

1

Introduction: why study polymers for the health sciences?

1.1 Polymers are large molecules that nature relies on	2	1.4 Morphology and nomenclature of polymers	6
1.2 A brief history of polymers	4	Bibliography	16
1.3 Definitions	5		

Are polymers really exotic in the domain of health?

In the common sense, polymers are ‘plastics’, i.e. useful everyday materials produced in huge amounts and known among other things for polluting our environment, especially seashores. However, with the development of biomaterials in the 1980s, specialised polymers have become increasingly used in medicine as components of medical devices. Classical polymers have also been present for years in pharmacy as excipients for the oral route. More recently, with the development of nanobiotechnology, more sophisticated polymers have been developed, for instance as constituents of nanoparticulate systems for vaccine and drug delivery.

According to specific requirements, polymers have been used in devices for replacing deficient parts or assisting different functions of the body, thanks to the various physical and mechanical properties resulting from the bulk of the material, e.g. compliance. At this level, the user of polymers should also be aware of the fact that living tissues are in contact with polymers by their outermost surface. Thus, in addition to the classical properties for which polymers are used, the reactions and even the fate of the living tissues can be determined by the properties of the surface. To illustrate this, let us examine a simple *in vitro* experiment in which cells are grown in a polymeric vessel. Petri dishes are usually made of polystyrene, which is a transparent and

cheap polymeric material. However, cells cannot grow on such a hydrophobic surface. The surface of tissue-culture polystyrene Petri dishes is thus treated to increase hydrophilicity and to make normal cell growth possible, whereas the bulk is pure polystyrene (see Section 2.4.2).

As with other compounds in contact with living tissues, regulations concerning polymer use are strict, in particular with regard to purity. However, as polymers are not pure crystalline low-molecular-weight compounds, a ‘pure’ polymer cannot be defined in similar terms. Moreover, further tests of characterisation, for instance concerning surface properties, are usually needed.

Thus, polymers are less and less exotic in the domain of health, and learning some basic concepts about polymers is necessary in order to design better-adapted devices and excipients and to understand what may happen when polymers are in contact with living tissues. In addition, the knowledge of some special features linked to the use of such specialised polymers is required for those using them in the domain of health.

1.1 Polymers are large molecules that nature relies on

Life on Earth is linked to the presence of water, and water is our main constituent. However, all kinds of living species are not simply ‘bags of water’ but are highly organised. This specialised organisation depends on, among other compounds, macromolecules (Box 1.1), i.e. polymers that are able to retain and structure water, as natural **hydrogels**.

Many polymers have a natural origin (mineral, vegetal or animal). Some of these have been used for centuries. In the vegetal kingdom, cellulose is the most abundant macromolecule. Cellulose is a **polysaccharide** composed of repeating units of cellobiose, i.e. it is a dimer of glucose.

In the animal kingdom, chitin, a polymer of *N*-acetylglucosamine, is widely distributed as the main constituent of the shell of arthropods. Proteins and nucleic acids are well known as supports of life, and these natural polymers retain and structure water.

Box 1.1

Macromolecule is a general name for a very large molecule. A high **polymer** is a macromolecule. A polymer produced by chemical synthesis is usually made from a limited number of repeating units, or **monomer** units. **Polypeptides** produced by chemical synthesis are made from amino acids. **Proteins** that are produced by biosynthesis contain mainly amino acids and may contain a few saccharidic or lipidic units.

For the sake of simplicity, the authors use the terms macromolecule and polymer interchangeably.

use, including in the biomedical and pharmaceutical fields. An even wider diversity of properties and uses has been obtained with the development of synthetic polymers, which can be prepared by different methods and processes of polymerisation of one or more monomers. In the domain of health, a very interesting property of purely synthetic polymers is their absence of immunogenicity, unlike many polymers of natural origin.

1.4 Morphology and nomenclature of polymers

A very large number of morphologies can be found in the world of polymers. The simplest polymers are composed of only one chain, sometimes called a backbone. These are named **linear polymers**, even if the shape is not really linear but is imposed by the angles of the successive chemical bonds. Linear polymers look like cooked spaghetti; the entangled chains are very difficult to separate from each other. The prolonged time that is usually necessary to dissolve polymers, and also many properties of polymers as solid materials, are explained by the entanglement of chains, as illustrated in Figure 1.3.

The morphology of polymeric chains is often more complicated than the morphology of linear chains. Polymers can be branched, comb-like, star-like, ladder-like, macrocyclic, dendritic or cross-linked, when chains are linked together, as illustrated in Figures 1.4 and 1.5.

1.4.1 Nomenclature of organic linear polymers

There are at least three nomenclatures for linear polymers. The official nomenclature has been defined by the International Union of Pure and Applied Chemistry (IUPAC) and is based on the simplest repeating unit present in the polymers. However, for several reasons the IUPAC nomenclature is not the most commonly used. The most common nomenclature, which is presented in this chapter, is based on the name of the repeating unit resulting

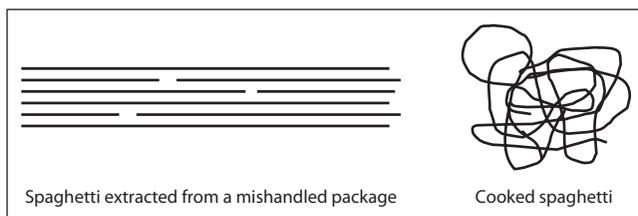


Figure 1.3 Linear polymers can be compared to cooked spaghetti. Polymolecularity: size of polymer chains is a statistical data. Entanglement: polymeric chains are entangled and difficult to separate. A cohesive mass is formed at solid state and dissolving a polymer is generally time-consuming.

