, 60, 67, 68, 75, 78] The radiation-induced grafting of *N*-vinylpyrrolidone is as a rule carried out by the direct method from its solutions in water, toluene, or methanol, using low radiation doses. As in the case of acrylamide, after the graft polymerisation of *N*-vinylpyrrolidone the hydrophilicity increases significantly with increasing amount of the grafted material. The antithrombogenic properties of polyesterurethane tubes modified by the radiation-induced grafting of 2-hydroxyethyl methacrylate have been investigated.[109] Tests *in vivo* showed that a considerable amount of graft is required for an appreciable enhancement of the antithrombogenic properties. The radiation-induced grafting of 4-vinylpyridine (4-VP) + 2-(*N*,*N*-diethylamino)ethyl methacrylate and 4-vinylpyridine + -methacrylic acid mixtures on polyethylene catheters has been studied.[110] The catheters were tested *in vivo*. The operational lifetime of the catheters depends significantly on the amount of graft. The haemocompatibility of the radiation-grafted PE polymers with poly(2-hydroxyethyl methacrylate) and poly(2,3-dihydroxypropyl methacrylate) has been studied.[111] In the investigation of the adhesion of thrombocytes on poly(vinyl chloride) with radiation-grafted polyacrylic acid, it was established that the adhesion of thrombocytes diminishes significantly with increase in the amount of graft and with decrease in the wetting angle.[112] One of the ways of enhancing the antithrombogenic properties of polymers involves the formation on their surfaces of polyelectrolyte complexes (PEC).[113, 114] PEC are formed on the surfaces of polymers as a result of the interaction of the radiation-grafted poly(acrylic acid) with polyamines. The appearance of PEC gives rise to the formation of a microheterogeneous structure with alternation of hydrophilic and hydrophobic sections.

Lundell *et al*.[40] investigated the radiation-induced grafting on the surfaces of PP of mixtures of *N*-vinylpyrrolidone and acrylic acid and also vinyl acetate and crotonic acid. Pronounced antithrombogenic properties were attained after partial neutralisation of crotonic acid with alkali. It was concluded that the negative surface charge plays an important role.[40–47] It was established [42] that polymers with grafted poly(vinyl acetate)

(with subsequent partial hydrolysis of the acetate groups) and *N*-methyl-*N*-vinylacetamide exhibit the best haemocompatibility.

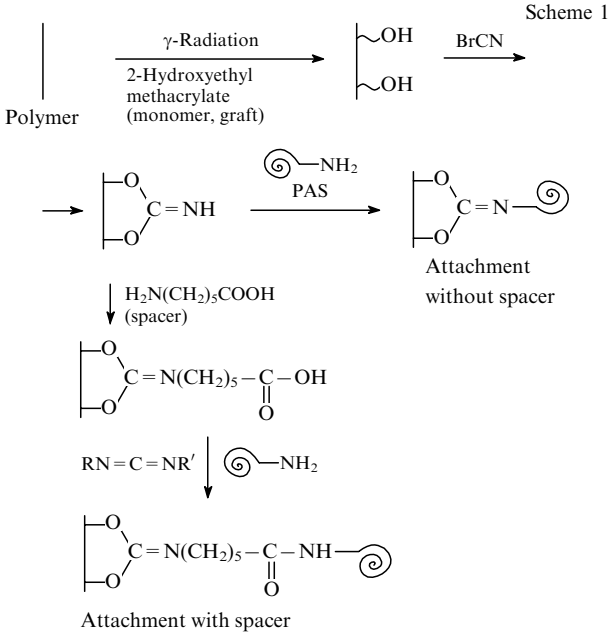
The main conclusion which may be reached from the data described above concerning the use of hydrophilic monomers in order to enhance the antithrombogenic properties of polymers is that, with increase in the water content, thrombogenesis diminishes, but, in prolonged tests *in vivo* the minimum thrombogenesis is attained for a definite water content.[105] Radiation-induced grafting of *N*-vinylpyrrolidone as well as acrylamide and its derivatives affords good results. The presence of negatively charged groups on the surface is important.[115] The adsorption of enzymes and blood cells diminishes with increase in the amount of graft.[116] The presence of certain admixtures in the monomers employed for radiation-induced graft polymerisation influences significantly the haemocompatibility because it can alter the nature of the sorption of proteins.[117]

An extremely promising aspect of the preparation of antithrombogenic polymeric materials involves the modification of the surface of polymeric materials by radiation-induced graft polymerisation followed by the introduction into the modified layers of physiologically active substances (PAS), which act in the blood clotting stage. The radiation-induced grafting of monomers with active functional groups capable of reacting with the PAS is usually carried out for this purpose. The form of the bond between the PAS and the polymer (covalent, ionic, or physical capure) as well as the microenvironment of the PAS in the polymer are important. Radiation-induced graft polymerisation has been used [63, 118–122] to obtain modified polymeric materials containing on the surface organic cations to which heparin is attached as a result of the formation of ionic bonds. As an example, styrene was grafted to different polymers with subsequent chloromethylation and quaternisation.[118] 4-Vinylpyridine was used for radiation-induced grafting followed by quaternisation.[119] Polyolefins, silicone rubber, and polytetrafluoroethylene have been used as the polymers. The modified polymers thus obtained exhibited a satisfactory haemocompatibility, possibly as a result of the partial washing away of heparin during use.[123] Another monomer which is employed for grafting to achieve ionic binding of heparin is 2-(*N*,*N*-diethylamino)ethyl methacrylate.[124, 125] In all probability, the covalent binding of PAS is more promising. Radiation-grafted polymers with grafted poly(2-hydroxyethyl methacrylate) chains, which were activated by bromocyanogen with subsequent addition of streptokinase (lysis of fibrinogen on the surfaces), were obtained.[123] Another method of binding enzymes is the radiation-induced grafting of methacrylic acid followed by the application of the carbodiimide method in order to bind the BAS.[123, 125] The employment of a spacer for the attachment of biomacromolecules to radiation-grafted polymers is very important in this procedure.[123]

The binding of albumin to the radiation-grafted hydrogel, obtained by the radiation-induced grafting of a mixture of *N*-vinylpyrrolidone and 2-hydroxyethyl methacrylate, greatly increases when a spacer is used.[123, 126] The process involving the attachment of PAS to modified polymer surfaces using bromocyanogen is illustrated in Scheme 1.[126]

A significant increase in the sorption of albumin after the modification of polytetrafluoroethylene by the radiation-induced grafting of *N*-vinylpyrrolidone has been established.[127] The copolymers obtained by the radiation-induced grafting of acrylic acid, 2-hydroxyethyl methacrylate, a mixture of maleic anhydride and acrylic acid, as well as a mixture of acrylic acid and acrylamide, which are used for the immobilisation of human albumin, were grafted by Müller-Schulte and Horster.[128] In the covalent binding of albumin, bromocyanogen, hydrazine and glutaraldehyde, as well as 1-hydroxybenzotriazole, which ensures the maximum binding of human albumin, were used as the condensing agents. Glutaraldehyde has also been used for the covalent binding of PAS to radiation-grafted polyacrylamide.[123]

Scheme 1



Novel methods for the enhancement of haemocompatibility using radiation-induced graft copolymerisation have been described.[23–26] One of them consists in the radiation-induced grafting on polymer surfaces of acrylic acid chlorides [23] and subsequent introduction of PAS.[26] Modified polymers containing on the surface heparin, various enzymes (for example, fibrinolysin), albumin, *etc*. have been obtained in this way. The simultaneous presence of heparin and enzymes on the polymer surface gives rise to effective thromboresistant properties of polymeric materials.[26] Reactive acid chloride groups may be obtained also by treating with thionyl chloride radiation-grafted copolymers with polyacrylic acid.[129] Another procedure consists in the radiation-induced grafting of allylamine on the polymer surface. The grafting of this monomer was achieved solely in the presence of orthophosphoric acid (suppression of the degradative chain transfer in the polymerisation of allylic monomers). Glutaraldehyde has been used to bind enzymes with an amino group.[25] Hydrazide groups may be used for the immobilisation of PAS. The hydrazidation of radiation-grafted copolymers of PE with acrylic monomers has been investigated.[59, 130]

Methods have been developed for the modification of polymer surfaces by the radiation-induced grafting of macromonomers in the presence of hydrophilic monomers (acrylamide, *N*-vinylpyrrolidone, *etc*.) and a cross-linking agent.[26, 131–133] The macromonomers may be obtained by introducing an active double bond into the PAS (heparin, enzymes) molecules in acylation by the chlorides of acrylic and methacrylic acids.[25, 134–136] It was established that the acylation process does not affect the structure of the molecules of the PAS and its physiological activity. The macromonomers are capable of entering into the copolymerisation reaction with various monomers (acrylamide, *N*-vinylpyrrolidone).[134] The homopolymerisation of macromonomers leads to the formation mainly of products with a low degree of polymerisation.[136]

The radiation-induced grafting of PAS macromonomers jointly with hydrophilic monomers on various polymeric materials afforded biospecific sorbents and modified materials employed in contact with blood. In the latter case, the polymer was modified by grafting the heparin macromonomer and trypsin or fibrinolysin as the fibrinolytic enzyme. It was shown that the polymers modified by a mixture of heparin and trypsin exhibit a higher haemocompatibility than the polymers containing only heparin. The increased thromboresistance of such materials, which has been investigated in experiments *in vitro* and *in vivo*, can be explained by the fact that heparin binds fibrinogen, which is

lysed by trypsin.[137–139] The grafting of a mixture of acrylamide and the cholesterol ester of *N*-methacryloyl-ω-aminocaproic acid on PE has been investigated.[140] The graft results in the formation on the PE surface of a hydrophilic layer in which cholesterol groups are immobilised covalently. This led to the formation of modified polymers capable of adsorbing heparin selectively from the blood flow.

It has been shown [89, 141] that the employment of *N*-methyl-*N*-vinylacetamide for the modification of polymers in order to increase their haemocompatibility is promising.[89, 141] Diverse polymers, modified by grafting *N*-methyl-*N*-vinyl-acetamide, have been investigated in detail by various physicochemical methods.[141] The haemocompatibility of ethylene–propylene rubber, modified by the radiation-induced grafting of acrylamide, *N*-vinylpyrrolidone, and 2-hydroxyethyl methacrylate, has been studied.[142, 143] The experiments were performed *in vitro*. It was established that there is no linear relation between the amount of the graft and the hydrophilicity, on the one hand, and the degree of haemocompatibility, on the other. The relation is complex.

During recent years, there has been a growth of interest in the use of polyphosphazenes as biomaterials. The radiolysis of polyphosphazenes has been investigated [144] and it has also been established (in experiments *in vivo*) that the modification of polyphosphazenes by the radiation-induced grafting of *N*-vinylpyrrolidone makes it possible to increase their haemocompatibility.[145] The influence of the preliminary ^{60}Co γ-irradiation of polyurethane on its coating with albumin has been studied.[146]

Radiation-induced graft polymerisation has been used to modify various polymers in order to accelerate the growth of endothelial cells on the surface.[147, 148]

It has been suggested [10] that the lack of success in the creation of polymeric materials designed for prolonged use in contact with blood within a living organism is associated with the inadequate knowledge of the biochemical processes occurring at the implant–blood interface and also with the attempts to relate to haemocompatibility to any one parameter of the surface (hydrophilicity, free surface, morphology, *etc*.).

Radiation-induced graft polymerisation has been used in a series of investigations [64, 149, 150] to modify the surfaces of polymeric articles used in contact with blood and its components. Studies have been performed in recent years on the preparation of haemocompatible polymers by radiation-induced graft polymerisation initiated when polymers are irradiated with accelerated heavy ions.[62]

Studies have been carried out on the use of radiation-induced graft polymerisation for the creation of various medical polymeric materials: blood vessel prostheses, intravenous catheters, implants, tissue-protecting, antiinflammatory, and opthalmological materials, *etc*. The materials have been called 'hydrografts'.[150]

III. Preparation of special sorbents

Radiation-induced graft polymerisation is used in the creation of carriers for affinity chromatography,[44, 61, 155] immunoadsorbents,[156–165] and biospecific sorbents [66, 148, 166, 167] and also for the growth of endothelial cells.[147, 168–171]

Effective sorbents for affinity chromatography, obtained by modifying polyamide-6 beads by means of radiation-induced graft polymerisation, have been described. Mainly 2-hydroxyethyl methacrylate, *N*-vinylpyrrolidone, and acrylamide have been used as the monomers.[44, 61, 151, 153–155] The conditions in the graft polymerisation and primarily the choice of solvents with specific solubility parameters, as well as the choice of swelling agents are very important.[61, 154] Compared with the known sorbents (agarose), the capacity of the sorbents obtained is appreciably higher in the separation of low-density lipoproteins and antibody immunoglobulin G. The properties of the adsorbents may be varied by varying the conditions in the graft polymerisation. The carriers obtained for affinity chromatography are cheaper compared with the known and expensive carrier — sepharose with protein A.[61]

The sorbents obtained may be used for the removal of excess cholesterol in patients suffering from cholesterinemia.[61]

It has been established that, when sorbents based on polyamide-6 modified by radiation-induced graft polymerisation are used, the amount of lectin extracted from mistletoe increases appreciably. Sorbents with immobilised urease may be used for the rapid determination of the content of urea in kidney diseases. The method is based on the continuous and rapid enzymic hydrolysis of urea and the determination of ammonia.[155]

The modification of polystyrene plates by the radiation-induced grafting of monomers containing hydrazide groups has been described.[156] The modified plates adsorbed effectively immunoglobulin E and low-molecular proteins. In order to increase the hydrophilicity of polystyrene, it is ^{60}Co γ-irradiated. By employing the modified polystyrene plates, it is possible to determine the concentration of immunoglobulin E (down to 0.1μg ml^{-1}).[156]

The modification of LDPE, poly(vinyl chloride) and polystyrene by the radiation-induced graft polymerisation of methacrylic acid and acrylamide with subsequent immobilisation of the Brucella antigen resulted in the formation of systems for diagnostic tests (ELISA). The sensitivity was improved and the reactivity of the antibodies increased significantly.[164]

Methods have been developed for the modification of agarose,[66] sepharose, and sephadex [166] by the radiation-induced grafting of *N*-acryloyloxysuccinimide with subsequent addition of bovine serum albumin (BSA). The separation of D,L-tryptophans was studied.[166]

Radiation cross-linked poly(vinyl alcohol) has been used in affinity chromatography. The carriers based on this polymer are distinguished by a satisfactory morphology, biocompatibility, and a high capacity.[152, 153]

Blood detoxicants based on modified polypropylene fibres have been obtained.[140] Specific sorbents for the removal of heparin have been created with the aid of radiation-induced grafting.[140]

Radiation-induced graft polymerisation has been used to modify various polymers in order to form on their surface a coating comprising endothelial cells.

