57 Advances in Polymer Science

Polymers in Medicine

Polymers in Medicine

Editor: Karel Dušek

With Contributions by
J. Drobník, R. Duncan, A. S. Hoffman,
Y. Ikada, J. Kopeček, F. Rypáček

With 52 Figures and 23 Tables

Springer-Verlag
Berlin Heidelberg New York Tokyo
1984

ISBN-3-540-12796-8 Springer-Verlag Berlin Heidelberg New York Tokyo
ISBN-0-387-12796-8 Springer-Verlag New York Heidelberg Berlin Tokyo

Library of Congress Catalog Card Number 64-642

Typesetting: Th. Müntzer, GDR; Offsetprinting: Br. Hartmann, Berlin;
Bookbinding: Lüderitz & Bauer, Berlin

2152/3020-543210

57 Advances in Polymer Science

Fortschritte der Hochpolymeren-Forschung

Editorial

With the publication of Vol. 51, the editors and the publisher would like to take this opportunity to thank authors and readers for their collaboration and their efforts to meet the scientific requirements of this series. We appreciate our authors concern for the progress of Polymer Science and we also welcome the advice and critical comments of our readers.

With the publication of Vol. 51 we should also like to refer to editorial policy: *this series publishes invited, critical review articles of new developments in all areas of Polymer Science in English (authors may naturally also include works of their own).* The responsible editor, that means the editor who has invited the article, discusses the scope of the review with the author on the basis of a tentative outline which the author is asked to provide. Author and editor are responsible for the scientific quality of the contribution; the editor's name appears at the end of it.
Manuscripts must be submitted, in content, language and form satisfactory, to Springer-Verlag. Figures and formulas should be reproducible. To meet readers' wishes, the publisher adds to each volume a "volume index" which approximately characterizes the content.

Editors and publisher make all efforts to publish the manuscripts as rapidly as possible, i.e., at the maximum, six months after the submission of an accepted paper. This means that contributions from diverse areas of Polymer Science must occasionally be united in one volume. In such cases a "volume index" cannot meet all expectations, but will nevertheless provide more information than a mere volume number.

From Vol. 51 on, each volume contains a subject index.

Editors Publisher

Table of Contents

Soluble Synthetic Polymers in Biological Systems

Jaroslav Drobník and František Rypáček
Institute of Macromolecular Chemistry, Czechoslovak Academy of Sciences,
16206 Prague 6, Czechoslovakia

This review summarizes facts and theories on the fate of a soluble polymer in an animal or human body, mainly from the point of view of therapeutic or diagnostic applications in medicine. Analytical methods which are the main source of our knowledge on this subject are discussed. A compartmental model is suggested and the importance of the individual compartmental barriers and the peculiarity of the polymer pharmacokinetics is documented: the molecular weight distribution changes with time in the circulating fraction; the various routes of parenteral administration are not equivalent. The main route of clearance from the body is the glomerular filtration, which is limited by the size and modified by the charge of the molecule. Polymers which pass through glomerulus may be reabsorbed in the tubulus by pinocytosis, which is largely dependent on the chemical nature of the polymer. Synthetic polymers may elicit antibody production, induce immunological tolerance, activate supressor cells, serve as a non-specific immunostimulator, particularity of the macrophage cytotoxicity, etc. Practical applications in medicine require more detailed knowledge of the fate of polymers in the body. Diagnostics is more a promising field for the immediate future.

Advances in Polymer Science 57

Abbreviations

DIVEMA	regular 1:2 copolymer of maleic anhydride and divinyl ether
DNP	2,4-dinitrophenol
GPC	gel permeation chromatography
HES	hydroxyethylstarch
MTX	methothrexate
PEG	polyoxirane (poly(ethylene glycol))
PHEA	poly-α,β[N-(2-hydroxyethyl)-D,L-aspartamide]
PHPMA	poly[N-(2-hydroxypropyl)methacrylamide]
PVA	poly(vinyl alcohol)
PVP	polyvinylpyrrolidone
PVPNO	poly(vinylpyridine N-oxide)
RES	reticuloendothelial system