Table 1.2 Repeating monomer unit, chemical name, abbreviated name and density of some linear polymers

Repeating monomer unit	Chemical name	Abbreviation	Density (g/cm ³)
Polyolefins			
$-(\text{CH}_2-\text{CH}_2)-$	Polyethylene	PE (HDPE and LDPE)	0.89–0.98
$-(\text{CH}_2-\underset{\text{CH}_3}{\text{CH}})-$	Polypropylene (polypropene)	PP	0.85–0.92
$-(\text{CH}_2-\underset{\phi}{\text{CH}})-$	Polystyrene	PS	1.04–1.06
$-(\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2)-$	1,4-Polybutadiene (<i>cis-trans</i>)	PB	
$-(\text{CH}_2-\underset{\text{CH}_3}{\text{C}}=\text{CH}-\text{CH}_2)-$	1,4-Poly(isoprene) (<i>cis-trans</i>)	PIP	0.92–1.00
Polyvinyls and polyvinylidenics			
$-(\text{CH}_2-\text{CHCl})-$	Poly(vinyl chloride)	PVC	1.38–1.41
$-(\text{CH}_2-\underset{\text{O-CO-CH}_3}{\text{CH}})-$	Poly(vinyl acetate)	PVAc	1.14–1.17
$-(\text{CH}_2-\text{CHOH})-$	Poly(vinyl alcohol)	PVAI	1.21–1.31
$-(\text{CH}_2-\text{CF}_2)-$	Poly(vinylidene fluoride)	PVDF	1.76
$-(\text{CF}_2-\text{CF}_2)-$	Polytetra-fluoroethylene	PTFE	2.10–2.30
$-(\text{CH}_2-\underset{\begin{array}{c} \text{N} \\ \diagup \quad \diagdown \\ \text{H}_2\text{C} \quad \text{C}=\text{O} \\ \diagdown \quad \diagup \\ \text{H}_2\text{C}-\text{CH}_2 \end{array}}{\text{CH}})-$	Poly(<i>N</i> -vinyl pyrrolidone)	PVP	

(continued opposite)

2

General characteristics of polymers

2.1 Characterisation of polymers	20	2.4 Properties of polymers as materials	48
2.2 Specific properties of polymers in the presence of liquid media	35	Bibliography	53
2.3 Relationships between structure of polymers and cohesion of materials	44		

In addition to properties shared with small molecules, macromolecules are endowed with specific properties that are linked to the length and organisation between molecules. Such specificities can be observed either in the presence of solvents or in solid state. For instance, polymolecularity is usually the rule and monomolecularity more the exception. Thus, molecular weight is usually an average; some methods used to determine the average molecular weights are presented in this chapter. As shown previously, most physical properties of polymers are independent of molecular weight. Dissolution of polymers in an adequate solvent can take a long (sometimes infinite) time and is always preceded by swelling of the chains. Unlike with metals, the probability of mixing together polymers to obtain alloys is generally low. Owing to the chain length and entanglement, the probability of spontaneous high long-range order inducing high crystallinity is low. A high level of crystallinity can be induced by further thermomechanical processes, in addition to structural requirements. As the thermomechanical processes are beyond the scope of this book, only the structural requirements are presented in this chapter.

2.1 Characterisation of polymers

In general, polymers for biomedical and pharmaceutical applications are characterised in order to determine their molecular weight, composition and thermal properties. All of these characteristics may influence the properties of the final device or medicine.

The molecular weight of polymers can vary from a few hundred to several million grams per mole, while cross-linked polymers have infinite molecular weight. Proteins that are obtained from biosynthesis are very homogenous. All molecules display the same molecular weight and composition because they are synthesised according to a well-programmed method by living organisms. However, despite the fact that they are also obtained by biosynthesis, polysaccharides are polymolecular and their composition can be heterogeneous. Polymers obtained from chemical synthesis form a family of macromolecular species characterised by a mean molecular weight with a certain distribution, termed the 'polymolecularity'.

In the case of copolymers, the composition is also a mean composition that generally reflects the composition of the different co-monomers used in the polymerisation medium after total conversion of the monomers into polymers. However, because the reactivity of monomers between each other can be quite different, the composition of the different molecules of copolymers in a single preparation can vary. Indeed, composition in monomer units of the copolymers formed at the beginning of the polymerisation reaction is not necessarily the same as composition of the copolymers formed at the end of the polymerisation reaction. This effect adds heterogeneity to chemically synthesised copolymers, and the only way to appreciate this effect is to analyse the composition of the polymers at low conversion degree during polymer synthesis.

2.1.1 Determination of molecular weight of polymers

As mentioned above, polymers synthesised by chemistry are not identical but form a family of macromolecules of different lengths that can be characterised by a size distribution with a mean value of the molecular weight. A typical distribution graph of the size of polymer chains present in a sample and constituting a polymolecular population is illustrated in Figure 2.1.

The distribution in molecular weight of each population of macromolecules appears as a Gaussian curve. Mathematical analysis of such a distribution curve can provide different average values that can be used to characterise the molecular weight of the polymer and the distribution of the molecular weights in the population.

