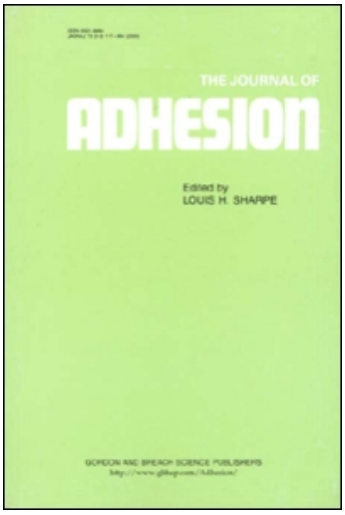

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On Surface Modification of Polymeric Biomaterials*

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Surface modification with hydrophilic polymers has been beneficial in improving blood compatibility of biomaterials. Formation of dense and tightly-bonded surface layers may prevent plasma protein adsorption owing to steric repulsion. General conditions for formation of layers, protecting blood components from direct contacts with the surface, are discussed. It seems to be necessary to ensure a delicate balance between adsorption energy of the attached chains and their length. The crucial point is to get a high grafting density which is more influential than high chain length. Length should be calibrated to the size of protein molecules to meet both effective repulsion and high density of the protecting chains and to avoid chain displacement by plasma proteins.

Keywords: Grafting density; steric repulsion; hydrophobic interaction; biocompatibility; protein adsorption; poly(ethylene oxide); triblock copolymer

INTRODUCTION

A broad variety of materials is used for biomedical applications. Among them, polymers and polymer composites turn out to be the most attractive class owing to several advantages they have: Versatility, physical and chemical properties, which can be tailored in wide limits, easy processability into various shapes or structures and potential for surface modification. However, these biomedical materials must meet several requirements, even contradictory ones, in addition, to fulfill

*One of a Collection of papers honoring Yuri S. Lipatov on the occasion of his 70th birthday, 10 July 1997.

necessary functionalities. In Table I a few of these requirements are summarized [1].

A tremendous number of high performance biomedical polymers has been developed in recent years. However, development of materials which fulfill medical requirements turns out to be a truly interdisciplinary challenge involving, apart from medicine, different branches of chemistry, biochemistry, and technology. Exchange of experience between these branches seems to be necessary for succeeding in design of effectively operating biomaterials.

The last term, mentioned in the table of requirements, is "biocompatibility". As far as the authors are aware, there is no generally accepted definition of this term, although everybody dealing with the subject agrees that biocompatibility is necessitated for biomaterials. Here, only one aspect of this quite general topic will be discussed. When a biomedical material comes into contact with a living body, two classes of reactions will occur: Material and biological responses. The material properties will be changed in the course of time under influence of biological active media leading to partial dissolution, even failure, of the material while the living system reacts with an immune reaction. Only the latter topic will be discussed here, not from a medical point of view due to matters of incompetence, but from a physico-chemical point of view which, hopefully, can elucidate a few aspects of this highly complex matter and even provide new insights.

BLOOD COMPATIBILITY

Again, we stick to a not quite well defined term and we do not intend to give a precise definition. Nevertheless, the phenomenon behind this

TABLE I Minimum requirements for biomaterials

Non-toxigenic	non-tumorigenic non-allergenic
Functionality	internal organ support organ replacement drug delivery
Sterilizability	radiation, dry heating
Biocompatibility	