1 Introduction

All living matter consists primarily of polymers. Therefore, when products or parts of organisms are used for any purpose, polymers of biological origin are used. In addition to applications in food, clothing, construction, etc., biological polymers have been used for healing purposes. Although nature provides a huge selection of different polymers, it is sometimes difficult to select a natural macromolecule which would fulfil all demands of pharmacy and medicine. Recent progress in macromolecular chemistry had led to the hope that synthetic polymers could be tailored to fit in desired functions in the body better than natural polymers. While the use of natural polymers has mostly been based on empirical experience, synthesis for a special purpose requires complete theoretical understanding of the role the synthetic polymer would play in the body. Our ignorance in this respect is the main barrier to the introduction of synthetic polymers in medicine.

Any substance of natural or artificial origin entering the *milieu interieur* of the organism must be considered as a "foreign body". Its interactions with the components of the biological environment determine the promptness of recognition and the intensity of the reaction of the organism in eliminating or isolating the intruder and re-establishing the internal equilibrium. From this point of view, it is quite correct to judge the application of synthetic polymers in the organism very carefully as the introduction of a foreign substance. Similar to other artificial invaders, including many synthetic drugs as well as the surgeon's scalpel or x-rays employed by the examining doctor, the ratio of positive and adverse effects is the decisive factor in the application of polymers in therapy and diagnostics. The understanding of their behaviour and fate in the organism must be sufficiently complete to allow the reliable evaluation of the benefits and risks. This problem is not, of course, the subject matter of a single discipline: polymer chemistry, physiology, pharmacology, immunology, medical science, biochemistry and other disciplines should combine in its solution.

In addition to the properties of a given polymer, the complex biological mechanisms involved in the handling of the polymer by the organism participate to a major degree in the fate of the polymer in the body. It is the purpose of this review to reveal the relationships between the particular polymer properties and the biological mechanisms they participate in and to indicate how many different factors, influences and rules must be considered when the fate of a synthetic soluble polymer in a living body is to be understood. In order to include at least the most important factors, we could not avoid describing some fundamental biological pathways and terms, that are already familiar to readers with a background in biomedical polymer research and that are, on the other hand, useful for explaning this subject to chemists who are just beginning to participate in this field.

2 Analytical Methods

Analytical methods are the only source of direct information on the fate of the polymer in the body. They include detection, identification and quantitative estimation of the polymer. Detection my be defined as tracing of the polymer by chemical techniques in the bulk of biological samples or as morphological localization in organs, tissues

and cells by histological and cytochemical procedures. Identification of the polymer should distinguish the polymer from other macromolecules in the biological milieu and, at the same time, should reveal all changes, both physical and chemical, that may occur with the polymer during its history in the organism. Quantitative estimation is a complex problem, particularly when the polymer has changed. If it has been degraded, then all of its products (metabolites) should be detected. Some typical approaches will be discussed.

2.1 Radioisotopes as Tracers of Synthetic Polymers in the Body

Radioactive labelling is based on either incorporation of the radioisotope into the polymer structure or on attachment of a radioactive tag to the polymer. All labelling methods are well known and have frequently been described; however, they may also be a source of certain pitfalls. These questions will be discussed later.

The incorporation of a radioactive isotope into the structure of the polymer leads to practically no changes in the chemical and physical properties of the macromolecule. It also enables tracing of the degradation products from biodegradable polymers. This advantage is offset by the tedious preparation. This procedure can hardly be used for pharmacological evaluation of industrial products, as it is practically impossible to prepare a labelled laboratory sample identical in all respects with the industrial product. Thus, this method is limited to research applications. Artefacts can be generated by isotope exchange and the effects of their specific activity are discussed below.

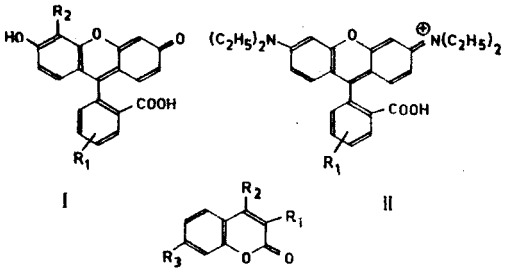
The attachment of a radioactive tag to the polymer is a much more versatile method; however, inherent changes of the macromolecule may result. The significance of these alterations should be assessed from the viewpoint of the purpose of the experiment. A compromise between this and the former method involves the use of a radioactive polymerization initiator which is incorporated into the polymer chain. However, the specific activity which can be achieved is very low.