For instance, the first moment gives the number-average molecular weight, M_n . This corresponds to the total weight of the sample, W , divided by the number of molecules included in this amount of sample, N_i , as shown

3

Main methods and processes to synthesise polymers

3.1 Why there is a need to synthesise polymers	55	3.5 Limitations of polymerisation	64
3.2 Introducing step and chain polymerisations	56	3.6 Overview of other synthetic methods	66
3.3 Some examples of step polymerisation: from small reagents and from prepolymers	58	3.7 Polymerisation reaction processes	73
3.4 Free radical chain polymerisation	59	3.8 Copolymerisation	80
		3.9 Modifications of polymers	81
		Bibliography	85

3.1 Why there is a need to synthesise polymers

It was shown in Chapter 1 that life is supported by many natural polymers or macromolecules. Natural polymers have been used for centuries, e.g. natural rubber. Modification of natural polymers permitted new useful goods to be made, but sometimes not very well adapted to everyday life, e.g. the highly flammable celluloid.

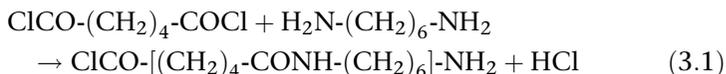
The domain of health provides remarkable illustrations of the necessity to create new polymers. Natural materials have been used for centuries to replace missing parts of the body: parietal plates made of gold or silver have been found in mummies; silk and ‘catgut’ sutures have been used for many years by surgeons; and cellulose and derivatives are still used as excipients in formulations of drugs designed to be administered by the oral route. However, such materials were not always adequate and their properties were not always reproducible. Some adverse reactions have occurred, leading to failure of the material, for reasons unknown at the time. Box 3.1 describes some examples of the problems associated with ‘technical-grade’ polymers.

slowly increasing length. Concentration of reactive groups decreases with increasing time and a long time is required to obtain high-molecular-weight polymers, at least when using small molecules as monomers.

Monomers used in chain polymerisation contain one or two double bonds, or a triple bond or a cycle. Following generation of an active site able to open the bonds or cycles, the chain grows by successive and fast additions of monomers. The molar fraction of monomers in the reactive medium decreases rather slowly, leading to formation of long polymeric chains. Thus, the reaction medium is composed of a mixture of monomer and high polymer, even at low conversion. The active sites usually have a short life and their concentration is low and almost constant with time. Increasing the reaction time increases the conversion yield of monomer into polymers but not the average chain length of the polymers.

3.3 Some examples of step polymerisation: from small reagents and from prepolymers

The first industrial success in step polymerisation was the synthesis and development by Carothers and co-workers at DuPont of the famous polyamide Nylon 6-6, starting from hexamethylene diamine and adipic acid dichloride. As shown in Equation 3.1, this reaction is favoured by elimination of hydrochloric acid.



The number average degree of polymerisation (DP_n) can be calculated as a function of functionality of the monomers, i.e. the number of reactive groups per monomer, and as a function of the extent of conversion. For a functionality of 2.000, i.e. corresponding to very pure difunctional monomers, and for 99.9% conversion, it can be calculated that $DP_n = 1000$, i.e. a number-average molecular weight of about 200 000.

The following conditions are required in order to obtain high-molecular-weight linear Nylon 6-6:

- highly purified monomers, as the presence of monofunctional impurities stops the chain growing and the presence of trifunctional impurities leads to branched polymers
- good control of stoichiometry
- long reaction time.

Thus, such a synthesis is expensive and Nylon 6-6 has now been replaced by Nylon 6 produced by ring-opening polymerisation (see Section 3.6).

Some high-molecular-weight polymers can be obtained by using reagents that are already small polymers, called prepolymers. This is the case for polyurethanes and poly(urethanurea)s. For instance, a poly(ether urethane)

4

Special properties of polymers, case studies and detailed examples of applications

4.1 Properties of block copolymers: phase separation in solution and at solid state	87	4.3 Applications of polymers in biomedical uses	98
4.2 Biodegradable and bioerodible polymers	91	4.4 Applications of polymers in pharmaceutical uses	114
		Bibliography	148

4.1 Properties of block copolymers: phase separation in solution and at solid state

Homopolymers are usually not miscible; hence, blending homopolymers generally leads to phase-separated large domains. As there are only weak interactions between phases, such systems are weakly cohesive. In block copolymers, blocks are also phase-separated but they are linked together by covalent bonds. Thus, solutions and solids composed of such systems possess special properties owing to the presence of the linkages between blocks. The organisation of the micro-domains formed by block copolymers and properties in solutions and in the solid state depend on the composition, structure, molecular weight and properties of the blocks. A few examples of their properties are presented below.

4.1.1 Solution properties

Block copolymers composed of two or three hydrophilic and hydrophobic blocks possess amphiphilic properties and are used widely as non-ionic surfactants. Poloxamers are triblock copolymers polyoxyethylene-polyoxypropylene-polyoxyethylene (PEO-PPO-PEO), commercially known

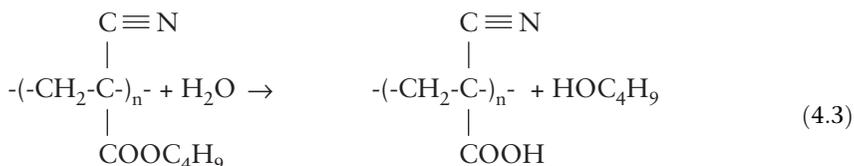
such polymers was a small issue when compared with the expected properties. Then biodegradable polymers were developed in order to solve environmental concerns, e.g. to avoid non-degradable polymer-based wastes polluting the landscape. In this case, the aim was to obtain materials for general uses, such as packaging and agriculture, and that degraded outside. Unlike for biomedical uses, large amounts of technical-grade polymers and low cost were required.