This problem has been examined in greatest detail by Kirkpatrick *et al*.[147] The radiation-induced graft polymerisation of 2-hydroxyethyl methacrylate, *N*-vinylpyrrolidone and 2-(*N*,*N*-dimethylamino)ethyl methacrylate on a whole series of polymers (LDPE, polytetrafluoroethylene, polyamide, *etc*.) has been investigated. It was established that the conditions in the graft polymerisation (solvent, composition of copolymers, *etc*.) are very important for the successful growth of cells. Electron micrographs of the surface with layers of endothelial cells have been obtained. It was noted that the presence of OH groups on the surfaces of polymers is important for cell growth.

Methods have been devised for the modification of polymeric materials,as a result of the application of which the polymers can undergo a change in their hydrophilic and hydrophobic properties under the influence of small changes in temperature. This makes it possible to regulate the adhesion and viability of the cultures.[168]

IV. Synthesis of polymeric carriers for medicinal preparations

Radiation-induced polymerisation is used in the synthesis of polymeric carriers for medicinal preparations (antibiotics, antiseptics, *etc*.). The following advantages of the radiation initiation of polymerisation in the synthesis of polymeric carriers for medicinal preparations compared with 'material' initiation have been noted. Firstly, fairly pure polymers are obtained (without initiator residues). Secondly, it is possible to regulate comparatively easily the molecular-mass characteristics of the polymers by

varying the radiation dose rate. Thirdly, in a number of instances the yield of the polymers is much higher than the yield obtained on initiation with 'material' initiators.

Radiation-induced polymerisation has been used in a series of studies [172–175] for the creation of copolymers based on *N*-vinylpyrrolidone with undecenoic, oleic, and crotonic acids. Modifying agents for PAS, ensuring a fairly intense hydrophobic interaction between the copolymer and the PAS, are obtained in this case. On initiation using 'material' initiators, it is impossible to obtain copolymers in a sufficiently high yield. The radiation-induced copolymerisation of *N*-vinylpyrrolidone with undecenoic and oleic acids in ethanol for doses of 50–150 kGy (dose rates of 0.23 and 0.04 Gy s^{-1}) has been investigated.[172] It was established that the yield of the copolymer and the rate of copolymerisation depend significantly on the mixture composition, a statistical copolymer without adjacent COOH units being formed. The relative reactivity of the acids is zero, while the reactivities of *N*-vinylpyrrolidone vary in the ranges $0.61 < r < 0.94$ for undecenoic acid and $0.90 < r < 1.31$ for oleic acid. The copolymer units are enriched in *N*-vinylpyrrolidone.

The radiation-induced copolymerisation of *N*-vinylpyrrolidone with crotonic acid in ethanol at different dose rates in the range 0.25–3.26 Gy s^{-1} has been investigated.[173] In the initial stage, the rate of polymerisation is proportional to the radiation dose rate raised to the power 0.5, but, with increase in the degree of conversion, the above parameter tends to 0.8. With increase in dose rate and degree of conversion, the molecular mass of the copolymer diminishes. The composition of the copolymer is independent of the dose rate and its molecular mass may be regulated by varying the dose rate. Copolymers with a viscosity-based mean molecular mass of 1.2×10^4 -7.0×10^4 have been obtained.

The dependence of the molecular mass and the molecular mass distribution in the radiation-induced copolymerisation of *N*-vinylpyrrolidone with crotonic acid (CA) in ethanol or 2-propanol on the dose for a constant monomer ratio *N*-vinylpyrrolidone : CA = 85 : 15 has been examined.[174] It was established that the molecular mass distribution can be regulated by selecting the radiation dose. It was shown that in alcohols the yield of the copolymer is high (93%–98%) for a dose of 4.5×10^4 Gy. The radiation-chemical yield of the copolymerisation is $(6-7) \times 10^3$ molecules per 100 eV (dose rate 0.28 Gy s^{-1}). The radiation-induced copolymerisation of *N*-vinylpyrrolidone with allylamine and 2-(*N*,*N*-dimethylamino)ethyl methacrylate in aqueous organic solvents and the properties of the copolymers have been studied. In this process, the copolymers are obtained in a high yield and with a narrow molecular mass distribution in the molecular mass range from 10^3 to 4×10^6.[175]

Thus copolymers based on *N*-vinylpyrrolidone can be obtained by the radiation-induced polymerisation method with a fairly high yield and their molecular mass characteristics may be varied in the required direction by selecting the polymerisation conditions. The rate of polymerisation depends significantly on the mixture composition, while the composition of the copolymer is independent of the dose rate. A distinctive feature of these copolymers is that, together with the strongly hydrophilic component (carboxy groups, *N*-vinylpyrrolidone units), the polymer chain contains a significant hydrophobic component (the hydrocarbon part of the carboxylic acids). Such copolymers are non-toxic.

The radiation-induced copolymerisation of *N*-vinylpyrrolidone with allyl alcohol in ethanol or 2-propanol at a dose rate of 2 Gy s^{-1} (for doses in the range 30–200 kGy) has been studied by Solovskii *et al.*[176] The radiation-induced and 'material' copolymerisations were compared. The yields in the radiation-induced copolymerisation exceed by a factor greater than 2 the yields in the 'material' polymerisation. The yield of the copolymer is 50%–90% and diminishes with increase in the concentration of allyl alcohol. The maximum yield occurs for a 30% content of the comonomers in the alcohol. Conditions for the preparation of copolymers with a low molecular mass and a narrow molecular mass distribution have been found.

The radiation-induced copolymerisation of *N*-vinylpyrrolidone with vinyl acetate at 5 °C and a dose rate of 14.5 Gy min^{-1} has been studied [177, 178] and the copolymerisation constants have been determined.

Panarin *et al.*,[179] investigated the radiation-induced polymerisation of *N*-vinylpyrrolidone under various conditions. The molecular-mass characteristics of *N*-vinylpyrrolidone were determined. An important advance in radiation-induced polymerisation is in this case the possibility of the fine regulation of the molecular-mass characteristics, which is particularly important for this polymer, used as a blood plasma substitute.

The carriers based on *N*-substituted acrylamide and methacrylamide are extremely interesting. The water content in these hydrogels depends significantly on the external conditions (temperature, pressure, *etc.*), which makes it possible to increase the effectiveness of the action of the medicinal preparations immobilised in them.[180]

The study of methacrylic acid–triethylene glycol dimethacrylate copolymers as carriers for medicinal substances (insulin) demonstrated their resistance to the action of the acid medium in the stomach and the rapid liberation of the hormone on entering the intestine.[181]

The radiation-induced copolymerisation of *N*-vinylpyrrolidone with various aminoacrylates and methacrylates has been investigated. Polymeric carriers for BAS with a high molecular mass have been obtained in a satisfactory yield.[182, 183]

The radiation-induced polymerisation of hydrophilic monomers is used for the creation of porous polymeric carriers for the immobilisation of insulin and interleukin. The pore dimensions and the rate of liberation of medicinal substances are regulated by the polymerisation conditions.[184] The radiation-induced copolymerisation of 2-hydroxyethyl methacrylate and methacrylic acid is used to prepare carriers for contraceptives.[185]

The radiation-induced polymerisation of acrylamide and *N*-vinylpyrrolidone in aqueous solutions has been investigated.[186] The influence of the dose rate and the concentration of monomers on the rate of polymerisation was studied. The role of the water radiolysis products in the initiation of polymerisation was established and the dependence of the gel formation dose on the concentration of monomers was determined.

The methods for the preparation and properties of antimicrobial polymers have been described in a monograph.[187]

Foss and Ebersol [188] used the radiation-induced polymerisation of acrylamide for the preparation of thin (0.25–1 mm) films of polyacrylamide gels with a specified pore distribution. The standard size distribution of pores was ensured by the conditions in the ^{60}Co γ-irradiation with computer control. The films were used for the high-resolution separation of proteins by electrofocussing and electrophoretic methods.

The employment of radiation-induced polymerisation for the preparation of polymer microspheres occupies a special place. The formation of microspheres from various acrylates as a result of radiation-induced polymerisation has been examined in a number of studies.[189–200] The diameter of the microspheres increases with increasing hydrophilicity of the monomer [189] and the nature of the solvent is also important.[190] Polymer microspheres containing amino acids have been obtained with the aid of radiation-induced polymerisation. The microspheres have been used for immunochemical assay in relation to malaria.[191]

The preparation of microspheres by the radiation-induced copolymerisation of diethylene glycol dimethacrylate with acrylamide has been described in review.[192] The size of the microspheres was 10–10 000 Å. The microspheres are used mainly for immunoassay. The synthesis of microspheres based on polyacrylamide, poly(2-hydroxyethyl methacrylate), poly(methyl methacrylate), and poly(acrylic acid) by radiation-induced suspension polymerisation in methanol has been described.[194] The radiation-

induced grafting of 2-hydroxyethyl methacrylate, acrylamide, and their mixtures on microspheres has been studied.[194]

The preparation of microspheres based on polyacrolein, on the surface of which there are aldehyde groups which react readily with proteins, is of significant interest.[195–197] Cross-linked polyacrolein has been synthesised by the radiation-induced polymerisation of acrolein in bulk or in a water–acetone mixture at temperatures ranging from −15 to 25 °C. The yield of this polymer depends on the reaction conditions and may reach 100%. The principal polyacrolein unit is a six-membered oxygen-containing ring and the interchain cross-links are formed by ester bonds; furthermore, free aldehyde groups are present in polyacrolein. It has been established by electron microscopy that polyacrolein consists of microspheres with a particle size of 1–30 μm. The size of the particles depends on the conditions in the preparation of the polymer. The formation of microspheres in the radiation-induced copolymerisation of acrolein with hydroxyethyl methacrylate or poly(ethylene glycol dimethacrylate) in 1% PVA solution at −78 °C has been studied.[196] The yield of the copolymers depends on the content of the vinyl monomer. The size of the microspheres increases with increase in the concentration of the vinyl monomer. The properties of the microspheres obtained, containing aldehyde groups, have been investigated.[197] Microspheres of the 'core–shell' type, having aldehyde groups on the surface, have been synthesised with the aid of the radiation-chemical modification of polystyrene particles (0.6 μm in diameter) by acrolein. The structure and properties of the polymers obtained were studied by various methods.[198] It was established that the content of aldehyde groups is 60% of the theoretically possible. A structure was proposed for graft polyacrolein. It was shown that the radical polymerisation of acrolein involves mainly the vinyl bond. The form of the microspheres does not change as a result of the polymerisation.[199]

The principal advantages of the preparation of polymer microspheres with the aid of radiation-chemical methods are the high purity of the product (the absence of impurities arising from the initiator) and the possibility of carrying out the polymerisation under a wide range of conditions (temperature, rate of initiation), and this makes it possible to regulate the size of the microspheres comparatively readily. It is sometimes possible to achieve relatively easily the radiation-induced cross-linking of the microspheres, which is difficult to do by traditional methods.

Thus the radiation-induced polymerisation is a promising method for the creation of polymeric materials used as carriers for medicinal preparations. In many instances, it is possible to achieve the synthesis of unique copolymers, the preparation of which with the aid of 'material' initiators is very difficult. The vast majority of studies have been devoted to the synthesis of copolymers based on *N*-vinylpyrrolidone. The choice of the solvent, of the radiation dose and of the radiation dose rate is very important for radiation-induced polymerisation, determining the yield of the copolymer and its molecular-mass characteristics.

V. Immobilisation of biologically active substances

1. Immobilisation of enzymes

During recent years, radiation-induced polymerisation has been used for the immobilisation of various BAS in polymer matrices. Such a process is carried out in order to fix the BAS for reuse in order to achieve economies in their employment (some are very expensive), in order to stabilise the BAS in relation to thermal influences, solvents, and pH, in order to prepare polymeric articles of different shape (films, tablets, needles, cylinders, *etc.*), for the controlled liberation of BAS under the conditions of a specific application, and for the employment of effects associated with the polymer matrix (strength, rheology, *etc.*). The immobilisation of BAS in polymer matrices is achieved by the joint polymerisation of monomers mixed with the BAS or by the covalent attachment of these compounds to different polymers with active functional groups. Reviews have been devoted to various aspects of the preparation of polymeric biomaterials by radiation-induced polymerisation and grafting.[201–211] A wide range of substances have been used as the BAS: enzymes,[212–265] yeast cells,[266–270] haemoglobin,[271–275] anticancer preparations,[276–279] chloroplasts,[280, 281] various medicines, antibodies, microorganisms and microbial cells.[281–297] Polymeric biomaterials with immobilised BAS have a wide range of applications. Allowance for the specific features of particular spheres of their application is important. Table 2 presents data on the immobilisation of BAS using radiation-chemical methods.

The radiation-induced polymerisation for the immobilisation of BAS has the following advantages.[201, 202]

1. The possibility of carrying out the process over a wide range of conditions, including polymerisation at low temperatures of supercooled viscous monomers, solid monomers and multiphase systems.

2. A fairly wide selection of monomers for polymerisation.

3. A decrease in the inhibiting effect of oxygen and other impurities.

4. The absence of residual amounts of the catalyst and the unpolymerised monomer in the polymer. The latter is very important, since a partly unpolymerised monomer has a toxic effect, particularly in the immobilisation of cells.

5. The ease of cross-linking to different extents by selecting the dose absorbed.

6. The comparative simplicity of the preparation of porous and complex composite structures.

7. The simplicity of the manufacture of preparations of any arbitrary shape (tablets, cylinders, needles, *etc.*).

8. A decrease in the deactivation of unstable BAS in the polymer.

9. The high productivity of the immobilisation apparatus when electron accelerators are used as the sources of radiation.