Iodination of the polymer with ^{125}I or ^{131}I is analogous to the method routinely used in biochemistry and results in only small changes in the polymer properties. However, the nature and the stability of the iodine-polymer bond must be carefully considered. For example, the use of radioactive iodine for labelling of PVP has been questioned [1]. The use of GPC or treatment with AgI powder in vitro and measurement of the radioactivity of the thyroid gland in vivo are believed to be sufficient control measures.

The attachment of a small molecule containing a radioisotope results in more alteration of the macromolecule; e.g., the acylation of amino groups by ^{14}C-acetic anhydride leads to changes in the charge and hydrophilicity reflected in the electrophoretic pattern [2]. We have studied the excretion of poly[(N-2-hydroxyethyl)-D,L-aspartamide]s (PHEA) of molecular weight about 10,000, where the 2-hydroxyethyl group was partly replaced by the 4-hydroxyphenetyl group which can be easily and safely iodized. We found that, up to 4 mol-% substitution, there were no changes in the excretion and deposition of the polymer in the kidneys. This does not imply that other biological effects are insensitive to the same level; e.g., immunological processes may be expected to respond at a much lower level of substitution [3].

The labelling with iodine radioisotopes showed the advantages of gamma emitters: they can be measured with minimum sample preparation, in a well-counter in whole organs and even in whole small animals, and with proper collimation in the body of patients and big animals by gamma cameras from outside. For patient's safety, short-lived nuclides are preferable. Because of the simple preparation in generators ^{113m}In and ^{99m}Tc are widely used in radiodiagnostics. Thus, labelling should be performed immediately before application and must, therefore, be limited to a very simple procedure. Attachment to the polymer can be achieved through a chelating group [5,6] which, however, by no means represents a negligible alteration of the polymer structure.

It follows from the labelling procedures discussed above that ^{3}H and ^{14}C nuclides are most often incorporated into the polymer molecule, as heteroatoms (S, P, etc.)



I II III

		R_1	R_2	R_3	Ref.
I.	a	-H	H	-	
	b	-NCO	H	-	15)
	c	-NCS	H	-	16)
	d	$-NHCSNHCH_2CH_2NH_2$	H	-	26)
	e	$-NHCOCH_2CH_2NH_2$	H	-	26)
	f	$-NHCSNH(CH_2)_2CONHNH_2$	H	-	27)
	g	-H	$-NHCO-C(CH_3)=CH_2$	-	11,12)
II.	a	-H	-	-	
	b	-NCS	-	-	16)
	c	$-NHCSNH(CH_2)_2CONHNH_2$	-	-	27)
III.	a	-H	H	H	
	b	$4-C_6H_4-NCS$	$-CH_3$	$-N(C_2H_5)_2$	17)
	c	-H	$-CH_2NH_2$	-OH	13)
	d	-H	$-CH_2NHCOC(CH_3)=CH_2$	-OH	13)

Fig. 1. Derivatives of fluorescein (Ia), rhodamine B (IIa) and coumarin (IIIa) that are most useful in fluorescence labelling

are rarely components of the polymer structure. The nuclide ^{14}C is the tracer of choice for bulk detection and estimation of the polymer and its possible metabolites. It is less suitable for morphological localization by microautoradiography because of its inherent low specific activity. It should also be noted that ^{14}C-labelled compound are quite expensive.

The use of ^{3}H avoids most of these problems. High specific activity can be cheaply obtained by catalytic exchange of protons in many compounds. The energy of the emitted electrons is low, yielding very sharp microautoradiograms. However, this simple labelling methods have some drawbacks: care must be taken to check reverse exchange with protons in vivo and during all laboratory manipulations. The availability of a high specific activity makes it particularly important to take radiochemical and/or radiobiological considerations into account when working with ^{3}H.