This chapter focuses on biodegradable polymers used in the health domain. Some examples of biodegradable and bioerodible polymers are presented in Table 4.1, and some of their thermomechanical properties are given in Table 4.2.

Table 4.1 Some biodegradable and bioerodible polymers

Name	Abbreviation	Repeating unit	Polymerisation
Poly(glycolide) or poly(glycolic acid)	PGA	$-(\text{O}-\text{CH}_2-\text{CO})-$	Synthetic
Poly(lactides) or poly(lactic acids)	PLA	$-(\text{O}-\overset{*}{\text{C}}\text{H}(\text{CH}_3)-\text{CO})-$	Synthetic
Poly(3-hydroxybutyrate)	P3HB	$-(\text{O}-\overset{*}{\text{C}}\text{H}(\text{CH}_2-\text{CH}_2-\text{CO})-\text{CO})-$	Biosynthetic
Poly(3-hydroxyvalerate)	P3HV	$-(\text{O}-\overset{*}{\text{C}}\text{H}(\text{CH}_2-\text{CH}_2-\text{CO})-\text{CO})-$	Biosynthetic
Poly(4-hydroxybutyrate)	P4HB	$-(\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CO})-$	Biosynthetic
Poly(malic acids)	PMA	$-(\text{O}-\overset{*}{\text{C}}\text{H}(\text{CH}_2-\text{CO})-\text{CO})-$	Synthetic
Poly(ϵ -caprolactone)	PCL	$[-(\text{O}-(\text{CH}_2)_5-\text{CO})-]$	Synthetic
Poly(sebacic acid)	PSA	$[-(\text{O}-\text{CO}-(\text{CH}_2)_8-\text{CO})-]$	Synthetic
Poly[1,3-bis(<i>p</i> -carboxy-phenoxy)propane]	PCPP	$[-(\text{O}-\text{CO}-\varphi-\text{O}-(\text{CH}_2)_3-\text{O}-\varphi-\text{CO})-]$	Synthetic
Poly(butylcyanoacrylate)	PBCA	$-(\text{CH}_2-\overset{\text{C} \equiv \text{N}}{\underset{\text{COOC}_4\text{H}_9}{\text{C}}})_n-$	Synthetic

of poly(butylcyanoacrylate).



Hydrophobic polymer \rightarrow water soluble polymer + alcohol

This degradation catalysed *in vivo* by various esterases proceeds at the surface, limiting the rate of production of degradation products. Toxicity could result from a rate of production exceeding the rate of elimination. As the shortest alkyl chain degrades the fastest, the alkyl chain of the monomers used *in vivo* is at least equal to or longer than a butyl.

4.3 Applications of polymers in biomedical uses

Polymers have been extensively used both as biomaterials, which are constituents of medical devices, and as constituents of drug-delivery systems. Many regulatory requirements must be met in order to use materials in the domain of human health. For instance, sterility is mandatory concerning materials in direct contact with living tissues in the absence of a barrier such as the intact skin. In addition, both polymers and devices have to be biocompatible, and their biocompatibility has to be evaluated by *in vitro* and *in vivo* tests.

However, the regulations differ depending on whether the polymer is a constituent of a medical device or part of a medication. If a drug is included in a medical device for an auxiliary action, then the regulations for medical devices are applicable. If the main action is linked to the presence of the drug, then regulations for medications are applicable.

The aim of this chapter is not to discuss regulatory affairs but to give a rationale for helping one choose the appropriate polymers for a given application. The choice of polymer or another material for making a device or drug-delivery system is directed by the function and the requirements. For instance, the requirement of either elimination or stability of the polymer *in vivo* is a prominent issue. Implanted devices that are supposed to remain functional as long as possible are made from biostable polymers. Injected drug-delivery systems that are administered several times are made from polymers that can be eliminated. In the following sections, some practical examples of existing applications are presented.

4.3.1 Processing and fabrication

In order to be transformed into items such as tubing, catheters and other medical devices, polymers have to be processed by different techniques, such

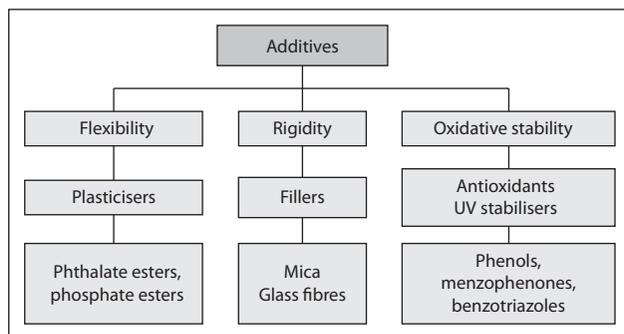


Figure 4.7 Schematic view of different additives used to modify the properties of polymers during processing.

as extrusion, moulding, spinning and dip-coating. To facilitate the processing and improve the properties, several additives are used, for instance to increase the stability of polymers during thermomechanical treatments and to modify their properties. A schematic view of additives used during processing is shown in Figure 4.7.

The addition of such products is important in the manufacture of useful items. However, most of these products are small molecules compared with the size of the polymers and therefore some are susceptible to migrating and inducing unwanted reactions in the surrounding living tissues, as explained later.