vague term is obvious. The long-term use of polymeric biomaterials in blood is limited by surface-induced thrombosis and biomaterial-associated infections [2, 3]. According to recent results, thrombus formation on biomaterial surfaces is initiated by plasma protein adsorption, especially fibrinogen, followed by adhesion and activation of platelets [4, 5], while biomaterial-related infections are caused by adhesion of bacteria onto the surface [6]. It seems to be that the detailed reactions of the living host to the biomaterial surface are not very well known. However, more generally, it may be indisputable that the contact of a biomaterial surface and molecular and cellular constituents of the living system causes molecular reactions of the latter. It is agreed that initially bioactive proteins, predominantly plasma proteins, are adsorbed leading ultimately to cell adsorption. Accordingly, surfaces of biomaterials should be inert to any protein adsorption to minimize, or even prevent, adverse reactions of the living system. Now, agreeing on that as a key problem, we enter the fascinating realm of colloid stability to which Yuri S. Lipatov so significantly contributed [7]. But, before doing so, let us summarize a few facts on human blood relevant for the following discussion. Blood consists of about 90% water and a complex mixture of proteins having a variety of functions in a living system. Proteins of blood plasma can be separated into four major groups: Albumin, globulins, lipoproteins, and fibrinogen. Features of these proteins are listed in Table II. Approximately, one may say, proteins are globular molecules of a size ranging from 10 to 50 nm.

STERIC REPULSION AND BIOCOMPATIBILITY

Many studies have been reported to delineate the mechanism of protein adsorption on surfaces. Electrically-charged surfaces should reduce protein adsorption owing to Coulomb repulsion. However, a positive entropy of adsorption, caused by interfacial unfolding of the protein, often leads to adsorption inspite of repulsion [9]. In addition, there exist differently-charged proteins mixed in living plasma. Hence, coverage of the surface with neutral, water-soluble polymers is considered as a promising approach to reject adsorption of proteins [10–12]. In fact, this is a problem closely related to steric stabilization of colloids [13]. Let us have a quick glance on essentials of steric stabilization.

TABLE II Dimensions, molecular mass, and shape of proteins (after Ref. 8)

Protein	*Shape*	*Dimension nm*	*Molecular mass*
Albumin	ellipsoid	axes: 15, 5	69,000
Haemoglobin	platelets	5	64,450
β_1-Globulin	strongly oblated ellipsoid	axes: 20, 3	90,000
γ-Globulin	as before	axes: 25, 5	156,000
α_1-Lipoprotein	as before	axes: 30, 5	200,000
β_1-Lipoprotein	sphere	20	1,300,000
Fibrinogen	rod	axes: 45, 9	340,000

We start with a simple problem which is illuminating for the whole business. Assume a polymer coil of dimension $\boldsymbol{R}$ is squeezed in the gap of width $\boldsymbol{h}$ between two plates (Fig. 1). If $\boldsymbol{h} > \boldsymbol{R}$ nothing will happen. However for $\boldsymbol{h} < \boldsymbol{R}$, the free energy of the deformed chain is increased because its number of conformations is decreased relative to the free chain in the same solvent. What we know is that the change in free energy must be extensive in the degree of polymerization, N:

$$\Delta f \sim N \tag{1}$$

The only relevant length scales are $\boldsymbol{R}$ and $\boldsymbol{h}$. Hence, we may say that the increase in free energy can be written in the form

$$\Delta f = kTg(x) \text{ with } x \equiv \frac{R}{h} \tag{2}$$

where g is some unknown function of $\boldsymbol{x}$. Moreover, $R \sim N^{\nu}$ which requires $g \sim x^{1/\nu}$ to fulfill Eq. (1). For ideal chains $\nu = 1/2$, and it follows

$$\Delta f \sim kT\left(\frac{R}{h}\right)^2 \text{ or } p \sim \frac{1}{h^3} \tag{3}$$