10. The possibility of preparing ultrathin particles and membranes.

There are three main immobilisation methods: covalent binding of the BAS to the polymer — the chemical method, ionic binding or physical adsorption of the BAS, and physical capture of BAS in the polymer. An advantage of the chemical method is the solid-phase fixation of the BAS and the impossibility of its removal on prolonged use. The disadvantage of the method are as follows: a comparatively low yield of the activity of the BAS (a significant loss of activity in the immobilisation process), an appreciable selectivity in relation to the BAS reaction conditions, and the difficulty of its employment for the immobilisation of microorganisms. The chemical immobilisation method works as a result of the formation of chemically reactive functional groups in the polymer, mainly $-COOH$, $-OH$, $-NH_2$, $-C(=O)Cl$ and others capable of covalent binding of the BAS. The reactive functional groups are introduced into the polymer by radiation-induced graft polymerisation (for more details, see Section II as well as other communications [2, 4, 18, 26, 210, 211]). Mainly the immobilisation of BAS as a result of physical capture, ionic binding, or physical adsorption in polymer matrices is considered in this section. The advantages of the physical capture method are as follows: comparative ease of application, a fairly high reactivity and universality of the BAS (BAS without specific functional groups — various microorganisms, cells, *etc.* — may be used for immobilisation), and the possibility of employing monomers with a wide range of hydrophilic and hydrophobic properties. The physical capture of the BAS in polymers is achieved by means of the radiation-induced polymerisation of the monomer mixed with the BAS.

Radiation-induced polymerisation for the immobilisation of enzymes was first described by Dobo,[212] who obtained immobilised enzymes in polyacrylamide matrices by the solid-phase polymerisation of acrylamides mixed with the enzyme. Subsequently Kaetsu and co-workers [201–205] developed a method for the immobilisation of BAS mixed with monomers capable of

Table 2. Immobilisation of BAS in polymer matrices with the aid of radiation-induced polymerisation.

Monomers, immobilisation components	Immobilisation conditions	Remarks	Ref.
BAS — trypsin			
Acrylamide	radiation-induced polymerisation of acrylamide mixed with the enzyme	solid-phase polymerisation using ^{60}Co γ-radiation	212
2-Hydroxyethyl methacrylate, tris(hydroxymethyl)propane triacrylate, 2-hydroxyethyl acrylate, poly(ethylene glycol diacrylate), methoxypoly(ethylene glycol methacrylate)	radiation-induced polymerisation of monomers mixed with aqueous BAS solution; irradiation was carried out at −78 °C with a dose of 10 kGy	polymerisation resulted in the formation of a porous structure; the influence of pore size on enzyme activity and the thermal stability of the immobilised trypsin were investigated	216
2-Hydroxyethyl methacrylate	radiation-induced graft polymerisation on polyethylene powder, hydrolysis of the copolymer and the attachment of the enzyme to the functional groups with the aid of the carbodiimide method	the influence of pH on the stability of the enzyme was studied	218
2-Hydroxyethyl methacrylate	radiation-induced graft polymerisation on natural rubber by the preirradiation method	the activity of the immobilised enzyme was studied	221
p-Nitrostyrene	direct radiation-induced graft polymerisation of *p*-nitrostyrene on polypropylene and poly(vinyl chloride)	the nitro groups in the graft copolymer are converted into isothiocyanate groups	219
	radiation-induced grafting of *p*-nitrostyrene to different polymers; radiation-induced grafting of polystyrene with subsequent nitration of polystyrene	the mechanism of the action of additives accelerating the graft polymerisation was examined	220
Acrylic acid, acrylonitrile, 2-hydroxyethyl methacrylate, *N*-vinylpyrrolidone, acrylamide	radiation-induced graft polymerisation using a wide range of monomers; trypsin was attached covalently with the aid of the carbodiimide method or glutaric dialdehyde	preparation of polymer membranes; the study of prospects for the employment of these membranes in the milk industry in order to diminish the allergenic effect of milk (decomposition of proteins with a low molecular mass)	217
BAS — trypsin, glucose oxidase			
2-Hydroxyethyl methacrylate	radiation-induced graft polymerisation by three different methods	it was established that the immobilised enzymes are stable over a wide pH range	222
BAS — α-chymotrypsin, ribose, urease, ribonuclease			
Methacrylic acid esters, acrylamide, and its derivatives	radiation-induced polymerisation of monomers in a mixture with aqueous enzyme solutions; irradiation at −20 °C; dose 5 kGy		224
BAS — α-chymotrypsin, trypsin, glucose oxidase, papain			
Methacrylic acid, 2-hydroxyethyl methacrylate	radiation-induced graft polymerisation of 2-hydroxyethyl methacrylate and methacrylic acid on polyethylene	covalent immobilisation on the grafted chains	259
BAS — α-chymotrypsin, trypsin, fibrinolysin			
Acrylic acid chloride, allylamine	radiation-induced graft polymerisation of acrylic acid chloride on various monomers with subsequent addition of the BAS *via* the acylation of the acid chloride group; graft polymerisation of allylamine and attachment of the BAS with the aid of glutaric dialdehyde	covalent binding of the BAS	215
BAS — urease			
Acrylamide	starch with grafted polyacrylamide	the dependence of the enzyme activity on the method of application was studied	213
Poly(dimethoxyethoxy)phosphazene	irradiation of enzyme in polymer solution	retention of 80% of enzyme activity	223
BAS — glucoamylase			
Poly(ethylene glycol diacrylate), 2-hydroxyethyl acrylate, tris(hydroxymethyl)propane triacrylate	irradiation by electron accelerator; dose 50 kGy	specimens of planar polymeric materials with immobilised enzymes were obtained	234

Table 2 (continued).

Monomers, immobilisation components	Immobilisation conditions	Remarks	Ref.
BAS — glucoamylase			
Hydroxyalkyl methacrylate, poly(ethylene glycol diacrylate)	radiation-induced polymerisation at a low temperature	the influence of the nature of the monomer on the character of the immobilisation of the enzyme was studied	252, 253
2-Hydroxyethyl methacrylate, *N*-vinylpyrrolidone, acrylamide	radiation-induced copolymerisation of 2-hydroxyethyl methacrylate with comonomers at a low temperature	immobilisation of enzymes in different copolymers; the influence of the composition of the copolymer on the immobilisation was studied	255
2-Hydroxyethyl methacrylate, diethylene glycol dimethacrylate	radiation-induced polymerisation at reduced temperature of the monomers mixed with an aqueous enzyme solution	the distribution of the enzyme in the polymer matrix and the rate of its liberation were investigated	235
Poly(vinyl alcohol) (PVA)	irradiation of aqueous PVA solutions in the presence of the enzyme up to a dose of 40 kGy	the influence of the irradiation dose on the enzyme activity was studied	236
	PVA was mixed with the enzyme and irradiated on an electron accelerator up to doses of 60 – 360 kGy	a linear accelerator with a beam energy of 7.5 MeV was used; a PVA strip 20 cm wide and containing the enzyme was irradiated	237
BAS — glucoamylase, β-galactosidase, invertase			
Acrylamide, *N*,*N*-dimethylacrylamide, 2-hydroxyethyl methacrylate, *N*-vinylpyrrolidinone, acrylic acid salts, acrylic acid	electron irradiation on accelerators was employed; radiation-induced grafting of poly(acrylic acid) with subsequent immobilisation of the BAS	the influence of the irradiation dose on the rate of liberation of the enzyme was studied, methods were developed for the preparation of membranes with immobilised enzymes, and procedures were devised for the preparation of spherical particles with immobilised enzymes	225 – 229
BAS — glucoamylase, AFP-antibodies			
Poly(ethylene glycol dimethacrylate), poly(ethylene glycol diacrylate), tris(hydroxymethyl)propane triacrylate	irradiation on an electron accelerator of thin monomer films containing the BAS at temperatures from −75 to 35 °C and for electron energies of 150 – 300 KeV	preparation of polymer membranes containing the BAS; the influence of the monomer concentration and of the dose on the enzyme activity was studied	233
BAS — glucoamylase, invertase, β-galactosidase			
Acrylamide	irradiation of enzymes in aqueous acrylamide solution	the method of preparation of the specimens was described in detail; the irradiation doses are given	256
BAS — amylase, yeast cells			
Acrylic acid	radiation-induced grafting of poly(acrylic acid) on low- and high-density polyethylene by the direct method from aqueous solution	covalent binding of the BAS	232
BAS — protease (Bacillus mesentericus)			
Acrylic acid, allyl alcohol	direct grafting of the monomers on polyethylene	preparation of polymers with hydrazide and azide groups; covalent binding	214
BAS — lipase			
2-Hydroxyethyl methacrylate, 2-hydroxyethyl acrylate, poly(ethylene glycol diacrylate), tris(hydroxymethyl)propane trimethacrylate	radiation-induced polymerisation in the presence of the enzyme at a low temperature; dose 10 kGy	the influence of the structure of the polymer matrix and the monomer concentration on the enzyme activity was studied	238
BAS — cellulase			
Hydroxylated acrylates	radiation-induced polymerisation at a low temperature	membranes with different monomer concentrations and different hydrophilicities were prepared	240
Poly(ethylene glycol diacrylate)	radiation-induced polymerisation at a low temperature; dose 10 kGy	the structure and nature of the pores in the polymer matrix and its influence on the enzyme activity were studied	

Table 2 (continued).

Monomers, immobilisation components	Immobilisation conditions	Remarks	Ref.
BAS — cellulase			
Glycidyl methacrylate, polystyrene	radiation-induced polymerisation of glycidyl methacrylate in the presence of polystyrene at −78 °C with subsequent immersion in cooled methanol; dose 10 kGy	polymer microspheres were obtained; the influence of the conditions in the preparation on the number and diameter of the microspheres were studied	242
Dispersed polyurethane prepolymer	toluylene and 2-hydroxyethyl methacrylate were mixed; the mixture was kept for several minutes and treated with an aqueous solution of cellulase; irradiation at −78 °C; dose 10 kGy	disperse particles of different size were obtained	243
2-Hydroxyethyl methacrylate	radiation-induced polymerisation at −78 °C in the presence of aqueous enzyme solution	discs 1 mm thick were prepared; the influence of the thickness of the disc and the monomer concentration on the enzyme activity was studied	244
2-Hydroxyethyl methacrylate, tetraethylene glycol diacrylate	radiation-induced polymerisation of monomers on the surfaces of tubes	tubular enzyme reactors were created	251
2-Hydroxyethyl methacrylate, neopentyl glycol dimethacrylate	radiation-induced polymerisation in the presence of sodium acetate	polymer particles 50–1000 μm in diameter were obtained; the influence of various factors on the enzyme activity was studied	254
BAS — cellulase, cellobiase			
2-Hydroxyethyl methacrylate	radiation-induced polymerisation of aqueous monomer solution in the presence of the enzyme; irradiation at −78 °C	discs 1–2 mm thick were prepared; the influence of added silica gel and poly(ethylene glycol) on the enzyme activity was studied	239
Acrylamide	radiation-induced polymerisation of acrylamide	the hydrolysis of plant raw material with the aid of immobilised cellulase is described in detail; methods for the determination of the activity of cellulolytic enzymes are described	245
BAS — catalase			
Acrylamide	radiation-induced polymerisation of the monomer at −78 °C in the presence of *N*,*N*′-methylenebisacrylamide	the enzyme was immobilised on polyacrylamide gels modified by acyl azide	246
BAS — glucose oxidase			
2-Hydroxyethyl methacrylate	the enzyme was deposited on a nylon net in the presence of the monomer with subsequent radiation-induced polymerisation	network materials with immobilised enzymes were obtained	248
Acrylic acid, methacrylic acid	radiation-induced graft polymerisation of the monomers on polyethylene	immobilisation using the carbodiimide method	263
BAS — glucose oxidase, α-amylase			
Acrylamide	irradiation of the enzyme mixed with an aqueous acrylamide solution	dose < 5 kGy	296
BAS — glucose oxidase, glucose peroxidase, urokinase			
Hydrophilic monomers	radiation-induced polymerisation at −78 °C; dose 5 kGy	immobilisation of the BAS on the surfaces of polyethylene and poly(vinyl chloride) tubes	249
BAS — penicillin acylase			
Acrylates, *N*-vinylpyrrolidone	irradiation of comonomers mixed with the BAS in the presence of a cross-linking agent — tris(hydroxymethyl) propane methacrylate; irradiation time 3.5 h at −78 °C; dose rate 0.65 Gy s^{-1}	the influence of the nature of the monomer and of the degree of its conversion on the amount of immobilised acylase and the rate of its liberation were investigated	250
BAS — asparaginase			
Methacrylic acid	radiation-induced grafting of poly(methacrylic acid) on porous polypropylene fibres	covalent immobilisation	257
	Radiation-induced grafting by the preirradiation method on ethylene–propylene rubber, a polypropylene film, and a porous polypropylene fibre	ditto	258

Table 2 (continued).

Monomers, immobilisation components	Immobilisation conditions	Remarks	Ref.
BAS — β-galactosidase, pepsin, invertase, phosphatase			
Acrylic acid	radiation-induced graft polymerisation of acrylic acid from aqueous solution on polyamide powder	the modified polyamide powder was used for the immobilisation of enzymes	260
BAS — tryptophan, insulin, albumin, lysozyme, peptides			
2-Hydroxyethyl methacrylate + poly(ethylene glycol)	radiation-induced polymerisation	the influence of the molecular mass of the BAS on the rate of their liberation was investigated	230
BAS — invertase, phosphatase, albumin, trypsin, galactosidase			
Acrylic acid	radiation-induced grafting of poly(acrylic acid) on polyethylene	activation of the graft copolymer by $SOCl_2$ and attachment of the BAS *via* the acid chloride groups or by means of the carbodiimide method	262
BAS — albumin, β-galactosidase, phosphatase			
Acrylonitrile	radiation-induced grafting of polyacrylonitrile to nylon	hydrolysis of the graft copolymer and the attachment of the enzymes to the hydrolysed groups; immobilisation of the enzymes in the nylon polymeric materials	265
BAS — horseradish peroxidase			
Acrylic acid, acrylamide	grafting on polyurethanes by the preirradiation method in air; grafting from aqueous solution in the presence of Fe^{2+} ions	immobilisation of the enzyme on the graft copolymers	261
BAS — yeast cells			
Methoxypoly(ethylene glycol methacrylate), glycol methacrylate, hexanediol methacrylate, 2-hydroxyethyl methacrylate	radiation-induced polymerisation of monomer mixtures; irradiation at −78 °C	the influence of the composition of the mixture of monomers on the activity of the cells was studied	266
2-Hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, *N*,*N*-dimethylacrylamide, *N*-vinylpyrrolidone methoxypoly(ethylene glycol methacrylate)	polymer hydrogels were obtained by the radiation-induced polymerisation of the monomers in water Irradiation with ^{60}Co γ-rays at −78 °C	the adhesion method for immobilisation on the prepared polymeric materials was used; electron micrographs of the polymer particles are presented; the fermentation of glucose was investigated and the yield of ethanol was determined as a function of the nature of the polymer used for immobilisation	267
Methoxypoly(ethylene glycol methacrylate), 2-hydroxyethyl methacrylate	radiation-induced polymerisation; irradiation at −78 °C; dose 10 kGy	adsorption of the cells on porous polymeric carriers	268
Tetraethylene glycol dimethacrylate	the monomer was deposited on muslin and irradiated with ^{60}Co γ-rays	the specific surface of the modified muslin is important for the enzyme activity	269
2-Hydroxyethyl methacrylate	radiation-induced polymerisation at a low temperature; dose 10 kGy	specimens of different forms were prepared	270
BAS — haemoglobin			
2-Hydroxyethyl methacrylate	radiation-induced polymerisation of the monomer in the presence of haemoglobin	the interaction of haemoglobin with CO and O_2 was investigated	271
Phospholipids with double bonds	radiation-induced postpolymerisation of the phospholipids; preparation of vesicles 200 nm in size	the radiation-stability of haemoglobin within the vesicles was studied	274, 275
BAS — CO-haemoglobin			
2-Hydroxyethyl methacrylate, tetraethylene glycol dimethacrylate	irradiation of the monomers jointly with haemoglobin at −5 °C; dose 5–15 kGy; preparation of semisynthetic blood	the CO-haemoglobin phase was obtained immediately after the removal of blood from the animal and oxyhaemoglobin was saturated with CO; CO-haemoglobin does not induce antibody–antigen reactions; a polymer film containing 0.4% of CO-haemoglobin was prepared	272
2-Hydroxyethyl methacrylate	radiation-induced polymerisation at a low temperature	the absorption of oxygen was studied	273

Table 2 (continued).