4.3.2 Sterilisation of polymers

Before contact with the living tissues of animals or humans, polymers and devices have to be sterilised. Even if fabrication is performed in a ‘clean room’, the materials and processing machinery are not sterile. In addition, it has been shown that some bacteria that are normally benign and easily eliminated by the body’s defence systems become pathogenic and drug-resistant when present on the surface of devices.

Current sterilisation processes are generally not well adapted to polymers, except in the cases of water-soluble polymers and colloids, which can be sterilised by filtration in solution. The simplest process is autoclaving with steam at 120 °C for 20 min. This process can be detrimental to devices that include polymers with thermomechanical properties not compatible with the temperature used in the sterilisation process.

Sterilisation by ethylene oxide is very efficient, whatever the shape of the device, as this molecule is very small and reactive. Some drawbacks are linked to these qualities, however. Ethylene oxide can easily penetrate into polymeric networks, and it may react with chemical groups present in some polymers. In the first case, a sufficient degassing time in sterile conditions is necessary

before the device is used in contact with living tissues. In the second case, modifications of the polymer, and especially of its surface, can occur and change the reactions of living tissues in contact with the device.

Sterilisation by high-energy beams, e.g. γ rays or fast electrons beams, is very efficient, as these beams are usually not stopped by materials. However, some covalent bonds of the polymeric network can be broken easily by such a high energy. Depending on the type of polymer and the dose and dose rate of the radiation, permanent chain scission or cross-linking can result from this process, modifying the polymeric structure and properties of the material.

Evaluating the mechanical and surface properties, toxicity and biocompatibility of polymers and devices before and after sterilisation is relevant in order to select for a given polymer or device a sterilisation process that is efficient against bacteria but is as benign as possible for the polymer, the device and the patient.

The drawbacks described above have emphasised the need for new sterilisation processes that are more compatible with polymers. However, these processes are still being evaluated for routine use.

4.3.3 Definition and concepts of biocompatibility

Biocompatibility was a vague concept until it was defined during a consensus conference organised in 1986 under the auspices of the European Society for Biomaterials at Chester as follows: 'The ability of a material to perform with an appropriate host response in a specific application.' This means that there is no 'intrinsically biocompatible' material. This precise definition excludes the common use of vague sentences such as 'The device is made from biocompatible materials', which sounds more like advertising copy than a scientific demonstration. The precise definition means that the animal model in which biocompatibility tests have been performed should be specified, as each animal species, including humans, has its own specificities. The application should be specified, as reactions of living tissues surrounding the material depend on many biological parameters and the type of material. A description of the local and systemic reactions should be provided as a function of time, as tissue responses also vary with this parameter.

Biocompatibility and toxicity

Biocompatibility is not equivalent to non-toxicity. Toxicity, either local or systemic, is related to cell death generally induced by soluble products, whereas biocompatibility is related more to the reactions of living tissues in contact with a solid material. Soluble products can be released by a material. Corrosion of metals and metallic alloys can produce multivalent ions, which are generally toxic. Multivalent ions used for in vivo imaging,

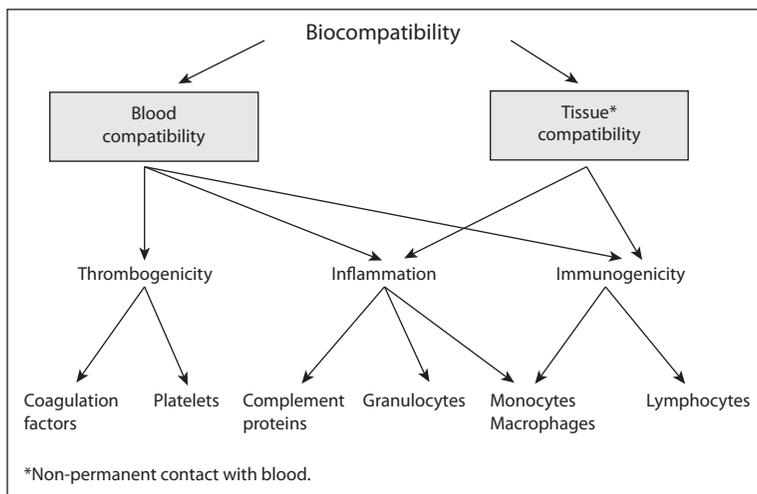


Figure 4.8 Schematic representation of possible reactions to contact between materials and some proteins and cells involved in the reactions. For the sake of simplicity, water and ions are not included.

Tissue compatibility

In this case, the reactions linked to the permanent presence of blood are excluded, even if a transient contact occurs during surgery. Two types of reaction can occur: inevitably inflammation and sometimes immunogenicity.

The unavoidable inflammatory response

Following the surgical trauma at the insertion of implanted materials, a non-specific tissue reaction inevitably occurs around the inserted material. The aim of the inflammatory reaction is to allow elimination of dead cell debris and further tissue repair. From the point of view of the inflammatory response, a material of optimal biocompatibility should neither add to the basic response in intensity and duration, nor prevent the tissue repair. All of these non-specific reactions occurring on the material's surface involve efficient cooperative processes between ions, proteins and cells.