First, it should be noted that each decay is accompanied by a chemical transmutation: $^{3}H \rightarrow {}^{3}He$, $^{14}C \rightarrow {}^{14}N$, $^{32}P \rightarrow {}^{32}S$, $^{35}S \rightarrow {}^{35}Cl$. The daughter atom receives the recoil energy from the emitted electron and is in the electronically excited state [6]. Second, the emitted electron ionizes the atoms it passes by stripping off their valence electrons losing about 33 eV per ionization. All these events usually lead to bond rupture in the vicinity of the transmutating nuclide and to energy transfer to the surrounding atoms and molecules. The density of ionization increases with decreasing electron energy, i.e. velocity. For example, each disintegration of ^{3}H yields an amount of energy equal to 10 rads (0.1 J kg^{-1}) to a sphere 1 μm in diameter [7]. Thus, energy transfer to the surroundings must be considered at high specific activities. It may generate chain scission, oxygen activation, radical generation and serious biological damage to the structures where the polymer accumulates. We have calculated [8] that the lysosomal membrane, in experiments with tritiated poly(acrylic acid)[9] with a specific activity about 10^{11} Bq g^{-1}, received a dose of 12 krads (120 J kg^{-1}) which, is more than sufficient to change its permeability [10] and thus generate artifacts.

In conclusion, radioactive labelling is a method of choice of a very sensitive tracing of the polymer and its possible metabolites in bulk biological material. It is less suitable for morphological analysis. Care must be taken to check for alternation of the polymer properties, the stability of the label and for radiochemical and radiobiological side-effects.

2.2 Fluorescent Labels

The labelling of polymers with fluorescence labels cannot avoid the addition of a new structure to that of the original unlabelled polymer. This obstacle need not be serious in the experimental research (in which labelled polymers are mostly used); however, the effect of perturbation of the properties of the polymer should be checked specifically in each experiment. If these precautions are taken, fluorescence labelling can be very useful.

In addition to minimal perturbation of the original polymer structure, the polymer-fluorochrome bond must be stable and the labelled polymer should have favorable spectral properties. The highly fluorescent derivatives of fluorescein (Ia), rhodamine (IIa) and coumarin (IIIa) have been studied in detail for analytical purposes in biological material (Fig. 1). Attachment of these substances to a polymer molecule by a co-

valent bond may be accomplished either by copolymerization of a polymerizable derivative of the fluorochrome or by a polymeranalogous reaction.

Polymerizable fluorescent vinyl monomers of fluorescein (Ig) [11,12] and coumarin (IIIa) were prepared [13]. Although, the polymerization of a well-defined fluorescent monomer seems to be an exact method for the preparation of well-defined labelled polymers, in practice this is rarely true. It is usually desirable to study polymers bearing not only the label but also other groups of special biological interest or useful for additional binding of such compounds. Therefore, at least terpolymerization should be the starting procedure. In addition, fluorochromes in general can easily form radicals, and may enter the polymerization in an unpredictable way either as a chain transfer or as a terminating group. On the other hand, these reactions were found to be useful for the preparation of fluorescent polymers, e.g. polyacrylamide, by polymerization in the presence of fluorescein as a chain transfer agent [14].

A polymeranalogous labelling reaction may employ either the reactive electrophilic group on the fluorochrome or on the polymer. For the former, the isocyanates and isothiocyanates, e.g., Ib [15], Ic, IIb [16], IIIb [17], are preferable and their usefulness has been confirmed in many experiments with labelled proteins (see Ref. 18 for a review). This approach was also followed in labelling of soluble polymers of biomedical interest, e.g. dextran [19,20] and other polysacharides [21,22], poly(ethylene oxide) [23], poly(ethyleneimine) [24], poly(2-hydroxypropyl methacrylamide) (PHPMA) and PHEA [25]. This method appears attractive because of its apparent simplicity, but our experience has shown that the results are not always satisfactory. The high reactivity of these derivatives may involve them in reactions with different types of nucleophilic groups on polymers. While the reaction with an amine yields a substituted urea derivative with sufficient hydrolytic stability at neutral and acid pH values, the product of reaction with a hydroxy group — present in most hydrophilic polymers — is substantially less resistant to hydrolysis [25]. Thus, labelling of hydrophilic polymers with fluorochrome isocyanates or isothiocyanates results in different types of polymer-fluorochrome bonds exhibiting also different degrees of stability.