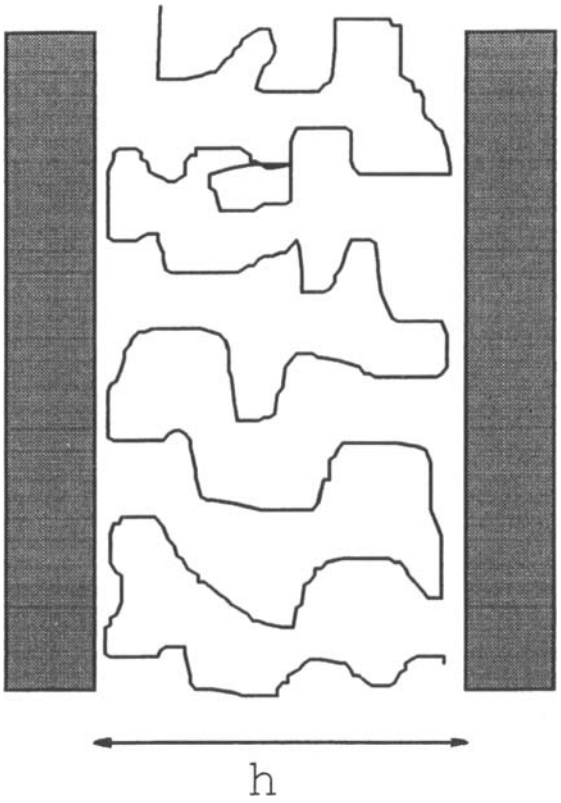

FIGURE 1 Polymer coil of dimension, R, in a gap of width, h.

where p is the disjoining pressure. In conclusion, the large polymeric length scale leads to an effective repulsion force between the surfaces which is in range comparable with R. This is the key to steric stabilization of colloids.

Now, we look at a surface covered with polymer chains and in contact with a solution (Fig. 2). The attaching groups are called anchors and the free or non-adsorbing polymer chains are referred to as buoys. Again, we have two length scales, the mean spacing between anchor points, d, and the thickness of the grafted layer, L. In a zeroth approximation, the following conditions must be satisfied to prevent adsorption of a foreign particle:

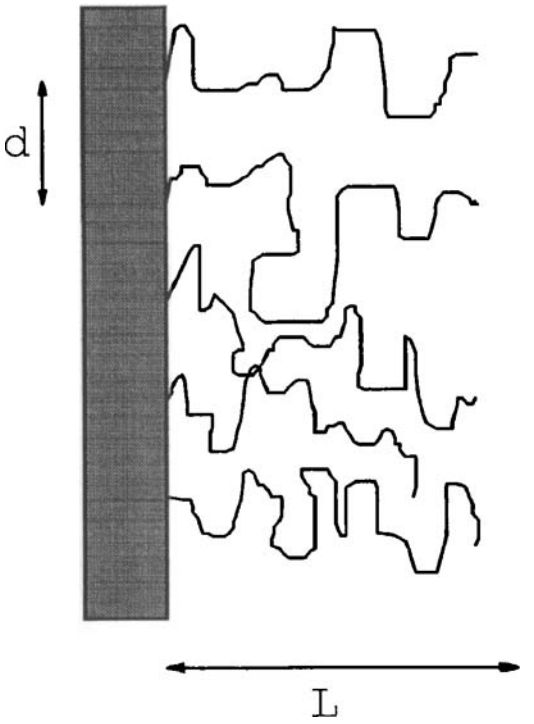

FIGURE 2 Surface covered with polymer chains. L is the thickness of the layer and d the spacing between grafting points.

i) The solvent should be good for the polymer so that effective polymer-polymer interactions are repulsive. For surface-modification of biomaterials that means only water-soluble polymers can be used.
ii) Polymer should strongly adsorb onto the surface and "saturate" surface sites to block sites for adsorption.

We will see that the second requirement cannot be fulfilled satisfactorily, which causes obviously bioincompatibility to a large extent. It should be noted that the layer thickness, L, of terminally-attached chains to the surface is generally greater than that of adsorbed homopolymers [14]. Here, we assume that the polymer comprises a number of anchor groups that stick to the surface.

Let us assume, for a moment, a fixed spacing, d, which is also equivalent to strong anchoring or the brush case depicted in Figure 2.

The thickness, L, of a grafted layer in a good solvent is then determined by a balance of an attractive energy of adsorption and a loss of entropy, where the latter is given by the swelling tendency of the chains associated with the positive osmotic pressure and the polymer elasticity which resists chain extension. This balance leads to [15]

$$L \sim Na\left(\frac{a}{d}\right)^{2/3} \tag{4}$$

(a being the length of a segment).
There are two obvious conclusions:

i) Linear dependence on N indicates stretching of the chains.
ii) As the density of grafting increases (d decreases), the polymers become increasingly extended.