Histologists have classified the inflammatory and healing processes as a function of the types of cell present around the implant. The **acute inflammatory phase**, normally lasting for a few days, is characterised by the presence of polymorphonuclear neutrophils (PMN). This phase is followed within 2 weeks by the **chronic inflammatory phase**, characterised by the presence of macrophages and lymphocytes. If the material is well tolerated, then this is followed by the **healing process**, characterised by the presence of fibroblasts and the growth of new capillaries, resulting in a thin capsule of fibrosis. If the material is not well tolerated, then inflammation is prolonged, with giant macrophagic cells and development of a thick capsule of fibrosis. Hence, it results that tissue compatibility of materials has to be evaluated at the

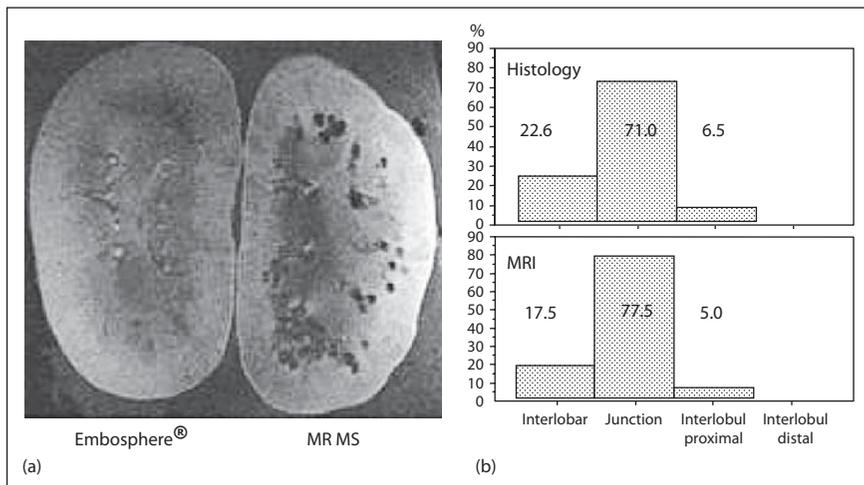


Figure 4.15 (a) Comparison of magnetic resonance imaging (MRI) of kidneys embolised either with normal Embospheres® (left kidney) or microspheres of similar diameter (500–700 μm) labelled with colloidal superparamagnetic iron oxide (MR MS) (right kidney). (b) Arterial level of occlusion of right kidney evaluated either by histology or by MRI.

inflammatory response that results from the large amount of degradation products, which are released faster than they can be eliminated. An important piece of work has been performed on microspheres based on natural polymers. These pose less toxicity and many are susceptible to biodegradation. However, the presence of antigenic determinants in such polymers is possible. Microspheres made from albumin, casein, gelatin, chitosan, starch, alginate and dextran have been proposed, and review papers are available.

Despite the fact that the presence of microspheres made from non-degradable polymers in pathological arteries induces a generally acceptable inflammatory response, embolisation is not definitive. In fact, revascularisation invariably occurs, excluding this foreign body from the lumen of the vessel at a rate that depends on the material, the animal and the embolised tissue. The molecular mechanisms occurring in this process are unknown.

4.4 Applications of polymers in pharmaceutical uses

4.4.1 Excipients for formulation of conventional dosage forms

Among the various ingredients that are commonly used as excipients in the formulation of dosage forms, polymers are widely used in pharmacy. These polymers are of semi-synthetic or synthetic origin. They are used because of their ability to confer various original functionalities, which can be finely tuned and cannot be achieved using other excipients. It should be noted that, except for parenteral delivery, degradability is not a major concern for most of

these applications. Because of the breadth of the subject, only some examples of applications are given here.

Excipients for tableting

Formulation of tablets requires the use of various excipients in order to confer a series of functionalities to these conventional dosage forms. A few polymers are currently used as excipients for tablets in various purposes. Cellulose and starch, which can be considered as natural excipients, can be used as diluents when the drug content is low. When tablets have to be prepared by the wet-granulation technique, the addition of a binder is used to agglutinate the powder particles and form grains that are more easily compressed and form strong enough tablets. Common binders include starch used in the form of starch paste, and cellulosic ethers such as carboxymethylcellulose (CMC) and hydroxypropylcellulose (HPC). Alternatively, poly(vinylpyrrolidone) (PVP) (Figure 4.16) in the proportion of a few per cent of the final preparation can be used as a binder.

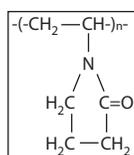


Figure 4.16 Repeating unit of poly(*N*-vinyl-2 pyrrolidone).

A series of linear homopolymers of vinylpyrrolidone synthetically produced by free radical polymerisation are commercially available. These products have a mean molecular weight ranging from 4000 g/mol to about 1 300 000 g/mol. As this is the case for many commercial brands, these values are only averages and their polydispersity may be rather large. PVP is freely soluble in water and in many solvents, including ethanol, making it an interesting excipient not only as a binder but also in various applications, including as a film-forming material, a thickener and an adhesive agent.

Because conventional tablets need to be rapidly disintegrated in water or gastric fluids in order to allow drug dissolution and absorption, it is generally necessary to add a disintegrating agent in the formulation. Pre-gelatinised starch or chemically modified starch, such as sodium starch glycolate (Figure 4.17) can be used for this purpose. The latter semi-synthetic polymer is called a 'super-disintegrant' owing to its capacity to induce fast tablet disintegration when used at levels as low as 2%. Sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch; the molecular weight of commercial brands typically ranges from 500 000 g/mol to 11 000 000 g/mol. It is insoluble in water and most solvents.