It is usually not difficult to prepare polymers containing various reactive electrophilic groups or to activate polymers for labelling by the latter method. Sometimes this step is already included in the preparation of tailored polymers. The primary amino group is then a suitable nucleophilic group for the fluorochrome. Derivatives of fluorochromes with an aliphatic amine have been prepared (Id, Ie in Ref. 26 and IIIc in Ref. 13) and their reactions, hydrolytic stability of the bond formed with polymer as well as their spectroscopic properties have been studied [13,26]. The acylation of an aliphatic amine, which proceeds most readily, does not affect the emission properties of the fluorochrome. The best results were obtained with the label Ie having an amide bond. In another approach, hydrazides prepared from isothiocyanates of fluorescein and rhodamine (If and IIc) [27] were used. This method was originally suggested for polysaccharides, but may be extended to the labelling of other polymers.

While the radioisotopic labelling method described above has some unquestionable advantages, the fluorescence labelling method has its outstanding features as well: the sensitivity of quantitative assays is at least comparable with isotopic methods. An amount of about 10 ng of polymer tagged with one mole of fluorochrome per thousand moles of monomer units can be quantitatively determined in biological

material using standard equipment [26]. If more advanced systems for fluorometric assay are used, the threshold of assay is decreased to a fluorochrome (fluorescein) concentration of 5×10^{-14} mol l^{-1} [28]. This offers, for example, the possibility of simple and convenient flow-through GPC and molecular weight distribution analysis in tiny samples of biological fluids [29]. In addition to quantitative measurements, fluorescence spectroscopy, including microfluorimetry, may also yield structural information on the nature of the fluorochrome microenvironment [30], interactions with cell structures [31], the mobility of side chains on polymer, etc. The morphological localization at a histological and cellular level of polymer deposition can readily be achieved with a fluorescence-labelled polymer. Cytofluorographs can be used for counting and separation of cells containing the polymer [32].

On the other hand, the nonspecific fluorescence background of some compounds occurring in the living tissues and fluids (liver, kidneys, bile etc.), emission quenching, and sorption of the polymer on components of the studied material place rigid requirements on careful preparation of the sample for quantitative measurements at a high sensitivity level [26]. Comparison with labelling by γ-ray-emitting isotopes emphasizes this fact. Possible alterations of the emission properties due to chemical modification of the fluorochrome, particularly as a result of the action of detoxicant enzymatic systems in the living body (see Chapter 4), should be also considered. Acetylation of 3′- and 6′-hydroxy groups of fluorescein (essential for emission) in plant cells has been reported [33] as well as glucuronidization in rat liver cells [34]. It is not clear, however, whether the macromolecular substrate can undergo the same type of reaction. Therefore, fluorescence labelling need not be fully reliable for long-term tracing of a polymer in the body, when the absolute quantity of the polymer in the tissue is the most important factor. Nevertheless, such advantage as simple and safe handling, high sensitivity, easy visual morphological and flow-through detection, low price, no problems with waste products, etc. may outweigh the above-mentioned shortcomings in many experiments.

2.3 Other Methods

Several other methods of polymer quantification in biological material have been used. In general, a polymer is usually isolated from biological material by a deproteinization procedure, extraction with organic solvents, etc., and then analyzed. Elemental analysis [35], viscosimetry [36], turbidimetry [37] and complexation with iodine [38,39] (for PVP) in extracts were used in early studies in this field. These methods are now rarely used and have been replaced by labelling methods. Among the classical analytical techniques, the anthrone reaction for the estimation of carbohydrate polymers (e.g. dextran [40], inulin [41]) has remained useful.

The morphological detection of synthetic polymers on the tissue and cellular level either by microautoradiography, microfluorography, or other methods has some general features worth of a more detailed discussion. Historically, the first demonstrations of polymer deposits in tissue were based on the observation of morphological changes resulting from the presence of the polymer in cells without direct identification of polymer material. Bargmann was the first to describe the swelling and vacuolization of the spleen reticulocytes and Kupffer cells of liver after administration of PVP [42]; most subsequent histological studies dealing with the storage of soluble polymers

in the body are based on these indirect observations. Several attempts have been made to stain the deposited polymer using histological stains [43-46], but these methods did not exhibit the desired specificity.