It follows that the establishment of $d \ll L$, necessary for biocompatibility, turns out to be complicated. Now, the total free energy per chain molecule consists of three terms: The stretching energy, excluded volume interactions and the adsorption or sticking energy. Using L of Eq. (4), the free energy of the layer with the surface density $(a/d)^2$ can be approximated by

$$\frac{\Delta F}{kT} \cong \left[-N_s u a^2 + \frac{L}{d} \right] \left(\frac{a}{d}\right)^2 = -N_s u a^2 \left(\frac{a}{d}\right)^2 + N\left(\frac{a}{d}\right)^{(11/3)} \tag{5}$$

where u is the sticking energy per kT and unit area and N_s is the number of anchor groups in the chain. Expression (5) can be minimized for further optimization with respect to the spacing, d. It results that:

$$\frac{d}{a} \cong \frac{1}{x^{3/5}} \quad \text{and} \quad \frac{L}{a} \cong N x^{2/5} \quad \text{with} \quad x \equiv N_s \frac{u a^2}{N} \tag{6}$$

These functions are plotted *versus* x in Figure 3. For $u = const.$, x decreases with increasing N and L approaches d. If d exceeds L, we do not have the brush case anymore and Eqs. (4) to (6) are not longer valid. This is indicated in Figure 3 only for the highest value of N.

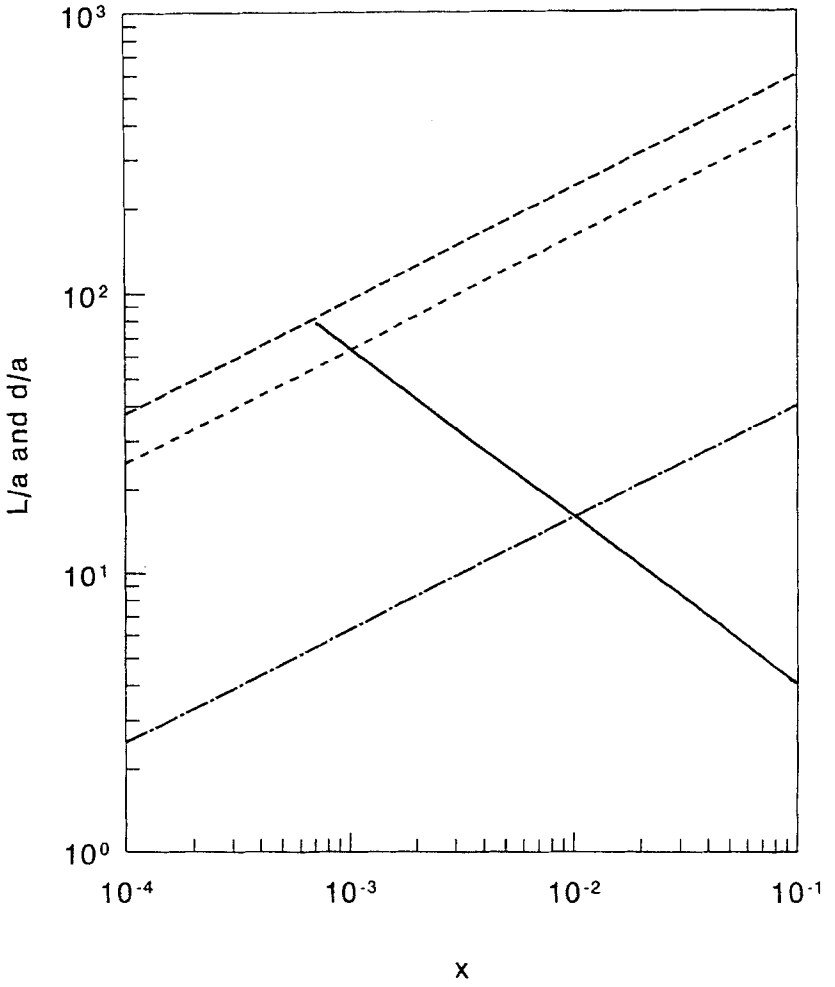

FIGURE 3 Characteristic length *versus* x.
The solid line (—) refers to d/a. The broken curves reflect L/a for:
$N = 1500$ (– –), $N = 1000$ (- - -), and $N = 100$ (- · -).