Alternatively, purely synthetic polymers such as cross-linked homopolymers of *N*-vinyl-2 pyrrolidone are commercialised under the trade name

Hydrophilic polymers for matrices formulation

Matrix systems provide controlled release of the drug via diffusion or erosion mechanisms. Insoluble polymers such as polyethylene or poly(alkylmethacrylates) can be used. In such cases, matrices are formed by tableting or hot melt extrusion processes, in which the drug to be released is generally dispersed as a powder. Because of the inertness of these matrices in contact with gastrointestinal fluids, drug release is governed mainly by diffusion, while the matrices remain almost intact during intestinal transit. However, much more commonly, controlled release is achieved by using water-soluble polymers that encapsulate the active ingredient in specific patterns (e.g. layers, cores, three-dimensional structures). The release of the active ingredient over time can be controlled mainly by diffusion. Typically, the matrix is swollen by water, which then dissolves the solid-state drug contained in the matrix, resulting in a further progressive diffusion through the swollen network. Alternatively, polymer can be dissolved in the gastrointestinal tract, leading to progressive erosion of the matrix and progressive release of the active ingredient. The rate of release can be adjusted by mixing or layering hydrophilic polymers with varying swelling/dissolution kinetics and by the use of innovative fabrication designs.

For common applications, polymers for controlling oral delivery are non-absorbable due to their high molecular weight and their hydrophilicity, making useless the use of degradable polymers from a toxicological standpoint. Thus, cellulose derivatives or hydrophilic gums are commonly used, especially methylcellulose (MC) (Figure 4.20) and hydroxypropylmethylcellulose (HPMC) (Figure 4.21).

Cellulose ethers have the polymeric backbone of cellulose, a natural carbohydrate that contains a basic repeating structure of anhydroglucose units. During the manufacture of cellulose ethers, cellulose fibres are treated with caustic solution, which in turn is treated with methyl chloride or propylene oxide. The chemical reaction yields a fibrous product, which is purified and ground to a fine powder. Commercial grades vary chemically and physically for matching the desired applicative properties.

The major chemical differences are in the degree of methyl substitution, hydroxypropyl substitution and polymerisation of the cellulosic backbone.

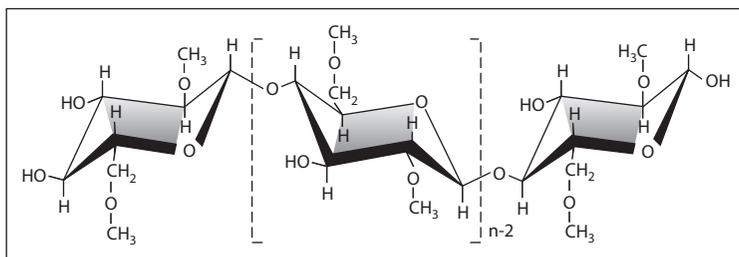


Figure 4.20 General structure of methylcellulose.

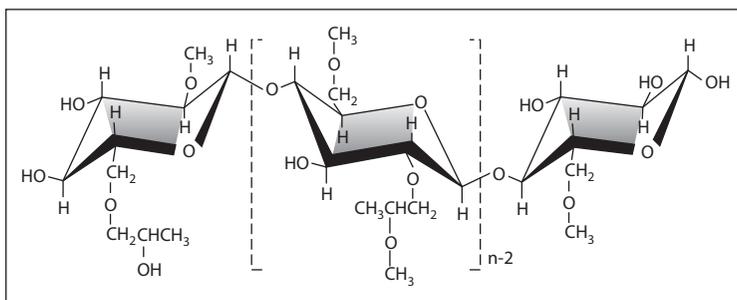


Figure 4.21 General structure of hydroxypropyl methylcellulose.

Although the molecular weights and polydispersity of these products can be determined, e.g. by intrinsic viscosity determinations, these data are generally unknown and commercial grades are characterised indirectly by the viscosities of 2% solutions of the polymer in water. These products possess varying ratios of hydroxypropyl and methyl substitution, a factor that influences properties such as organic solubility and the thermal gelation temperature of aqueous solutions. As an example, the percentages of methyl groups and hydroxypropyl groups in the K HPMC grades commonly used for matrices formulation are 19–24% and 7–12%, respectively. For more detailed information, the reader is referred to the technical bulletins of the commercial producers.

Apart from these widely used products, other cellulosic ethers such as HPC, hydroxyethylcellulose and CMC are often used in the formulation of controlled pharmaceutical delivery systems.

Controlled release in specific regions of the gastrointestinal tract

Specific polymers have been designed to release drugs into specific regions of the gastrointestinal tract. For this purpose, methacrylic polymers with pH-dependent solubility have been used widely. As described above, commercial-grade polymers characterised by their solubility at different pH can be used to adjust the level of delivery in the intestine. Further, azopolymers have been developed to target the colon, which is of great interest for the local treatment of inflammatory diseases and colitis. An example of azopolymer is presented in Figure 4.22.

The diazoic bond is stable in the gastrointestinal fluids, except in the colonic environment because of the presence of colonic bacterial flora, which produce enzymes able to cleave such bonds. Such polymers can be used to form matrices or coatings that are progressively eroded, allowing localised release of the drug.

Bioadhesive polymers for mucosal delivery

Following administration, bioadhesive dosage forms are intended to adhere at the surface of a mucosa, either to prolong the duration of activity of a drug locally or to enhance the permeation of the drug and thus enhance its systemic

high specificity of the coupling reaction. The PEG chains are positioned exactly on the O-glycosylation site of the protein. This method of grafting was applied for PEGylation of three clinically used proteins – granulocyte colony-stimulating factor (G-CSF), interferon alpha2b (INF- α 2b), and granulocyte/macrophage colony-stimulating factor (GM-CSF).