Autoradiography can directly identify and localize radiolabelled polymers in tissues [47]. Autoradiograms have very impressively shown the overall topography of polymer distribution in whole-body [48] or organ sections [49]. Similar techniques have been adopted for fluorescence-labelled polymers [50].

However, the growing interest in targeting drugs carried by polymers and, consequently, in the investigation of the mechanisms of polymer interactions with the cells surfaces and cellular capture requires more detailed morphological information. Both radioactive and fluorescence labelling could probably provide polymer identification, but the resulting accuracy in polymer localization mostly depends on the success in the preservation of its original in vivo deposition pattern. In vivo, polymers are stored in precisely localized deposits, because of the semipermeability of biological membranes (see Chapter 3). The procedures and chemicals commonly used in histology for the fixation of tissues impair the semipermeability of biological membranes but, unfortunately, they usually leave the synthetic polymers soluble (not only in water but also in organic solvents) and thus susceptible to diffusion. They may be washed out or adsorbed artificially on other structures. The dispersion of a polymer in a cell may also occur during long-term exposure in the autoradiography of frozen sections kept at a temperature slightly below zero (-5 to -20 °C) [51], since these temperatures are not low enough to solidify the concentrated electrolytes in frozen cells. However, these obstacles can be overcome using appropriate methods. Rapid procedures of tissue fixation using glutaraldehyde and osmium tetroxide have been developed in electron microscopy for ultrastructural localization of dextran as well as PVP deposits [52,53]. The immediate *post mortem* perfusion of the blood system of the organ under study by fixation solution containing paraformaldehyde and glutaraldehyde was successfully used in preserving the true cellular localization of fluorescence-labelled polyaspartamide polymers [50] (Figs. 9, 10). A method based on ultrarapid deep-freezing of the tissue sample, followed by controlled freeze-drying and subsequent vacuum embedding in a paraffin-like medium was suggested as generally applicable for any water-soluble polymer [54]. This procedure decreases to a minimum the possibility of artificial translocation of polymer during the preparation of the sample.

In conclusion, most analytical problems of tracing the polymers in the body can be solved by proper labelling. Radioisotopes are very helpful in bulk analysis, whereas fluorescent tags provide excellent morphological information. Of course, modification of the polymer structure in labelling must be considered. In morphological studies by any method, the crucial role is played by the sample preparation. All steps from killing the animal to mounting on the slide should be carefully checked to prevent the movement and delocalization of the polymer.

3 Movement of Polymers in the Body Compartments

3.1 The Compartment Model of an Organism

Polymers entering the *milieu interieur* of an organism cannot move randomly but their movement is controlled by anatomical and physiological barriers. In pharmacokine-

tics, which describes and quantifies the dynamic processes of absorption of chemicals in the body, their distribution to various tissues, reactions with tissue components and their elimination from the tissue and the body *via* metabolism and/or excretion, it has appeared useful to represent the body by a system of compartments. These compartments need not have physiological or anatomical counterparts. While the body is composed of an infinite number of compartments, in pharmacokinetics, a compartment refers to all those organs, tissues and cells for which the rates of uptake and subsequent clearance of a chemical are sufficiently similar to preclude pharmacological resolution [55].

We will utilize such a multicompartment model of an organism to describe factors and mechanisms controlling the movement in the body of a macromolecular substrate — a synthetic water-soluble polymer. Compartments in our definition are characterized rather by similarity in mechanisms of crossing of compartmental barriers. The macromolecular character of polymers is an important factor in these crossings. Biopolymers, which are endogenic in nature, i.e., mainly proteins, play an indispensible role in the homeostasis of the organism, both structural as well as functional, and at the same time they all participate through their macromolecular nature in the determination of the osmotic, rheologic and ionic properties of body fluids. An exo-