Now, when a foreign particle approaches to a distance $h \leqslant L$, the segmental concentration in the layer increases, which leads to a disjoining pressure, π. This pressure is given by the second virial coefficient, $\pi = kTa^3(c^2/2)$ where $c = (N/d^2h)$. Hence, if follows with Eq. (4) for $h \ll L$

$$\pi \cong kT\left(\frac{L}{h}\right)^2 \frac{1}{(ad^8)^{1/3}} \tag{7}$$

which should provide a sufficient barrier to prevent adsorption of the foreign particle *via* attractive van der Waals forces between proteins and plastic substrate across the attached layer. The disjoining pressure due to nonretarded van der Waals forces is given by $\pi_d = |A|/6\pi h^3$ with A as the Hamaker constant (order of magnitude, $A = 10^{-20}$ J). Adopting the relevant lengths for a, d and h of 0.5, 5 and 10 nm, respectively, the ratio of π_d and π of Eq. (7) is in the order of 10^{-4}. Hence, the van der Waals attraction between substrate and protein across the layer of attached chain molecules is negligible compared with the steric repulsion associated with the compression of the layer.

Eq. (7) shows that steric repulsion starts at longer distances, h, if N increases at $d = const.$ or *vice versa* if d decreases at $N = const.$ However, decrease in d has a more pronounced effect on steric repulsion than variation of chain length.

According to Eq. (6), $L > d$ requires $x > 10^{-3}$ ($N = 10^3$). To prevent adsorption of protein molecules, we need $d < 2$ nm. This results in $x > 0.1$. If one assumes an adsorption energy of 10 kJ/mol and an adsorption density of 10^{14} per cm^2, one gets $x \sim 10^{-2}$ (with $N = 10^3$, $N_S = 10$ and $a = 0.5$ nm). Hence, physical adsorption may not meet the requirements necessary for prevention of protein adsorption. Only chemical termination can provide sufficiently large values of the control parameter x.

Reduction of N, *i.e.* adsorption of shorter chains, would also enhance the parameter x. However, this can be done only to a certain extent, owing to Eqs. (1) or (7), since decrease in N results in decrease of the repulsion or steric stabilization of the surface.

The situation becomes even more disadvantageous if there exists a hydrophobic attraction between the hydrophobic substrate and the protein molecule. These attractive forces are stronger than the van der Waals forces when the hydrophobic surfaces approach to distances below 20 nm [16].

Disjoining pressure, π, is related to free energy by

$$\pi = c^2 \frac{\partial}{\partial c}\left(\frac{F}{c}\right).$$

Starting from Eq. (7), the steric repulsion free energy per unit area can be approximated by

$$\frac{\Delta F_s}{kT} \cong \frac{x^{8/5}}{a^2}\left[\left(\frac{L}{h}\right)^2 - 1\right] \tag{8}$$

since it disappears for $h = L$. The quantities x and L are given by Eq. (6). For hydrophobic interaction, we adopted the free energy function per unit area (nm^2) determined experimentally in Ref. 16 for dihexadecyldimethylammonium acetate monolayer surfaces

$$\frac{\Delta F_h}{kT} = -14e^{-h/1.4} \tag{9}$$

where h is the distance between surface and protein in nm. Combination of Eqs. (8) and (9) results in potential energy curves depicted in Figure 4 for $N = 10^3$ and $a = 0.5$ nm. At sufficiently high values of parameter x, which corresponds to low spacing d or high surface density of attached chains, the surface exhibits repulsion. As x decreases, strong attraction occurs below approximately 10 nm even when the equilibrium layer thickness exceeds this distance. Again, optimization of spacing and chain length must be considered under this condition to prevent protein adsorption.