Monomers, immobilisation components	Immobilisation conditions	Remarks	Ref.
BAS — antitumour preparations (Ara-C)			
Methyl methacrylate, ethyl methacrylate, butyl methacrylate, 2-hydroxyethyl methacrylate	the immobilisation of anticancer preparations in polymer matrices obtained by radiation-induced polymerisation at room temperature was studied	the influence of various factors on the rate of liberation of medicinal substances from polymer matrices was investigated	231
2-Hydroxyethyl methacrylate with added hydrophobic monomers	radiation-induced polymerisation of the hydrophilic monomer with added hydrophobic monomers	the influence of various factors on the rate of liberation of Ara-C was investigated; it was established that the addition of hydrophobic monomers diminishes the rate of liberation of Ara-C	295
BAS — antitumour preparations (Ara-A)			
Methyl ester of *N*-acryloyl-L-proline	radiation-induced polymerisation	immobilisation of Ara-A in a thermosensitive gel	247
BAS — antitumour preparations: mitomycin, 5-fluorouracil, 1-(2-tetrahydrofuryl)-5-fluorouracil			
2-Hydroxyethyl methacrylate	immobilisation of anticancer preparations in a poly(2-hydroxyethyl methacrylate) matrix	the effect of ionising radiation on the anticancer preparation was investigated	264
BAS — antitumour preparations: mitomycin, adriamycin, 1-(2-tetrahydrofuryl)-5-fluorouracil			
Diethylene glycol dimethacrylate, tris(hydroxymethyl)propane trimethacrylate	radiation-induced polymerisation at −78 °C	the rate of liberation of medicinal substances from polymer matrices was investigated	276
BAS — antitumour preparations: mitomycin, bleomycin, 5-fluorouracil			
Diethylene glycol dimethacrylate	irradiation at −78 °C of the monomer in a mixture with anticancer preparations and added polystyrene, poly(methyl methacrylate), polyvinylformal, and poly(ethylene glycol); dose 20 kGy	the specimens were prepared in the form of discs, a powder, *etc.*; the rate of liberation of medicinal substances from the specimens was studied	277
BAS — antitumour preparation: methoxyprogesterone acetate			
Poly(ethylene oxide)	radiation-induced crosslinking of poly(ethylene oxide) with incorporation of the BAS	tests *in vivo* and *in vitro*	278
BAS — antitumour preparation: narciclasine			
2-Hydroxyethyl methacrylate, tris(hydroxymethyl)propane trimethacrylate, methyl ester of poly(ethyleneglycol)	radiation-induced polymerisation; additives regulate the rate of liberation of the medicinal substance	tests *in vivo*; the structure of the matrix was investigated	279
BAS — chloroplasts			
2-Hydroxyethyl methacrylate, poly(ethylene glycol) dimethacrylate, methoxypoly(ethylene glycol methacrylate), glycidyl methacrylate, tetraethylene glycol diacrylate, tetraethylene glycol dimethacrylate	radiation-induced polymerisation at −78 °C; dose 10 kGy	the influence of the nature of the monomer on the activity of chloroplasts and the distribution of the chloroplasts in the polymer matrix were investigated	280
BAS — chloroplasts from spinach			
2-Hydroxyethyl methacrylate, poly(ethylene glycol)	radiation-induced polymerisation at −24 °C in the presence of additives preventing the deactivation of chloroplasts	the liberation of O_2 and the influence of ^{60}Co γ-radiation were investigated; the stability of chloroplasts increases appreciably on immobilisation	281
BAS — pilocarpine hydrochloride			
Acrylamide	radiation-induced grafting of polyacrylamide on polyester materials by impregnating the monomer with subsequent irradiation	a review article on the modification of polyester blood vessel prostheses by the grafting of polyacrylamide; preparation of polyacrylamide disc containing pilocarpine hydrochloride	282

Table 2 (continued).

Monomers, immobilisation components	Immobilisation conditions	Remarks	Ref.
BAS — salicylic acid			
Methyl methacrylate, methacrylic acid	radiation-induced graft polymerisation of a mixture of methyl methacrylate with methacrylic acid on porous cellulose spheres	the sorption of salicylic acid on a modified polymer from aqueous alcoholic solution was investigated	283
BAS — steroids: cholic acid, testosterone, progesterone, corticosterone			
Styrene	radiation-induced grafting of polystyrene on polytetrafluoroethylene, polyamides, poly(*p*- xylylene); nitration of the graft polystyrene and reduction of the nitro group to an amino group	introduction of the thiosemicarbazide group, which is capable of reacting with the carbonyl group of steroids	284
BAS — acetylcholine, serotonin, secretin, actinomycin			
2-Hydroxyethyl methacrylate, methyl, ethyl, glycidyl, and lauryl (meth)acrylates, acrylic acid, acrylonitrile, vinyl acetate, styrene	radiation-induced polymerisation at 28 °C for 2 h; dose rate 5 kGy h^{-1}	the rate of liberation of the BAS from the polymer matrices was investigated; it was established that the rate of liberation of medicinal substances may be controlled by selecting the polymerisation conditions	286
BAS — thermolysin			
2-Hydroxyethyl methacrylate, tetradecaethylene glycol dimethacrylate	radiation-induced polymerisation at room temperature	the thermal stability of the immobilised thermo lysin was investigated	287
BAS — medicinal drugs with antiandrogenic properties, steroids, and hormones			
Diethylene glycol dimethacrylate, poly(ethylene glycol dimethacrylate)	the medicinal drugs were mixed with the monomer and irradiated with ^{60}Co γ-rays at −78 °C for 2 h; dose rate 5 kGy h^{-1}	the rate of liberation of the medicinal substances was investigated; tests *in vivo* and *in vitro*	285
Microorganisms			
Acrylic and methacrylic acid chlorides	radiation-induced graft polymerisation of acrylic or methacrylic acid chlorides and covalent binding of photobacteria	a review article on the covalent immobilisation of cells; biosensors based on the immobilisation of photobacteria were made; the functional activity of cells may be regulated	288
A fumarase producing microorganism			
Acrylamide	irradiation of the BAS mixed with an aqueous solution of acrylamide in the presence of a cross-linking agent; dose 0.5 kGy	the immobilised microorganism exhibits a high fumarase activity and converts fumaric acid into L-malic acid; the preparation was produced in the form of grains	289
Enzymes and subcellular organelles			
Acrylic acid, allyl alcohol	radiation-induced graft polymerisation of acrylic acid and allyl alcohol on polyethylene	the enzymes were attached to graft polymers by the carbodiimide method; the stability of the enzymes was investigated; the use of the immobilised enzymes in the hydroxylation reaction was investigated	290
Enzymes, antibodies			
Diallyldimethylammonium chloride	the monomer was deposited on electrodes and irradiated; dose 10 kGy	cross-linked products containing enzymes strongly bound to the electrode were obtained	293
Various BAS			
Diethylene glycol dimethacrylate, acrylamide	radiation-induced polymerisation	preparation of polymer microspheres	191
Various BAS containing an NH_2 group			
Acrolein	radiation-induced polymerisation of acrolein	preparation of microspheres with aldehyde groups for the immobilisation of the BAS	195
Mixture of the BAS isolated from leeches			
Acrylic acid	radiation-induced grafting of poly(acrylic acid) to polyethylene and treatment with $SOC1_2$	the components of the BAS are bound covalently to the modified polymer	90

Table 2 (continued).

Monomers, immobilisation components	Immobilisation conditions	Remarks	Ref.
Bacillus Stearohermpohelus cells			
Maleic anhydride, styrene vinyl acetate	reaction copolymerisation of the monomers	immobilisation of the cells on the copolymer	291
Microbial cells			
2-Hydroxyethyl methacrylate	2-hydroxyethyl methacrylate deposited on a sheet of paper and irradiated with ^{60}Co γ-rays; a medium for the dilution of microbes was created	it was established that an increase in the hydrophilicity by adding methoxytetraethylene glycol methacrylate leads to an appreciable increase in the activity of the microbes	297
Monoclonal antibodies			
Methacrylic acid	radiation-induced grafting of poly(methacrylic acid) on the ethene–propene copolymer	immobilisation of antibodies with the aid of the carbodiimide method	292
BAS — transferrin, heparin, rabbit antibodies			
Glycidyl methacrylate	radiation-induced grafting of poly(glycidyl methacrylate) on polyethylene and polystyrene	the BAS were attached to the copolymer *via* the epoxide groups; the biological activity was retained	294

forming glassy viscous liquids in the supercooled state (usually at −78 °C, dry ice). In the supercooled state, the BAS are little damaged on irradiation and the yield of their activity is high. Doses of 10 kGy (^{60}Co γ-radiation) and a dose rate of 5 kGy h^{-1} are usually employed for radiation-induced polymerisation. For such does, the enzyme activity of the BAS hardly changes.

Glass-forming alkyl acrylates and methacrylates of the type $CH_2=CXCOO(CH_2)_nOH$ and $CH_2=CXCOO(CH_2CH_2O)_m-OCXC=CH_2$, where X = H or CH_3, are usually employed as the monomers. 2-Hydroxyethyl methacrylate is widely used. The presence of water and the enzyme accelerates the radiation-induced polymerisation. The immobilisation process consists of the following stages: mixing of the biocomponent with the monomer, preparation of the mould, cooling, and polymerisation. A mixture of the glass-forming monomer with the usual monomers (styrene, methyl methacrylate, vinyl acetate, acrylamide, *etc.*) is used in some cases. Aqueous solutions of the BAS at specific pH are normally employed for immobilisation. The phase state of the system is altered on freezing the monomer mixed with an aqueous solution of the BAS. Phase analysis showed that an appreciable proportion of the water begins to crystallise at a temperature below −24 °C, forming a suspension of ice in the supercooled monomer.

The radiation-induced polymerisation results in the formation of a porous system and the BAS is partly located on the surfaces of the pores. This immobilisation method has been called the adhesion method. The distribution of the BAS between the aqueous phase and the porous polymer (the degree of adhesion of the BAS on the surface) depends on the nature and concentration of the monomer. The rate of freezing also influences in many instances the pore dimensions. The monomer concentration is very important. With its increase (above 30%), the porosity of the matrix begins to diminish and the activity of the BAS falls. At a monomer concentration in excess of 50%, part of the BAS is captured by the polymer and does not participate in the reaction.

Thus the adhesion method requires the optimum (as a rule ~30%) monomer concentration.[201] Under these conditions, 20%–30% of the activity of the BAS is usually retained and changes little on reuse of the BAS. The hydrophilic or hydrophobic properties of the monomer are very important. With increase in the hydrophilicity of the monomer, the rate of liberation of the BAS during use also increases. In certain cases, this rate may be regulated by mixing hydrophilic and hydrophobic monomers and also by employing mixtures of glass-forming monomers with natural polymers (albumin, collagen, *etc.*). The addition of various cross-linking agents as well as BAS adsorbents (for example, silica gel) to the monomers has a significant influence on the rate of liberation of the BAS. By selecting glass-forming monomers and the conditions for the radiation-induced polymerisation, it is possible to regulate the rheological properties of polymer matrices with immobilised BAS.

Another method of obtaining biocomposites involves the mixing of the BAS with the polymer (usually in the form of a powder) and pressing under a pressure of ~100 kg cm^{-1} with subsequent cross-linking under the influence of radiation (with a dose of ~10 kGy).[204] However, this method is used much more rarely. Its main disadvantage is that it is difficult to achieve a uniform mixing of the BAS with polymers.

The immobilisation of glucoamidase, invertase, and β-galactosidase in polymer gels obtained by the radiation-induced polymerisation of acrylamide, *N*,*N*-dimethylacrylamide, 2-hydroxyethyl methacrylate, and *N*-vinylpyrrolidone and by the radiation-induced cross-linking of poly(vinyl alcohol) has been described.[225–228] The influence of the irradiation dose on gel formation processes has been investigated. For each monomer, there is a definite dose above which the enzyme ceases to be liberated. If the *N*-vinylpyrrolidone irradiation dose is above 30 kGy, while that for PVA is above 50 kGy, enzymes are not liberated. By selecting the dose, it is possible to regulate the rate of liberation of the enzyme. Satisfactory results have been obtained using acrylamide and *N*,*N*-dimethylacrylamide (for a dose of 10 kGy). In the case of 2-hydroxyethyl acrylate, gel formation begins at a dose of 2.5 kGy and the enzyme is liberated within a fairly wide dose range. Yoshida and Kaetsu[235] investigated the immobilisation of glucoamylase in polymer matrices obtained by the low-temperature radiation-induced polymerisation of 2-hydroxyethyl methacrylate (hydrophilic monomer) and diethylene glycol dimethacrylate (hydrophobic monomer) in the presence of the enzyme in an aqueous buffer solution (for a dose of 5 kGy). In the case of the hydrophilic matrix, the glucoamylase was in the gap between a thin polymer layer (polymer membrane), formed on radiation-induced polymerisation, and the porous structure of the polymer, as well as partly in the polymer itself, but in the hydrophobic matrix the glucoamylase was present virtually only on the surface of the porous structure of the polymer. The rates of liberation of glucoamylase from the hydrophilic and hydrophobic polymer matrices were compared. Fluorescence photomicrographs were obtained for the distribution of glucoamylase in various polymer matrices. It was established that the diffusion of glucoamylase diminishes appreciably with

increase in the content of the monomer in the mixture. The highest rate of liberation is observed at a monomer concentration of 10%.