In recent years, another enzymatic mediated modification was applied with success to bind PEG on proteins of clinical interest. The enzyme, a transglutaminase, allowed the transfer of an amino derivative of PEG, PEG-NH₂, on a glutamine residue of the protein located in a flexible or unfolded region of the peptidic chain. Specificity of the enzyme was high and led to a very high degree of specificity for the PEGylation of the protein. This method of protein PEGylation has already been used successfully to produce several PEGylated proteins of clinical interest, including human growth hormone and interleukin 2. A promising development for the PEGylation of therapeutic peptides and proteins is expected in the future. Indeed, recent work has opened up the possibility of predicting sites of transglutaminase-mediated PEGylation of therapeutic proteins. This discovery has paved the road towards predicting the possible effects caused by the modification of the physicochemical and functional properties of the protein and will be very useful in the design of proper strategies for the modification of proteins.

Polymeric nanoparticles for drug delivery

Nanoparticles, i.e. particles with a size usually in the range 50–1000 nm, have drawn the attention of researchers designing drug-delivery systems that can be injected intravenously owing to their small size. Nanoparticle is a general name for nanospheres and nanocapsules. Nanospheres have a matrix-type structure, whereas nanocapsules are hollow and have a liquid core surrounded by a polymeric wall, as illustrated in Figure 4.34.

Several methods have been developed for preparing nanoparticles. They can be classified into two main categories according to whether the formation of nanoparticles occurs during a polymerisation reaction or whether it is achieved directly from already prepared macromolecules.

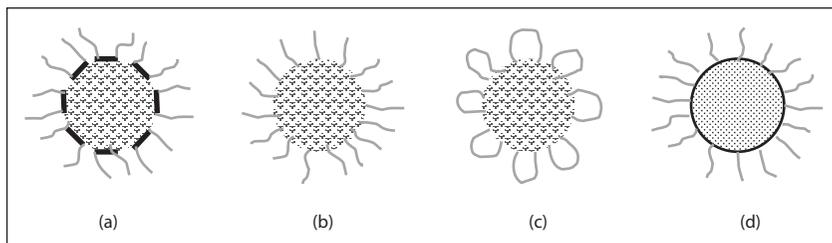


Figure 4.34 Different types of nanoparticle: (a) nanosphere stabilised by an adsorbed non-ionic surfactant; (b) core-shell nanosphere with a brush shell structure; (c) core-shell nanosphere with a loop shell structure; (d) core-shell nanocapsule with a brush shell structure.

hydrophilic shell. Sugars are present on the surface of cells and are involved in many surface properties of the cells. Therefore, biomimetic strategies could be developed that take advantage of the presence of polysaccharides on the surface of the nanoparticles. A few polysaccharides are already administered to humans, for instance dextran and heparin. Heparin is well known for its anticoagulant activity and has been shown to act as a physiological inhibitor of complement activation. In order to mimic the behaviour of cells and pathogens that normally escape recognition by complement and phagocytes, block copolymers of heparin and poly(methylmethacrylate) or PACA have been produced and heparin-coated nanospheres have been prepared. These nanospheres have been shown to be non-activators of complement *in vitro*. *In vivo*, after intravenous administration to mice, these nanospheres could remain in the bloodstream and show long circulating properties. In addition, it has been shown that the conformation of the polysaccharide chains grafted on the nanosphere surface could play a very important role in defining the fate of the colloidal particle after intravenous administration. Indeed, a long enough dextran bound to nanospheres by one end, i.e. in brush conformation (Figure 4.34b), has been shown to be as low an activator of complement as soluble dextran, whereas the same dextran bound by several bonds, i.e. in loops and train conformation (Figure 4.34c), is as strong an activator as cross-linked dextran, i.e. Sephadex. Block copolymers obtained from other polysaccharides and PACA could be obtained in brush conformation. Provided that the polysaccharide chains are long enough, they could be low activators of complement and have been developed for purposes in which at least long-circulating properties are required.

Core-shell nanoparticles with a heparin and/or dextran shell in brush conformation have been shown to be able to carry functional haemoglobin and to protect it from degradation. Similarly, core-shell nanoparticles with a chitosan shell in brush conformation have been shown able to carry siRNA active against cancer in a mice model after intravenous administration.

4.4.7 Safety and recognition of new polymers as excipients

Pharmaceutical excipients have a vital role in drug formulations. However, the development of new excipients is often neglected because of a lack of mechanisms to assess the safety of excipients outside a new drug application process. Existing regulations and guidelines state that new excipients should be treated as new chemical entities with full toxicological evaluation. Therefore, successful development of new polymeric excipients depends on obtaining appropriate toxicological data on the safety and biocompatibility of such excipients. There exist specific relevant guidelines for specific delivery systems, such as implant applications, which have been developed by the United States Pharmacopoeia (USP) for testing of the polymer safety and

tissue irritability. One example of such a test is the USP Biological Reactivity Test, *in vivo*, which includes the systemic injection test, the intracutaneous test and the implantation test. Such guidelines may be of relevance when developing a polymer excipient for parenteral controlled-release applications. Other guidelines from the European Medicines Evaluation Agency (EMEA) and the FDA describe the type of data package required in the preclinical development of a new excipient.

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