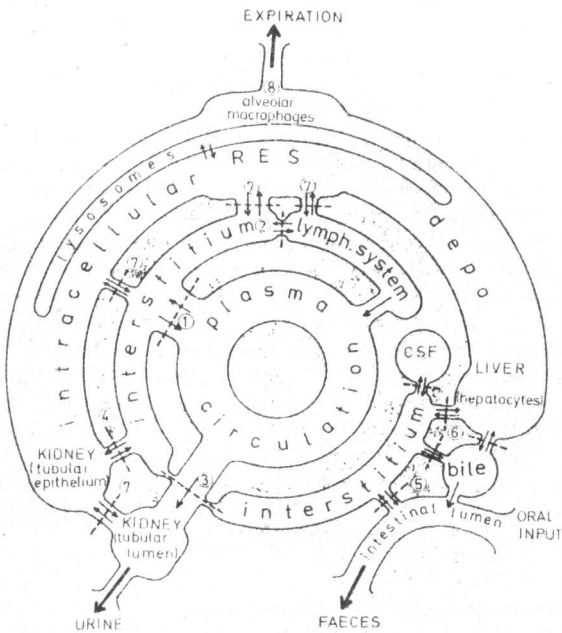


Fig. 2. Multicompartment model of organism. Areas depict the body compartments, connecting corridors represent possibilities of polymer transfer between compartments either restricted by compartmental barriers (dashed lines) or occurring as flux transfer (simple arrows). The numbers refer to the paragraphs in which the given barrier crossing is discussed

genic macromolecule, e.g., a synthetic polymer, entering any compartment will disturb its equilibrium state, and therefore may be either transferred to other compartments or subjected to processes which usually tend towards re-establishment of the original equilibrium.

In general, during its transfer the foreign macromolecule may "employ" the transport mechanisms "already prepared" for endogenic macromolecules. Obvious exceptions are due to the fact that polymers under consideration are mostly unable to fit into the biologically specific mechanisms developed during the evolution for particular biomacromolecules. The limited biodegradability of synthetic polymers leads to the most serious consequence of this general feature.

In Fig. 2, the body compartments are schematically depicted as areas connected by corridors symbolizing the pathways of possible solute exchange between compartments. The pathways are interrupted by dashed lines (barriers); the mechanisms of crossing these barriers are the subject of the following paragraphs. Simple arrows indicate unrestricted flux transfer for solutes. The central compartment – plasma circulation – is the only compartment through which the exchange of compounds between remote parts of the body may be accomplished. The large intracellular compartment, joined graphically in one area, comprises all the cells of the body. The participation of cells of the reticuloendothelial system (RES), kidney tubular epithelium, and liver hepatoxytes is so important that it should be discussed separately.

3.2 Ways in which Synthetic Polymers Cross Compartmental Barriers

The distribution of a polymer in the body, the rate of its clearance, the site and time duration of its retention, i.e., all the basic factors determining the availability of a medical polymer for biological activity may be understood as resulting from its partitioning at compartmental barriers. These particular barriers may have various compositions (see below) but mostly their crossing includes some means of crossing of a biological membrane, which will be briefly characterized below.

A biological membrane (a plasma membrane, plasmalemma, cell membrane, etc.) is a lipoprotein membrane (Fig. 3). Lipids are arranged as a double layer of molecules with the hydrophobic portion facing inwards and hydrophilic portion outwards, and are maintained in this position by hydrophobic forces. Between the lipid molecules, the proteins are intercalated, being bound to the lipid layer by hydrophobic interactions. The proteins are not held rigidly in place but can move laterally along the lipid membrane forming a fluid mosaic pattern. Many cell membrane proteins have polysaccharides bound to their outer surfaces, they may participate in determining the antigenic specificity, and together with others secreted by the cells, they form a coating layer, called the glycocalyx. The glycocalyx may be of various thickness and density on various cells. In principal, this structure of the lipoprotein membrane (unit membrane) is common for all other membranes enveloping the cell organels (nucleus, lysosomes, plasmalemma vesicles, etc.) [172].

The transport of low-molecular weight compounds (water, ions) is not accompanied by any visible morphological changes. It proceeds by passive diffusion or an active transport process, depending on the polarity and size of the transported molecule and presence of a specific carrier protein in the membrane. Water-soluble polymers