We have to add here that hydrophobic interaction between surface and protein is certainly exaggerated in adopting Eq. (9). Hydrophobic interaction depends on the size of the protein molecule or its hydrophobic area. Expression (9), however, refers to an infinitely-extended protein molecule which does not meet reality. Nevertheless, steric repulsion and hydrophobic attraction may compete at sufficiently low distances and lead to protein adsorption. It seems to be even true in the presence of a hydrophilic layer of attached chain molecules. There is experimental evidence that an increase in volume fraction of poly(ethylene oxide) (PEO), due to protein approach, causes an increased hydrophobicity of PEO [17].

In principle, the same results as before ensue, if one coats the surface of the biomaterial with a diblock copolymer comprising hydrophobic and hydrophylic blocks of lengths N_A and N_B, respectively.

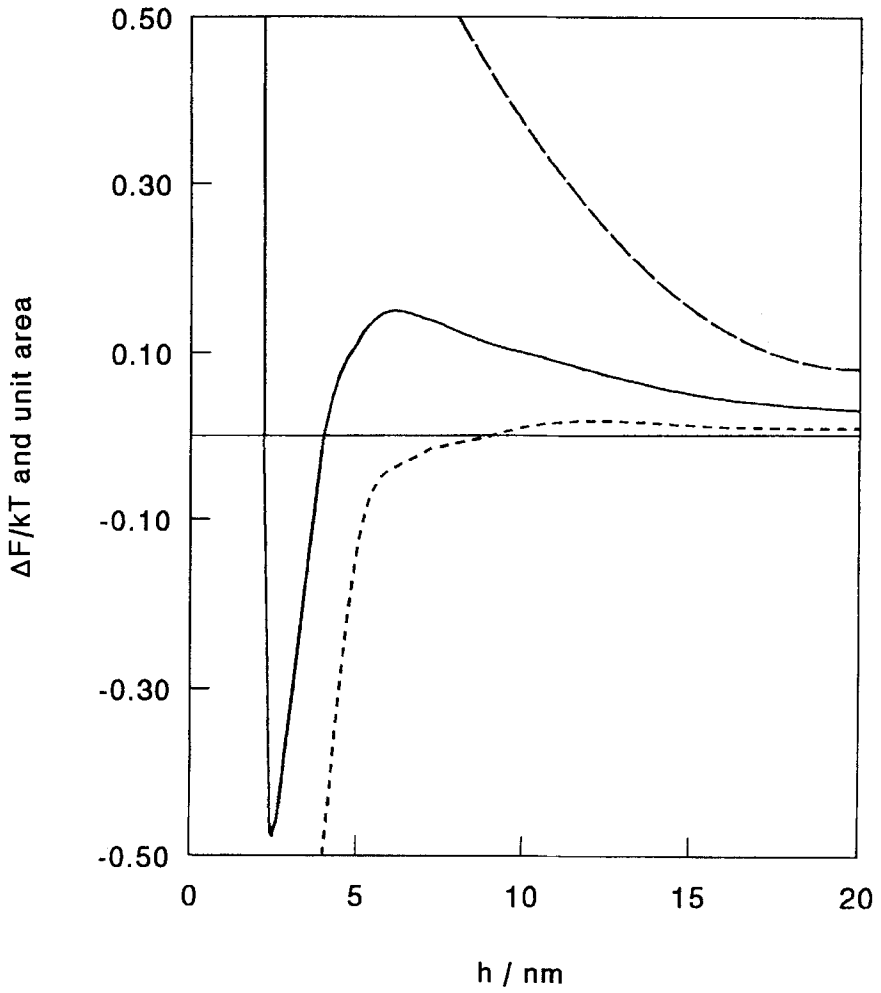

FIGURE 4 Free energy per unit area of steric repulsion and hydrophobic attraction according to Eqs. (8) and (9) for different values of x:
$x = 4.5 \cdot 10^{-3}$(---), $x = 9 \cdot 10^{-3}$ (——), $x = 14 \cdot 10^{-3}$(— —) which corresponds to $L = 55$, 75 and 90 nm, respectively.