The immobilisation of glucoamylase in thin polymer membranes, formed on irradiation of hydrophilic or hydrophobic polymers by a low-energy electron beam in the presence of an aqueous solution of the enzyme, has been investigated.[233] The polymers employed were poly(ethylene glycol dimethacrylate) or poly(ethylene glycol diacrylate). Thin polymer membranes with a high enzyme activity were obtained. The influence of the irradiation dose, the energy, and the concentration of the polymer on the enzyme activity of the membranes was studied. In the presence of tris(hydroxymethyl)propane triacrylate (a hydrophobic monomer), the activity of the membranes depends to a considerable degree on the irradiation conditions and the monomer concentration.

The immobilisation of glucoamylase in a poly(vinyl alcohol) gel on electron irradiation [236] has been investigated.[235, 236] Doses ranging from 60 to 360 kGy were used. At 120 kGy, the enzyme activity fell appreciably, while at 360 kGy it vanished completely. A strip which moved under the beam from the accelerator was used for irradiation. The immobilisation of invertase and glucoamylase in a PVA gel obtained on γ-irradiation of the above polymer in the presence of an aqueous enzyme solution was studied in detail. The irradiation dose is very important. The enzyme was liberated only for doses not exceeding 40 kGy. Up to 70 kGy, the dose does not affect the enzyme activity. A disadvantage of the immobilisation of enzymes in the poly(vinyl alcohol) gel was noted — an unduly high (75% – 90%) loss of enzyme activity.

The immobilisation of urease on starch with grafted polyacrylamide has been studied.[213] The use of low irradiation doses is important. The activity of urease fell to 60% of the initial value after the enzyme had been used seven times.

Kumakura and Kaetsu [238] investigated the immobilisation of lipase by the low-temperature polymerisation of 2-hydroxyethyl methacrylate, tris(hydroxymethyl)propane trimethacrylate, and poly(ethylene glycol diacrylate) in the presence of an aqueous enzyme solution. All the specimens had a porous structure. The enzyme activity was a maximum in 40% solution of the monomer. It was established that the maximum enzyme activity of the lipase is attained for the optimum hydrophobicity of the polymer matrix. When poly(ethylene glycol) is used in the immobilisation the enzyme activity increases with increase in the number of ethylene glycol units in the monomer molecule.

The communication of Guanghui *et al.*[246] is devoted to the study of the immobilisation of catalase on acyl azide-modified porous polyacrylamide particles obtained by the radiation-induced polymerisation of acrylamide in the presence of *N*,*N*′-methylenebisacrylamide at -78 °C. The activity of catalase increases appreciably on immobilisation via glycine groups. The immobilised catalase has been used to decompose H_2O_2 in irradiated wines.

Kaetsu *et al.*[201] studied the immobilisation of α-amylase in polymer matrices produced from the copolymer of 2-hydroxyethyl methacrylate and poly(tetraethylene glycol diacrylate). The immobilisation was carried out by the radiation-induced polymerisation of a mixture of monomers containing an aqueous BAS solution and using a dose of 10 kGy at -24 °C. At a certain temperature, the phase state of the system changes and the ice phase is formed. The biologically active substance is concentrated on the surface of the porous polymer matrix. In the case of a hydrophobic polymer matrix, an appreciable proportion of the BAS remains in the ice, so that the activity of the BAS increases with increase in the monomer concentration. However, starting from a certain monomer concentration, the activity of the test substance diminishes owing to occlusion within the polymer. Photomicrographs of the polymeric composite with the immobilised BAS have been published. In the case of the hydrophilic polymer matrix, the reactions of α-amylase take place as a result of the diffusion of the enzyme in the swollen polymer gel.

A method has been developed for the preparation of spherical particles (100 – 150 μm) in the copolymerisation of hydrophilic and hydrophobic monomers (neopentyl glycol diacrylate or tetraethylene glycol diacrylate). In this case, the activity of the enzyme is independent of the monomer concentration in polymerisation at -78 °C and for a dose of 10 kGy. Methods have been developed for the preparation of tubes and filaments containing immobilised BAS. The immobilisation of α-amylase in poly(2-hydroxyethyl methacrylate) matrices has been investigated [296] with the aid of radiation-induced polymerisation (dose 5 kGy). The immobilisation of trypsin using low-temperature radiation-induced polymerisation has been investigated in detail.[216] The enzyme activity was studied in the hydrolysis of casein (substrate). 2-Hydroxyethyl methacrylate, poly(ethylene glycol diacrylate), and methoxypoly(ethylene glycol methacrylate) were used as the components for the immobilisation of trypsin.

The irradiation of the monomers mixed with an aqueous enzyme solution was carried out at -78 °C with a dose of 10 kGy. If the monomers are hydrophilic, the enzyme activity falls with increase in their concentration, whereas in the case where they are hydrophobic the activity passes through a maximum. When 2-hydroxyethyl methacrylate is used, a porous polymer matrix with a pore size of 1 μm at a monomer concentration of 50% – 70% is formed. With increase in this concentration, the pore size diminishes. When tris(hydroxymethyl)propane triacrylate (a hydrophobic monomer) is used for immobilisation, a polymer is formed in the form of a suspension with a particle size of 50 – 200 μm and the enzyme is immobilised on the polymer surface. In the case of poly(ethylene glycol diacrylate), the degree of hydration and the enzyme activity increase with increase in the number of oxyethylene units $-CH_2CH_2O-$ (n). For $n \leqslant 4$, large formations 100 – 200 μm in diameter are produced, whereas for $n \geqslant 9$ a continuous porous structure is formed. If methoxypoly(ethylene glycol methacrylate) is used, a cross-linked structure appears. Such a matrix is soft and hydrophilic and the enzyme is readily trapped in it. The study of the influence of the nature of the polymer matrix on the thermal stability of the immobilised enzyme showed that the highest thermal stability occurs when 2-hydroxyethyl acrylate and 2-hydroxyethyl methacrylate are used. The thermal stability of the enzyme depends on the hydrophilicity of the polymer matrix; the maximum stability is attained on increase in the degree of hydration, which is associated with the influence of the latter on the rigidity of the matrix.

The immobilisation of trypsin in the radiation-induced polymerisation of crystalline monomers (acrylamide, methylenebisacrylamide, and acrylic acid salts) has been investigated.[212, 229] A deficiency of the polymer matrix was discovered — an unduly high hydrophilicity.

The communication of Carenza *et al.*[230] was devoted to the study of the influence of the molecular mass of proteins and peptides on the rate of liberation of these compounds from hydrogels obtained by the radiation-induced polymerisation of 2-hydroxyethyl methacrylate. It was established that the rate of liberation diminishes linearly with increase in $\log M_w$. The rate of decrease may be regulated by adding poly(ethylene glycol) with different M_w to 2-hydroxyethyl methacrylate. The immobilisation of glucose oxidase, glucose peroxidase, and urokinase on the inner surfaces of poly(vinyl chloride) tubes and on LDPE films has been described.[249] The immobilisation method consists in the preliminary radiation-induced polymerisation of 2-hydroxyethyl methacrylate and the subsequent decomposition on the grafted surface of a mixture of the monomer with an aqueous solution of the enzyme. The tube is frozen and irradiated at -78 °C (dose 5 kGy).

The structure of the surface depends on the polymerisation conditions and the nature of the monomer. These factors influence the uniformity of the coating. The thinnest and most uniform coatings are obtained when a 1 : 1 mixture of 2-hydroxyethyl methacrylate and tetraethylene glycol diacrylate is used. A high

stability of the immobilised enzymes was established, which can be partly accounted for by the employment of cross-linked systems. Glucose oxidase and glucose peroxidase have been used to assay glucose in blood.[234,248] The immobilisation was carried out in such investigations by irradiating the monomers mixed with an aqueous enzyme solution. The mixture was deposited on a nylon net or filter paper in a thin layer and was irradiated in an accelerator (dose 10 kGy). Poly(ethylene glycol diacrylate) and tris(hydroxymethyl)propane triacrylate were used as the components for the immobilisation. The maximum activity of the enzymes was attained at a concentration of the components of 20% – 30% and the highest enzyme activity was observed when poly(ethylene glycol diacrylate), deposited on a nylon net, was employed. Polymer sheets with immobilised enzymes were obtained as a result.

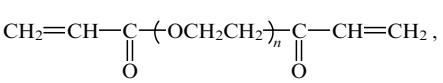
The immobilisation of fumarase in a polyacrylamide gel has been described (dose 5 – 10 kGy).[289] A high activity of fumarase was achieved under the conditions of the enzymic synthesis of malic acid from fumaric acid.

The results of the study of the immobilisation of penicillin acylase in polymer matrices of different hydrophilicity (2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, *N*-vinylpyrrolidone, *etc*.) by means of low-temperature radiation-induced polymerisation have been described.[250] The influence of the monomer : enzyme ratio on the immobilisation was investigated. It was established that the rate of liberation of the enzyme is independent of the nature of the monomer, the degree of polymerisation, and the porosity, but does depend strongly on the presence in the system of the cross-linking agent tris(hydroxymethyl)propane trimethacrylate even in small amounts ($\sim$0.03% – 0.04%). The enzyme is retained in the polymer matrix as a result of hydrophobic interactions. The activity of penicillin acylase is preserved for a long time in the presence of the cross-linking agent.

A series of publications [239 – 244, 251, 270] have been devoted to questions concerning the immobilisation of cellulase. The immobilisation of cellulase and cellobiase in polymer matrices obtained by the low-temperature polymerisation of 2-hydroxyethyl methacrylate in the presence of an aqueous enzyme solution has been studied in detail.[239] The enzyme activity was determined from the yield of glucose in the decomposition of cellulose. It was noted that in the presence of additives in the monomer [silica gel and poly(ethylene glycol)] the enzyme activity is retained for a longer time. The effectiveness of the additive depends on the monomer concentration. The maximum activity is attained at a monomer concentration of 60%. Discs 12 mm thick containing the immobilised enzyme were obtained.

Kumakura and Kaetsu [240] studied the immobilisation of cellulase in polymer membranes prepared from hydroxylated acrylates. The maximum activity of cellulase was attained at a monomer concentration of 20% and for a membrane thickness of 1 mm, which is associated with the formation of the most porous structure of the polymer under these conditions. The dependence of the enzyme activity on the water content in the polymer has a maximum. In the immobilisation of cellulase in the porous polymer matrix formed by the radiation-induced polymerisation of poly(ethylene glycol diacrylate), the pore structure is determined to a large extent by the polymer concentration and temperature.[241]

The enzyme activity depends on the pore size, the degree of hydration, and the particle size of the composite. The degree of hydration of the polymer increases with increase in the number of oxyethylene groups in the monomer.



n = 2, 3, 4, 9, 14.

Continuous changes in the porous structure associated with the change of the polymerisation phase have been noted in the temperature range from -10 to -40 °C. With increase in pore size, the enzyme activity falls.

Yoshida *et al*.[242] achieved the immobilisation of cellulase in polymer microspheres. The latter were formed as a result of the radiation-induced polymerisation of glycidyl methacrylate in the presence of polystyrene and the enzyme with subsequent immersion of the mixture in cooled methanol. The influence of various conditions on the number and diameter of the microspheres was investigated. Soft and hard microspheres with different diameters were obtained. The enzyme activity of cellulase in the soft microspheres was 4.6 times higher than in the hard ones.

The communication of Kumakura and Kaetsu [243] was devoted to the study of the immobilisation of *Streptomyces phalochromogenes* cells (which produce cellulase) using the 2-hydroxyethyl methacrylate + methoxytetraethylene glycol methacrylate mixture. The mixture together with the cells was deposited on paper and irradiated. Paper sheets with immobilised cells were obtained.

The immobilisation of cellulase in poly(2-hydroxyethyl methacrylate) polymer matrices has been described.[244] The immobilisation was carried out by the low-temperature polymerisation of 2-hydroxyethyl methacrylate in the presence of an aqueous enzyme solution. The specimens were prepared in the form of discs. The enzyme activity is a maximum at a monomer concentration of 50% and the optimum thickness of the disc is 1 mm. With increase in cellulase concentration, the specific enzyme activity diminishes. Photomicrographs of the specimens with the immobilised cellulase were published. The immobilised cellulase preparation may be used repeatedly. In another study, Kumakura and Kaetsu [251] immobilised cellulase on the inner surfaces of polyethylene tubes by the low-temperature radiation-induced polymerisation of a mixture of 2-hydroxyethyl methacrylate and tetraethylene glycols diacrylate. The mixture of the monomers with the enzyme was deposited on the inner surfaces of the tubes, frozen, and irradiated (dose 10 kGy). The thickness of the layer of coating was 300 μm, the optimum monomer concentration was 60% – 70%, and the enzyme concentration was 0.5%. This immobilisation method can be used to create enzyme reactors. The immobilisation of yeast cells in various hydrogels has been studied and the conditions for the maximum yield of ethanol in the enzyme hydrolysis of a cellulose-containing raw material were discovered.[270] Immobilised cellulase has been used for the enzymic hydrolysis of a cellulose-containing raw material: paper waste,[270,297,298] starch,[299,300] biomass (wood chips, sugar beet waste, rice straw),[299,300] and lignin-containing waste.[245] After the preliminary irradiation of the cellulose-containing waste (paper, sawdust, *etc*.) with a dose up to 1 MGy, the yield of glucose in the hydrolysis of the raw material increases appreciably (by a factor of $\sim$3),[297 – 301] which is associated with the appreciable decrease in the degree of polymerisation of cellulose and the partial breakdown of its structure. The yield of ethanol in the hydrolysis of plant waste after preliminary irradiation has been studied in detail.[270] For the successful enzyme hydrolysis of lignin-containing waste, it is desirable to subject it to preliminary irradiation (dose 1 MGy) and grinding. The influence of preliminary irradiation up to different doses on the subsequent hydrolysis of cellulose (from rice, straw, *etc*.) has been described.[301] The results of the employment of the radiation technique for the conversion of biomass into sugar and its fermentation in order to obtain ethanol have been surveyed in a review.[300] The possibility of the reuse of the immobilised enzymes has been studied.

Functional polymers, obtained by radiation-induced graft polymerisation, have been used in a series of studies for the immobilisation of enzymes. A method for the covalent binding of enzymes, based on the grafting of *p*-nitrostyrene to polymers (mainly polyolefins), the reduction of the nitro groups to amino groups, and the conversion of the latter into isocyanate groups, which readily react with enzymes, has been devised.[210,219,220] In

the case of amino groups, glutaric dialdehyde was used for the covalent binding of enzymes. Another procedure consists in the radiation-induced grafting of styrene with subsequent nitration of the graft copolymer. Trypsin was used as the enzyme.

A method for the immobilisation of asparaginase on porous polypropylene fibres, an ethene – propene copolymer, and a polypropylene film has been created.[257, 258] The first stage is the radiation-induced grafting of acrylic acid, after which asparaginase is attached covalently to the carboxy groups by the carbodiimide method. An enzyme reactor was developed and was tested *in vitro* and *in vivo*. The immobilisation of enzymes and subcellular organisms in polyethylene has also been described.[290] The activity and stability of the enzymes were investigated.

The immobilisation of papain, trypsin, glucose oxidase, and α-chymotrypsin on powdered polyethylene with grafted poly(methacrylic acid) and poly(2-hydroxyethyl methacrylate) has been studied.[259] The covalent binding of the enzyme was achieved with the aid of the carbodiimide method. It was established that each enzyme requires its own microenvironment. α-Chymotrypsin proved to be the most active. The best results were obtained in the grafting of poly(2-hydroxyethyl methacrylate) with subsequent partial hydrolysis. The covalent immobilisation of invertase, phosphatase, albumin, trypsin, and galactosidase on polyethylene modified by the grafting of poly(acrylic acid) has been described.[262] The enzyme was attached by means of the carbodiimide method. The influence of the methods used for grafting and activation of poly(acrylic acid) on the activity of the enzymes was examined.

The immobilisation of horseradish peroxidase on segmented polyesterurethane films has been described.[261] The immobilisation of glucose oxidase on polyethylene films has been investigated.[242] A study has been made of the influence of the degree of grafting, the hydrophilicity, and the electrical properties on the enzyme activity.

The radiation-induced grafting of 2-hydroxymethyl methacrylate has been used to bind trypsin and glucose oxidase to natural rubber.[221, 222]

Cyanuric chloride and toluene-*p*-sulfonyl chloride were used for the covalent binding. The immobilisation conditions and the activity of trypsin have been examined in detail. The immobilisation of enzymes on polyamide materials (with the aid of radiation-induced graft polymerisation of acrylic acid or acrylonitrile) has been described.[260, 264, 265] The immobilisation of protease with the aid of radiation-induced grafting of acrylic acid has been investigated.[214]

The reactivity of α-chymotrypsin immobilised on radiation-grafted hydrogels obtained by the grafting of 2-hydroxyethyl methacrylate and methacrylic acid on silicone rubber has been studied.[302, 303] α-Chymotrypsin was bound covalently using *N*-hydroxysuccinimide. The influence of pH and the content of acrylic acid on the enzyme activity was investigated (hydrolysis of *N*-acetyl-L-tyrosine). The rate of hydrolysis is greatly influenced by the negative charge of the hydrogel. The immobilisation of trypsin on a wide range of polymers modified by the radiation-induced grafting of poly(acrylic acid), polyacrylonitrile, poly(2-hydroxyethyl methacrylate), poly(*N*-vinylpyrrolidone), polyacrylamide, *etc*. has been studied in detail.[213, 214] The covalent binding of trypsin was achieved by means of the carbodiimide method or glutaric dialdehyde. The polymer membranes obtained were designed for use in the milk industry.

Methods for the covalent immobilisation of enzymes with the aid of aldehyde groups, which readily react with amines, have been devised.[198, 199, 304, 305] The methods involve the radiation-induced graft polymerisation of acrolein. The reactivity of the aldehyde groups was studied.

Radiation-induced graft polymerisation is used for the modification of agarose (by grafting a complex of *N*-acryloylsuccinimide and BSA) in order to obtain a material for the chromatographic separation of biomacromolecules.[306]

Novel methods for the immobilisation of enzymes on polymeric materials have been developed by Platé and Valuev.[215] This is a new aspect of the use of radiation-chemical methods for the immobilisation of BAS, because it concerns the radiation-induced graft polymerisation of macromonomers formed by the introduction of a reactive double bond into BAS macromolecules.

Thus the nature of the monomer and in the first place its hydrophilic and hydrophobic properties as well as the monomer concentration are important in the immobilisation of BAS with the aid of radiation-induced polymerisation. These factors influence most significantly the activity of the enzyme, the duration of its use, and its thermal stability. Cross-linking agents and BAS adsorbents can be usefully added at a low concentration in a number of instances in order to regulate the rate of liberation of the enzyme. The radiation dose should not exceed 10 kGy in most cases.

The modification of various polymers by the radiation-induced grafting of acrylic acids or 2-hydroxyethyl methacrylate with subsequent binding of the enzymes by the carbodiimide method is employed most frequently for the covalent binding of enzymes. The specific activities of the enzymes fall with increase in their content in the modified layer (a 5% – 10% graft is optimal). The method for the covalent binding of the enzyme is very important. Radiation-induced graft polymerisation makes it possible to employ polymers of virtually any nature and form (powders, fibres, films, *etc*.) for the binding of enzymes. The possibility of creating enzyme reactors has been demonstrated.

2. Immobilisation of medicinal preparations

In the employment of radiation-induced polymerisation for the immobilisation of medicinal substances, the greatest advances have been achieved in the immobilisation of antitumour compositions in polymer matrices. The antitumour substances employed have been adriamycin, mitomycin C, and 5-fluorouracil. In many cases, treatment with immobilised antitumour preparations is combined with hormone therapy. The immobilised antitumour substances are used as a rule in the form of polymer tablets or needles which are inserted in the tumour. The application of immobilised antitumour preparations has the following advantages compared with their introduction in the form of injections or orally: a low concentration of medicinal preparations in the blood, the medicine spreads from the administered preparation into a small region. This reduces to a minimum the side effects of the medicines. The duration of the use of the immobilised antitumour preparations is several months. These preparations have undergone extensive tests in many Japanese clinics.[204] In the vicinity of the preparation introduced into the tumour, the cancer cells undergo necrosis and the diffusion of the antitumour preparations terminates in the necrosed layer. The rate of liberation of medicinal substances does not change in the course of 40 days. The number of specimens introduced into the tumour, their density, and form (needles, tablets) are very important.

The concentration of antitumour substances in the blood is insignificant. A mixture of poly(ethylene glycol dimethacrylate) (20%) and diethylene glycol dimethacrylate (80%) is usually employed for the immobilisation of the antitumour preparation mitomycin C.[204] The behaviour of the immobilised antitumour preparations in the organism and the methods for the treatment of cancer have been examined in a number of studies.[307 – 312] Methods whereby immobilised antitumour preparations can be produced have been described in detail in a series of studies.[204, 205, 249, 276, 278, 313, 314] The low-temperature polymerisation of diethylene glycol dimethacrylate mixed with various polymers [polystyrene, polyvinylformal, poly(ethylene glycol), poly(methyl methacrylate)] is used for the immobilisation of mitomycin, 5-fluorouracil, and bleomycin. It is emphasised that irradiation must be carried out in an oxygen-free medium and the dose must not exceed 10 kGy. Otherwise the activity of the antitumour preparations is significantly reduced.[277] Specimens

with the immobilised antitumour preparations are made in the form of a powder, tablets, cylinders, membranes, *etc*.[277]

The immobilisation of multicomponent cytotoxic (antitumour) agents in polymer matrices based on poly(diethylene glycol dimethacrylate) and poly[tris(hydroxymethyl)propane trimethacrylate] has been studied. The cytotoxic agents employed are mitomycin C, adriamycin, and 1-(2-tetrahydrofuryl)-5-fluorouracil. The rate of liberation of the medicinal preparations is regulated by introducing a pore-forming agent or adsorbent (for example, activated charcoal) into the polymer matrix. The surfaces of the polymers obtained with the immobilised cytotoxic agents have been studied by electron microscopy.[276]

The immobilisation of the antitumour preparations 5-fluorouracil and mitomycin C by dispersing the preparations in polymer matrices obtained by the radiation-induced polymerisation of 2-hydroxyethyl methacrylate, 2-hydroxyethyl acrylate, and methyl methacrylate has been examined.[313] A cross-linking agent — ethylene glycol dimethacrylate — is added for the effective control of the rate of liberation of the medicinal preparations. The rate of liberation of medicines from polymer matrices obtained under different conditions has been studied in detail. The rate of liberation increases with increase in the hydrophilicity of the matrix and diminishes significantly with increase in the content of the cross-linking agent. The influence of the porosity of the matrix on the liberation of medicinal substances has been studied and electron micrographs of the porous structure have been published. A study has been made of the therapeutic effect of immobilised preparations placed in the form of tablets in the vicinity of a tumour (sarcoma) in mice. The slow liberation of the medicinal drugs led to a greater therapeutic effect compared with direct injection.

The methods and results of clinical tests of the local chemotherapy of malignant glyoma have been examined. The following immobilised antitumour preparations have been used: adriamycin, 5-fluorouracil, and nimustine hydrochloride.[314]

The preparation of poly(ethylene oxide) gels with immobilised hydroxyprogesterone acetate for the treatment of carcinoma has been described.[278] The controlled liberation of adriamycin from polymer needles has been investigated.[315]

Summarising the foregoing, one may conclude that the application of antitumour preparations immobilised in polymeric materials is promising. When they are used, the cancer cells undergo necrosis within the limits of 0.5–1 cm^2 around the specimen and the diffusion of the antitumour preparations ceases in the necrosed layer. The number of specimens in the tumour and the rate of liberation of the preparation, which may be regulated within wide limits are very important. Side effects are not observed when immobilised antitumour preparations are employed. The technology of the use of immobilised antitumour preparations may be improved by varying the hydrophilic-hydrophobic properties of the polymer matrix and also by using biodegradable polymers (polypeptides or polylactides).

Methods have been developed for the immobilisation of the antitumour preparation narciclasine.[279,316] Chemical and radiation methods for the initiation of polymerisation with the aim of its immobilisation have been compared. A study has been made [231] of the immobilisation of the antitumour preparation Ara-C in hydrophobic matrices obtained by the radiation-induced polymerisation of alkyl acrylates and methacrylates. It was shown that the rate of liberation of Ara-C may be varied widely by altering the composition of the matrices. The prospects for the employment of thin polymer particles, obtained by emulsion polymerisation (0.1–3 μm particles) or suspension polymerisation (10–100 μm particles), for immobilisation have been noted.[205] Significant results in therapy have been achieved in the joint study of immobilised antitumour preparations and hormones. The immobilisation and use of the immobilised hormones (testosterone) have been described.[317–320] The hormones were immobilised in polymer needles. An important feature is that the hormones enter the organism for a long time in small amounts. Definite successes have been achieved in the treatment of the cancer of digestive organs, the bladder, pancreas, the brain, *etc*.

Radiation-induced polymerisation has been used in a series of studies [159,202,205,321–325] for the immobilisation of antibodies in order to investigate the antibody–antigen reactions. The sensitivity of the reactions of the immobilised antibody with the antigen depends on the choice of monomer and its concentration needed to create a porous medium. An important problem is the minimisation of nonspecific reactions of the polymeric carrier with the antigen. For this purpose, it is necessary to make the polymer matrix more hydrophobic. The immobilised preparations are usually made in the form of microspheres or microcapsules. Microspheres obtained by the polymerisation of acrolein or its copolymers with 2-hydroxyethyl methacrylate or methacrylic acid are also used for the immobilisation of antibodies.

Within the framework of the program of the International Atomic Energy Agency, studies with immobilised monoclonal antibodies have been carried out at the Pasteur Institute (Paris).[205,292] The immobilisation of the latter is achieved by the low-temperature polymerisation of 2-hydroxyethyl methacrylate.

An advantage of radiation-induced polymerisation for the immobilisation of antibodies is the fairly high purity of the product obtained.[326,327] These preparations may be used for immunological assay.

The immobilisation of a calcium antagonist in a prepolymerised poly(2-hydroxyethyl methacrylate) gel has been described.[285] The rate of liberation of the medicinal preparation can be varied widely by means of the radiation-induced cross-linking of the gel and the added methyl methacrylate and *N*–vinylpyrrolidone.

The immobilisation of hydrocortisone in gels obtained by the radiation-induced polymerisation of acrylic acid has been investigated. The rate of liberation is regulated by the irradiation dose and by treating the gels with zinc acetate.[317]

3. Immobilisation of blood components

Haemoglobin has been immobilised in a poly(2-hydroxyethyl methacrylate) polymer matrix using radiation-induced low-temperature polymerisation.[271–273] Special attention was devoted to the selection of the optimum immobilisation conditions in order to protect the haemoglobin. Haemoglobin is convenient for the study of the state of the immobilised molecule in a polymer matrix, since it has a characteristic optical absorption. The haeomoglobin in the membrane was subjected to reversible oxygenation, which may take place to almost the same extent as in native haemoglobin. A method for the preparation of semisynthetic blood based on immobilised carboxyhaemoglobin has been described.[272] Radiation-induced polymerisation has been used for the immobilisation of erythrocytes in the form of cells without haemolysis.

The radiation-induced polymerisation of phospholipids has been used for the immobilisation of haemoglobin.[274,275] The phospholipids contained two long polymerisable octadecadienyl groups. Artificial red blood cells were obtained by encapsulating haemoglobin with the aid of the radiation-induced polymerisation of bilayer phospholipids — liposomes. The artificial blood cells proved to be mechanically stable and readily withstood freezing. The oxygen transport is similar to the transport by native haemoglobin. Tests *in vivo* (on mice) were carried out and indicated the biocompatibility of such cells.

Methods have been developed for the preparation of polycationic carriers for red blood cells.[85] The carriers were formed by the polymerisation and grafting of 2-(*N*,*N*-dimethylamino)ethyl methacrylate. The grafting was carried out on poly(vinyl chloride) beads by a method involving preliminary irradiation. 2-(*N*,*N*-Dimethylamino)ethyl methacrylate was polymerised in bulk in the presence of tris(hydroxymethyl)propane trimethacrylate and also in suspension and in emulsion. Cationic immunoadsorbents were obtained. Their adsorption capacity was determined. The density of the positive charges on the adsorbent is important.