Then, quite naturally, N in Eq. (4) has to be replaced by N_B. Furthermore, the equilibrium thickness of layer A may be given by

$$\tau = \frac{N_A a^3}{d^2}.$$

Finally, one arrives at

$$\frac{d}{a} \cong \frac{1}{\sqrt{y}} \text{ and } \frac{L}{a} \cong N_B y^{1/3} \text{ with } y \equiv \frac{\tau}{N_A a} \tag{6'}$$

The exponents are slightly modified, but the qualitative results still obtain. However, the requirements to prevent protein adsorption seem to be easier to meet than before. For $d < 5\,\text{nm}$, $y > 0.01$ is needed which can be fulfilled for $\tau > 5\,\text{nm}$.

DISCUSSION AND CONCLUSIONS

Results discussed before are confirmed experimentally. Surfaces rich in poly(ethylene oxide) (PEO) were prepared by physical adsorption of the polymer [18]. Only high molecular weight PEO homopolymers were used ($N > 2000$; this corresponds to x in the order of 10^{-2} according to Eq. (6)); however, the effect on biocompatibility has been reported to be modest. In contrast, covalent grafting of PEO to surfaces turned out to be very effective. Polyurethanes with PEO-grafted side chains were found to be highly blood compatible [19, 20]. Plasma protein adsorption was significantly decreased when PEO-monoacid ($N \approx 200$) was grafted to cellulose membranes [12]. About a 50% decrease in plasma protein adsorption and more than a 90% decrease in platelet adsorption was observed on PEO-grafted poly(ethylene terephthalate) surfaces ($N \approx 400$) [21]. Clinical application of PEO-grafted ($N \approx 100$) PVC tubes showed reduced potential for thrombogenicity compared with control PVC tubes [22].

To our knowledge, no detailed studies on coating of surfaces with diblock copolymers have been reported, as yet. A promising approach seems to be application of triblock copolymers, PEO-X-PEO, where X represents a hydrophobic block sticking on the surface [23]. Adsorption strength of the block copolymer can be controlled by the length of block X. For X = poly(propylene oxide) (PPO), it was found that albumin could easily displace the block with $N_{\text{PPO}} = 30$ while not with $N_{\text{PPO}} = 56$ and the triblock copolymer having two tails with $N_{\text{PEO}} = 129$ effectively reduced the adsorption of plasma proteins onto styrene particles [24].

Several attempts have been made to utilize poly(vinyl alcohol) (PVA) as biomedical material [25–29]. However, one has to recognize the fact that PVA is a crystallizable polymer. Crystallinity is favourable for mechanical responses but results also in significant interactions with blood components. Obviously, there is a delicate balance for formation of bulk crystal morphology, needed for mechanical stability and insolubility, and an amorphous surface layer which is necessary for water solubility and formation of a diffuse layer comprising tethered molecules which extrude from the surface into the outer aqueous solution. Annealing of PVA in presence of glycerol results obviously in a diffuse surface layer which protected blood components from direct contact with the surface [30].

In conclusion, for effective blood compatibility water-soluble chain molecules must be densely and tightly bonded to the material surface. The attached chains should possess a degree of polymerization, N, high enough to ensure repulsion of proteins, but as low as possible to avoid replacement by foreign molecules and to ensure high adsorption or grafting density (low spacing d) of attached chains. High grafting density turns out to be more important than high chain length, as Eq. (7) shows. The polymer molecular weight should be calibrated to the size of protein molecule under this condition. The higher the bonding energy to the surface of the biomaterial the longer the chains that can be used for layer formation. To meet these conditions, it seems that grafting techniques have to be improved. Block copolymers, especially triblock copolymers satisfying the above mentioned conditions, should be useful in development of biocompatible polymeric materials.

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