4. Immobilisation of yeast cells and microorganisms

In a series of studies,[202, 266, 269, 328, 329] radiation-induced polymerisation has been used for the immobilisation of yeast cells in order to employ the resulting preparations for the synthesis of ethanol from plant waste.

The nature of the carrier, especially its porosity, plays an important role. The porous matrix is formed as a result of the copolymerisation of methoxypoly(ethylene glycol methacrylate) and 2-hydroxyethyl acrylate. The yeast cells are adsorbed on this matrix, are coated by methoxypoly(ethylene glycol methacrylate), and are polymerised at -78 °C (dose 10 kGy).[268] The activity of *Saccharomyces formosensis* cells (yeast cells) on polymeric carriers obtained by the radiation-induced polymerisation at -78 °C of mixtures of 45% of methoxypoly(ethylene glycol methacrylate) containing 23 ethylene glycol units, 45% of hexane diol methacrylate, and 10% of water (fine pores and a low water content) or 15% of methoxypoly(ethylene glycol methacrylate), 15% of 2-hydroxyethyl methacrylate, and 70% of water (structure with wide pores). In the first case, the immobilised cells had an activity greater by a factor of 6 than in the second case. As a rule, the activity of the immobilised cells increases with increase in the water content.[266] The influence of the composition of the monomer mixture and the conditions in the immobilisation of yeast cells on the yield of ethanol has been studied in detail.[267] Conditions have been found for the multiplication of the yeast cells and for the manifestation of their high activity. A significant role of water in the activity of the cells was observed. A study has been made [269] of the immobilisation of *Trichoderma reesei* (QM 9414) cells. Muslin was used as the carrier, which was coated with a solution of the monomer mixed with the cells and irradiated. It was shown that the concentration of the monomer used for immobilisation exerts a significant influence on the activity of the cells.

The capture of the microorganism producing fumarase in a cross-linked polyacrylamide gel has been investigated. A preparation with a high enzyme activity and an increased thermal stability was obtained.[330] The immobilisation of bacteria in hydrophilic gels based on poly(ethylene glycol) and poly(propylene glycol) led to the creation of a bioreactor.[331] The rate of liberation of testosterone was regulated by immobilising it in a thermosensitive gel obtained by the radiation-induced polymerisation of the methyl ester of acryloyl-L-proline.[332]

A method for the covalent immobilisation of luminescent bacteria on the surface of a polyethylene film has been developed with the aid of the radiation-induced graft polymerisation of methacryloyl chloride on the film.[288, 333]

5. Immobilisation of photosynthetic substances and organelles

Chloroplasts and chlorophyll may be immobilised with the aid of low-temperature radiation-induced polymerisation.[202, 280, 281] The immobilisation of chloroplasts extracted from spinach was achieved by the radiation-induced polymerisation of 2-hydroxyethyl methacrylate in the presence of special additives which prevent the deactivation of the chloroplasts. The liberation of O_2 and the influence of γ-radiation on this process were investigated. The influence diminishes appreciably on irradiation at reduced temperatures (-24 and -78 °C). The chloroplasts immobilised at reduced temperatures in a hydrophilic polymer matrix exhibited a stable long-term liberation of O_2: more than 700 h at 4 °C. The thermal stability of chloroplasts increases appreciably on immobilisation.

The photoreductive activity of chloroplasts falls to zero after 5 min at 50 °C, whilst immobilised chloroplasts retain their activity for more than 60 min.[281] The influence of the nature of the monomer and its concentration on the activity of immobilised chloroplasts was investigated.[280] 2-Hydroxyethyl acrylate, poly(ethylene glycol diacrylate), poly(ethylene glycol dimethacrylate), methoxypoly(ethylene glycol methacrylate), glycidyl methacrylate, glycidyl diacrylate, tetraethylene glycol diacrylate, and tetraethylene glycol dimethacrylate were used as the monomers. The optimum monomer concentration was 10%. The best monomer for immobilisation proved to be a mixture of methoxypoly(ethylene glycol methacrylate) and 2-hydroxyethyl acrylate. The activity of the immobilised chloroplasts (liberation of O_2) was high and was retained for 30 days. When hydrophobic monomers were used, the activity of the chloroplasts decreased rapidly as a function of time.

6. Preparation of polymer implants

Technical procedures and methods used for the immobilisation of BAS (radiation-induced polymerisation) may be employed for the preparation of implants of various kinds, mainly for the therapy of damaged sections of the skin and also for the creation of prostheses. Methods have been developed for the preparation of collagen implants by irradiating mixtures of monomers or polymers with collagen.[334–336] The implants are satisfactorily compatible with blood and do not give rise to inflammation. The implants are used in surgery and can be employed as substrates in biotechnology.[334] Prostheses based on polyesterurethane with a radiation-modified inner surface have been investigated. The modification was achieved by the radiation-induced grafting of 2-hydroxymethyl acrylate or acrylamide on the inner surfaces of the tubes. The prostheses were studied *in vivo*. The histological and mechanical properties were investigated. Their improved thromboresistance was established.[337] A method has been developed for the modification of polymer fillers used in dental technology. The fillers based on glass or quartz fibres were modified by the radiation-induced grafting of acrylic acid from the vapour phase. The physicomechanical properties of resins containing different amounts of the modified filler were studied in detail. The advantages of the modified filler employed compared with the filler modified by silanes were noted.[338] Polymeric-ceramic materials for dentistry have been created by irradiating mixtures of alumina and acrylic acid.[339] Implants for the therapy of the skin on sections of the human body damaged by burns have been created with the aid of radiation-induced graft polymerisation.[340, 341] Silicone rubber modified by the grafting of hydrophilic monomers or natural rubber modified by vulcanisation are normally employed for this purpose.[341] A method for the hydrophilisation of silicone contact lenses has been created with the aid of radiation technology. As a result of hydrophilisation, the wetting angle decreases from 150 ° to 20 ° and the hydrophilic effect persists for a long time.[342]

Radiation-modified polymers have been used for the initiation of the growth of various cells.[147, 343, 344]

7. Preparation of 'smart' polymers and their use for the immobilisation of biologically active substances

'Smart' polymers have acquired in recent years an increasing importance for medicine and biotechnology. This is the term given to polymers capable of responding to small changes in the environment (temperature, pH, electric field, *etc.*).[345] 'Smart' polymers with immobilised BAS are used for the liberation of medicinal substances under certain conditions, usually at a specified temperature or pH. 'Smart' polymers are normally obtained by traditional methods, but radiation-induced polymerisation has also come to be employed recently for this purpose.[165, 247, 332, 346] Among the 'smart' polymers, the greatest number of publications have been devoted to poly(*N*-isopropylacrylamide) (poly-*N*-IPAA).[345, 347] This polymer has a lower consolute temperature (LCT) of $\sim$32 °C in water, *i.e.* close to the temperature of the human body. Phase separation, caused by the conformational transition of the poly-*N*-IPAA macromolecule from a loose globule to a compact coil,[345, 348, 349] which is accompanied by a sharp decrease in the size of the macromolecule, takes place above 32 °C.[350]

The radiation-induced polymerisation of *N*-isopropylacrylamide has been investigated.[351–353] Poly-*N*-IPAA gels have been obtained by irradiating aqueous solutions of the monomer. The gel formation dose is 71 Gy (dose rate 1 kGy h^{-1}). The temper-

ature dependence of the swelling in water of these gels, obtained for different doses, has been studied. It was established that the degree of collapse of the gels beyond the phase transition point depends significantly on the dose, which was explained by the structure of the polymer network. An important factor is that by selecting the dose it is possible to achieve a fairly fine regulation of the degree of collapse of the gels.

The radiation-induced polymerisation of *N*-isopropylacrylamide in water and the cross-linking of the resulting gels have been investigated [352] by nuclear magnetic resonance. The influence of solvents on the radiation-induced polymerisation of *N*-isopropylacrylamide and the molecular mass of the resulting polymers have been studied.[353] The lower consolute temperature of the resulting polymers is in the range 30.5 – 31.50 °C and depends little on the polymerisation conditions.[353]

The radiation-induced copolymerisation of *N*-isopropylacrylamide with *N*-acryloyloxysuccinimide has been investigated.[354] The resulting copolymer was used for the immobilisation of bovine serum albumin, horseradish peroxidase, and monoclonal antibodies. It was shown that the dose at which the copolymer was obtained influences significantly the immobilisation process. The lower consolute temperature of the copolymers is in the range 30 – 35 °C and depends little on the concentration of the comonomers and the chain length. Asparaginase was immobilised in the gel obtained. The influence of temperature and the pH on the activity of the immobilised BAS was studied.

Radiation-induced copolymerisation led to the formation of copolymers of *N*-isopropylacrylamide and methacrylic acid.[355] pH-Sensitive hydrogels were obtained by the radiation-induced copolymerisation of polydimethylsiloxane, containing vinyl groups, with *N*-isopropylacrylamide and acrylic acid. The lower consolute temperatures of the copolymers depend on the pH. The immobilisation of indomethacin [356] and amylase [357] in gels has been investigated and it has been established that indomethacin and amylase are slowly liberated from the hydrogels at 37 °C and pH 1.4 (the conditions in the stomach), but at pH 7.4 (conditions in the intestine) the liberation of the medicinal substances is appreciably accelerated. The copolymers of *N*-isopropylacrylamide with polydimethylsiloxane containing vinyl groups have been used for the immobilisation of progesterone. These copolymers were obtained for a dose of 10 kGy (dose rate 5 kGy h^{-1}). They have the same LCT as pure poly-*N*-IPAA. The gels contract rapidly on passing through the LCT. The microdomain structure of the gels was established.[358] Thermosensitive gels based on alanine derivatives have been obtained.[359] Radiation-induced graft polymerisation of *N*-isopropylacrylamide on silicone rubber has been studied.[360] The hydration of the resulting graft copolymers has been investigated as a function of temperature and the copolymer composition. The unusual character of the hydration, influenced by the phase transitions in the grafted chains, was established.[79]

The preparation of another 'smart' polymer — the methyl ester of poly(acryloyl-L-proline), which is synthesised by the radiation-induced polymerisation of the methyl ester of acryloyl-L-proline — has been described.[352, 361] This polymer has a LCT of 14 °C.[361] The LCT of the polymer may be regulated either by the radiation-induced copolymerisation with 2-hydroxypropyl methacrylate [361] or by adding sodium dodecyl sulfate.[362] The coil – globule transitions and the cross-linking of the methyl ester of poly(acryloyl-L-proline), obtained by radiation-induced polymerisation, have been investigated.[363]

Testosterone was introduced into the gel of the methyl ester of poly(acryloyl-L-proline) by means of radiation-induced polymerisation. It was established that testosterone is uniformly liberated from the gel (30 mg per day) in the course of 54 weeks (tests on rats). The gel shrinks on the surface during dehydration, forming a rigid membrane barrier lacking micropores. Compact clusters are formed above the LCT.

A gel of the methyl ester of poly(methacryloyl-D,L-alanine) has been obtained by the radiation-induced polymerisation of the methyl ester of methacryloyl-D,L-alanine.[364, 365] The kinetics of the swelling and dehydration of the gel were investigated. It was established that, on dehydration at 40 °C, a bark (skin) is formed on the surface of the gel, closing the pores. The gel was studied by scanning electron microscopy. The gel contracts rapidly on heating.[364] The radiation-induced grafting of the methyl ester of acryloyl-L-proline on polymeric materials irradiated by heavy ions has been studied.[365, 366] The influence of surfactants on the phase transitions in polymers with amino acid side groups has been investigated.[367]

The antitumour preparation 9-β-D-arabinofuranosyladenine (Ara-A) was immobilised in a thermosensitive gel based on the copolymer of 2-hydroxyethyl methacrylate, styrene, and the methyl ester of acryloyl-L-proline cross-linked by nonaethylene glycol dimethacrylate. The gel was obtained by radiation-induced copolymerisation. The phase transition occurs at 14 °C. The gel shrinks rapidly on passing through the phase transition point. The liberation of Ara-A was investigated at 10 – 37 °C. The gel operates *via* a pulsating mechanism resembling a pump. Rapid shrinkage and liberation of Ara-A take place at 37 °C.[368] Thermosensitive gels, obtained by the radiation-induced cross-linking of poly(methyl vinyl ether) (PMVE) dissolved in water, have been described.[369 – 372] The phase transition is at 38 °C. Porous and fibrous gels were obtained and their swelling was studied under various conditions. Artificial muscles and fingers have been created on the basis on the PMVE gels.[369] According to the data of Kobra *et al.*,[370] the LCT for aqueous PMVE solutions is in the range 34 – 38 °C. By selecting the irradiation conditions, it is possible to obtain PMVE gels with high rates of swelling and dehydration.[370 – 371] Aqueous 50% solutions of PMVE and doses of 60 – 110 kGy are used. A characteristic feature of the PMVE gels is larger volume changes compared with other thermosensitive gels. On heating, the gels contract rapidly and a microporous structure develops.[372, 373] The transitions in the PMVE gels have been investigated.[374] The immobilisation of exo-1,4-α-D-glucosidase in the PMVE gel has been described.[375] The formation of glucose from maltose with the aid of this enzyme has been investigated and a marked influence of temperature on the activity of the enzyme has been established, this being associated with a phase transition in the gel.[374]

A series of data on the application of radiation-induced polymerisation and cross-linking for the creation of 'smart' polymers and their employment for the immobilisation of various medicinal preparations have been presented in reviews.[346, 376 – 378] The problems of the employment of radiation-induced polymerisation for the creation of signal-sensitive systems consisting of a biosensor, an activator, and a reservoir have been considered.[346, 378] Special systems with a biosensor for glucose are being developed. They are switched on in accordance with the on – off principle for the liberation of specific portions of insulin immobilised in gels.[377, 378] New thermosensitive hydrogels have been obtained by the radiation-induced copolymerisation of vinyl ethers of glycols with various alkyl vinyl ethers.[379] Certain theoretical problems associated with 'smart' polymers have been considered in a review.[380]

VI. The use of radiation-induced cross-linking for the preparation of polymeric biomaterials

The interest in the preparation of polymeric biomaterials by radiation-induced cross-linking has grown significantly at the present time. Such cross-linking is most frequently used to prepare hydrogels, mainly based on polyacrylamide poly(vinyl alcohol), poly(ethylene oxide), and poly(*N*-vinylpyrrolidone).[381 – 383] An advantage of the radiation-induced cross-linking is the comparative simplicity of its implementation, the possibility of the wide scale regulation of the network density by selecting irradiation conditions (dose rate, dose), the possibility of using reduced temperatures, the purity of the product obtained (the absence of initiators), and simultaneous sterilisation. The radiation-cross-

linked hydrogels are used as BAS (enzymes, medicinal substances, *etc.*) carriers, implants, prostheses, eye lenses, medical membranes, dressings, and biological media for the study and culturing of microorganisms.

The methods of preparation and properties of hydrogels based on radiation-cross-linked polyacrylamide have been studied in greatest detail.[384–401] The formation of gels of this compound on irradiation of aqueous acrylamide solutions over a wide range of conditions (monomer concentration, dose, and dose rate) has been investigated.[282, 384, 388, 398]

The dose for gel formation is in the range 0.1 – 2.5 kGy. It falls rapidly with increase in the monomer concentration and increases with increase in dose rate. On irradiation of aqueous acrylamide solutions up to high doses, decomposition with formation of aldehydes and carboxylic acids takes place.[388] The mechanism of the cross-linking of polyacrylamides is associated with the abstraction of a hydrogen atom from a tertiary carbon atom.[387] Various procedures for the preparation of gels based on polyacrylamide have been studied.[395] Using radiation-induced polymerisation, it is possible to obtain readily hydrogels of this polymer with a wide range of properties (hydrophilicity, modulus of elasticity, swellability, *etc.*). The hydrogels formed as a result of the radiation-induced copolymerisation of acrylamide and maleic acid exhibit a satisfactory biocompatibility with the serum prepared from human blood.[391]

Methods have been developed for the preparation of dressings based on radiation-cross-linked polyacrylamide gels [282, 385] as well as polymer eye lenses.[282] A three-stage radiation technology for the manufacture of dressing hydrogels to achieve the healing of extensive areas of burns and its advantages over other technologies have been described.[401] Polyacrylamide, obtained by radiation-induced polymerisation, has been used as the coating agent in X-ray films in order to economise on silver.[386]

A series of studies [397, 402–420] have been devoted to the preparation of hydrogels by the radiation-induced cross-linking of poly(vinyl alcohol). The mechanism of the formation of its gel on irradiation in water and the properties of the gels,[402, 403] in particular their swelling,[397] have been studied in detail. The hydration of poly(vinyl alcohol) gels leads to crystallisation. Biomembranes for the selective transport of macromolecules as well as materials used as cartilage for joints have been obtained from radiation-cross-linked poly(vinyl alcohol).[406] Radiation methods for the immobilisation of heparin,[407] cellulase, urease,[409] glucoamylase, and invertase [405] as well as other BAS in poly(vinyl alcohol) hydrogels have been developed. Data on the use of radiation-cross-linked poly(vinyl alcohol) hydrogels for the fixation and controlled liberation of BAS have been presented in a review.[411] A disadvantage of such gels is their low mechanical strength. The use of poly(vinyl alcohol) hydrogels as dressings has been described [418] and its advantage over muslin has been noted: homogeneous adhesion to the entire wound and easy removal without damaging the skin. Schemes for the preparation of heat-resistant hydrogels have been described [418, 419] and methods have been proposed for the improvement of their mechanical properties.[418]

Radiation-cross-linked poly(ethylene oxide) hydrogels have been investigated in fair detail.[397, 421–431] A characteristic feature of such gels is an anomalous decrease in swelling and an increase in the modulus of elasticity on drying, caused by the formation of additional units as a result of crystallisation. The possibility of obtaining porous gels in which the pore size can be varied widely as a function of the irradiation dose is very important. The structure of the ultrahigh-molecular poly(ethylene oxide) after γ-irradiation has been investigated.[430, 431] It has been suggested that radiation-cross-linked hydrogels of this polymer be used as the medium for the culturing of microorganisms.[429] The preparation of biocompatible materials based on radiation-cross-linked poly(ethylene oxide),[420] the hydrophobic properties of which may be enhanced by the radiation-induced grating of butadiene, styrene, or ethene,[420] has been described.[420]

Hydrogels based on poly(*N*-vinylpyrrolidone) are highly hydrophilic and are satisfactorily biocompatible.[432–442] The methods of preparation of such gels by the irradiation of aqueous *N*-vinylpyrrolidone solutions have been studied in detail.[438, 443] The radiation-induced cross-linking and degradation of poly(*N*-vinylpyrrolidone) have been studied.[435] The radiation technology for the preparation of gels of this polymer, used as a material for the treatment of burns and trophic ulcers, has been described in detail.[436, 440] These materials are sold in Poland under the commercial names HDR^R and AQUA-Gel^R. A therapeutic system based on the poly(*N*-vinylpyrrolidone) gel has been developed for use in obstetric practice to accelerate births and to induce abortions. In this case, the gel consists of a thin rod containing prostaglandin. The methods for the preparation of such gels have been described in detail.[432, 436] Data on the biological and physical properties of the hydrogels used as dressings have been described and compared with the usual muslin bandages.[441] The influence of the irradiation dose on the mechanical properties of poly(*N*-vinylpyrrolidone) gels filled with agar and poly(ethylene glycol) has been studied (Fig. 1).[442]

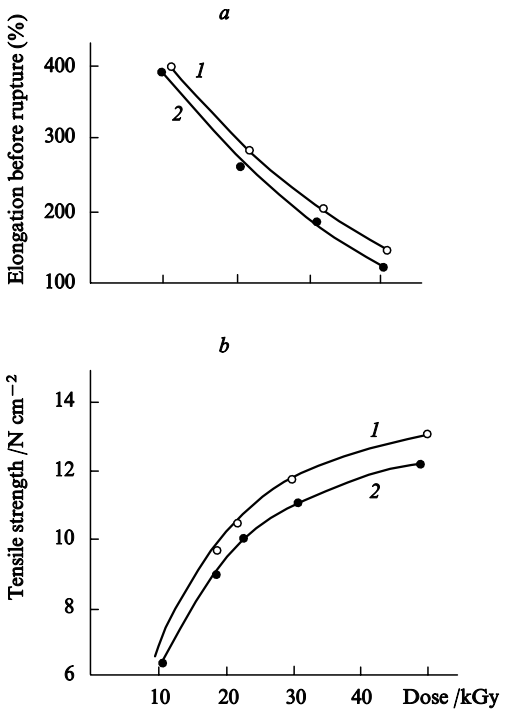


Figure 1. Dependence of the elongation before rupture (*a*) and of the tensile strength (*b*) on the irradiation dose for poly(*N*-vinylpyrrolidinone) gels 2.5±0.5 mm thick. (*1*) Gels filled with agar and poly(ethylene glycol); (*2*) gels filled with agar.

The technology for the preparation of hydrogels for dressings has now been developed in fair detail and they have undergone extensive clinical tests.[439] An important factor is the possibility of obtaining gels for dressings containing medicinal preparations (for example, chloramphenicol).[440] In the case of large wounds, such a hydrogel is significantly more effective than the usual dressings. Radiation-cross-linked hydrogels based on poly(*N*-vinylimidazole), the properties of which are close to poly(*N*-vinylpyrrolidone) gels,[444, 445] as well as radiation-cross-linked gels based on microbial poly-γ-glutamic acid with a high moisture-absorbing capacity [446] and hyaluronic acid gels with a high biocompatibility [447] have been obtained. Practical advice concerning the preparation of various hydrogels — optically homogeneous and with a minimal content of the residual monomer — has been given.[448]

Interesting studies have been carried out in order to obtain polymeric materials based on collagen.[334–336,449–454] The formation of gels on irradiation of collagen solutions has been studied in detail.[449,454] These solutions have been used for the creation of radiation-modified medical implants.[449–451,454] Collagen coatings on silicone rubber, subsequently radiation-cross-linked and sterilised, are used in medicine.[453] Another natural product employed for the preparation of biomaterials is gelatin.[454–457] The radiolysis of gelatin has been studied and the conditions for the formation of three-dimensional structures on irradiation of its solutions have been discovered.[454] It has been suggested that a radiation-cross-linked composition comprising poly(vinyl alcohol) and gelatin be used as a dressing.[457]

Gels based on polyphosphazenes have been investigated.[458] A new method has been proposed [459] for the preparation of hydrogels using natural polymers: gelatin, dextran, and albumin. The method consists in the functionalisation of natural polymers by introducing into them double bonds with subsequent cross-linking by γ-irradiation. The method makes it possible to introduce a large amount of a BAS into the hydrogels.

Radiation-induced cross-linking has been used for the preparation of medical articles made from polysiloxanes: biologically inert porous cord, syringe tubes, capillaries,[460] and various implants.[461–463] In the radiation-induced cross-linking of polydimethylsiloxane under specially pure conditions, its haemocompatibility increases significantly.[462] The radiation-cross-linked polyvinylmethylsiloxane has been used to prepare thin membranes for the making of medicinal preparations (for example, levonorgestrel).[463]

The radiation-induced cross-linking of trans-1,4-polyisoprene has been used to create thermoshrinking materials for the tying of large blood vessels. The materials have undergone extensive tests *in vitro* and *in vivo* (on dogs).[464,465] Radiation modification makes it possible to improve the properties of medical prostheses based on polyolefins.[466] Polymeric biomaterials with enhanced adhesion to human skin have also been obtained with the aid of radiation-induced cross-linking.[466,467]

The manufacture of a synthetic dressing, obtained by the radiation-induced grafting of hydrophilic monomers on polyurethane, has been initiated in Israel. The material is water-impermeable and transparent, is readily attached to the skin, and is permeable to medicinal drugs. The material is manufactured under the name Omiderm.[468]

A pilot plant has been created for the manufacture of radiation-cross-linked natural rubber latexes.[469] The production of the plant is 1000 tonnes of the product per year (Malaysia). These materials are used to manufacture high-quality medical gloves, thin-walled articles, *etc*.[469–471] Radiation-induced cross-linking polymerisation is particularly important in the manufacture of polymeric biomaterials for ophthalmology. Procedures for the hydrophilisation of contact lenses by the radiation-induced graft polymerisation of *N*-vinylpyrrolidone [472–476] or hydroxyethyl methacrylate [477,478] have been described. Methods have been developed for the preparation of an artificial cornea and contact lenses with a high swellability in water from radiation-cross-linked poly(vinyl alcohol) with added sodium chondroitin sulfate.[479]

Ionising radiation has been used to ensure complete hardening and to minimise the amount of residual monomer in the preparation of contact lenses.[480–482] In order to increase significantly the permeability of the contact lenses to oxygen, it is suggested that they be irradiated with accelerated heavy ions having a mass of 2–100.[483] Hydrogel materials for soft contact lenses have been created with the aid of radiation-induced polymerisation.[484,485] These materials are produced in China.[485]

Radiation-cross-linked collagen, isolated from the sclera of animal eyes, has found an application in the manufacture of ophthalmological materials. This material has been used for the creation of temporary allodrainages in antiglaucoma operations.[486]

Thus the use of ionising radiation for the preparation of polymer hydrogels is promising. Considerable progress has been achieved in the study of the mechanisms of the radiation-induced cross-linking of hydrogels and their practical applications have expanded, particularly in the preparation of polymeric materials used for the rapid healing of various wounds.

An advantage of the radiation-induced cross-linking is the possibility of regulating comparatively easily not only the network density but also the nature of the radiation-induced cross-linking itself by varying the dose rate and the polymer concentration. It has been established that, at a low polymer concentration and at a high dose rate, intramolecular cross-linking predominates over intermolecular cross-linking.[487,488]

VII. Conclusion

The scale and level of studies on the employment of radiation-chemical methods for the preparation of polymeric biomaterials designed for application in medicine and biotechnology has expanded significantly in recent years. Certain advantages of these methods compared with traditional ones have been clearly established. The use of ionising radiation for the preparation of polymeric biomaterials is one of the examples of the application of atomic energy for the benefit of humanity.

Considerable advances have been achieved in the employment of low-temperature radiation-induced polymerisation for the immobilisation of various BAS. The immobilisation of antitumour preparations has been studied in greatest detail and extensive investigations of their application in clinics have been performed.

Low-temperature radiation-induced polymerisation has been applied in the immobilisation of enzymes designed for the enzymic hydrolysis of plant waste (Japan). Extensive studies on the use of the radiation-chemical technology for the processing of plant raw material have been carried out in Russia.

Sorbents which have increased significantly the effectiveness of the chromatographic separation of mixtures of certain BAS have been created with the aid of radiation-induced graft polymerisation. Much work has been done on the application of radiation-induced graft polymerisation for the modification of polymeric materials in order to increase their haemocompatibility.

A whole series of novel methods for the immobilisation of BAS using radiation chemistry have been developed in our country.[1]

Studies on the employment of radiation-chemical methods for the preparation of a wide variety of polymer hydrogels have been developed very successfully. Some of them (in the form of dressings and polymer eye lenses) have been introduced into clinical practice (Poland, Israel, China). Immunodiagnostic sets employing the radiation-induced polymerisation of 2-hydroxyethyl methacrylate are being manufactured on an industrial scale [K Vacek (Czech Republic), private communication]. The immunodiagnostic sets are used to determine the activity of phagocytes. The radiation-induced graft polymerisation of organotin monomers has been used to prepare modified polymers with fungicidal properties.[489]

New extremely promising aspects of the application of radiation-chemical methods for the preparation of 'smart' polymers designed to be used in biotechnology and medicine have appeared in recent years. They are designed in particular for the deliberate introduction of medicinal substances at the required site in the human organism and also for the preparation of polymer membranes responding to changes in the environment (pH, temperature, *etc*.), which may find an important application in medicine and biotechnology. In all probability, there is a great future for this aspect of the application of radiation-chemical methods.

Studies on the use of ionising radiation for the creation of polymeric biomaterials are being coordinated by the International Atomic Energy Agency (IAEA) and are being prosecuted most vigorously in the USA and Japan.[490]

Significant advances have been achieved by specialists in Poland.[491,492]

Hydrogels are being developed most vigorously at the Institute of Applied Radiation Chemistry at the Technical University of Lodz in Poland. Two of the polymer hydrogels developed for the treatment of bed sores, burns, wounds, and transplanted skin tissues and also in the therapy of ulcers have become commercially available in a number of European countries.[492] The development of materials for an artificial pancreas (it produces insulin), graft tissues for blood and other vessels, and materials for employment in ophthalmology and dentistry is in the completion stage.[492]

There is no doubt that one may expect in the immediate future the appearance in the market place of new polymeric biomaterials obtained with the aid of radiation-chemical methods.

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