精细高分子化学学术论文报告会

预印集

1986年12月1－5日

中国　　广州

中国化学会高分子委员会

精细高分子化学学术论文报告会筹委会

SYMPOSIUM ON FINE POLYMERS

PREPRINTS

Guangzhou, China
December 1—5, 1986

Organizing Committee
of
the Fine Polymer's Symposium
Polymer Division of the Chinese Chemical Society

Organizing Committee
of
the Fine Polymer's Symposium
Polymer Division of the Chinese Chemical Society

Chairmen:

冯新德 FENG Xinde, 何炳林 HE Binglin

Members:

邹 翰 ZHOU Han, 王有槐 WANG Yuhuai,
孙树门 SUN Shumen, 丘坤元 QIU Kunyuan,
江英彦 JIANG Yingyan, 吴世康 WU Shikang,
黄志镗 HUANG Zhitang, 焦书科 JIAO Shuke,
曹 镛 CAO Yong, 周其庠 ZHOU Qixiang,
周其凤 ZHOU Qifeng, 金仁华 JIN Renhua,
李预枝 LI Yuzhi, 王俊景 WANG Junjing
徐国凤 XU Guofeng.

I-1

"A Critical Review of Methods for Surface Modification and Characterization of Biomaterials and their Applications in Medicine and Industry"

By Prof. Allan S. Hoffman
Center for Bioengineering and
Department of Chemical Engineering, FL-20
Seattle, Washington 98195 U.S.A.

Part I: "A Critical Review of Methods for Surface Modification and Characterization of Biomaterials"

The two major methods which have been used for biomaterial surface modification are radiation grafting and gas discharge polymer deposition. These technologies will be compared and contrasted. Surface characterization of such modified biomaterials involves a number of methods, ranging from contact angles to SEM, EDXA-STEM, ATR-FTIR, and ESCA. These analytical methods will also be compared and contrasted. The lecture will finish with a review of correlations of biointeractions using surface characterization results, particularly utilizing to contact angle and ESCA measurements.

Part II: "Novel Biomaterials Based on Ionizing Radiation and Plasma Gas Discharge Technologies"

Both ionizing radiation and plasma gas discharge treatments may be used to chemically modify polymeric surfaces as well as to synthesize new polymer compositions. Such modifications may render a material more or less interactive with proteins and cells.

The treatments may also be applied for immobilization of biologically active molecules such as enzymes, antibodies, drugs, and antithrombogenic agents. There are many therapeutic, diagnostic, and bioseparation applications of these process technologies. This talk will cover a number of well known as well as new processes utilizing this free radical based technology for biomaterial development.

I-2

INTERRELATIONSHIP BETWEEN POLYMER SURFACES AND BLOOD ARTIFACT OR REAL

S. A. Barenberg
(E. I. du Pont, Wilmington, DE 19898)

The interfacial interrelationship between the surface chemistries and physics of materials and the biological milieu exists in a dynamic non-steady state. The questions which need to be addressed, are how does the interphase and the interface change as a function of time and the microenvironment and concurrently how does this dynamic interface affect the biological microenvironment. To date, a number of studies have presented evidence as to (1) What the effects of a hydrophobic/hydrophilic surface has on the biological response, but neglected the concepts of bound water and bridged water, (2) The effects of microdomains (block copolymers, polyurethanes) on the biological response, but have not taken into account the true-surface morphologies and/or how these morphologies may be altered as a function of hydration, liquid uptake or molecular motions of the chains, (3) The effects of side chain length and specific chemistry, but do not take into account the intercalation of ions, electrolytes, oligomers, etc. Further the majority of surface characterization has been done under nonphysiological conditions (dehydrated, high vacuum/the vacuum). The primary characterization techniques being employed electron microscopy, ESCA, IR, etc..

However, with time, the above are beginning to be addressed. It is therefore, the intent of this paper to address the artifacts, the current state-of-the-art, and the new results which are beginning to afford us a new insight into the polymer surface/biological milieu microenvironment.

I-3

Applications of Polylactides to Surgery

Yoshito Ikada and Suong-Hyu Hyon
Research Center for Medical Polymers and Biomaterials
Kyoto University
53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606, Japan

Recently a variety of polymeric materials have been utilized for replacement and reconstruction of defective organs and tissues in surgery. They are divided into two groups; non-bioabsorbable and bioabsorbable materials. Most of the artificial organs are constructed with the non-bioabsorbable materials, whereas the bioabsorbable materials are preferable in case that the damaged organ and tissue are self-repairable. The reason for the necessity of biomaterials even for such self-repairable organs is to help the healing of organs, for instance, by maintaining them at a most desired position in the body or by providing a scaffold for cell ingrowth until the healing is completed. The assist material should be bioabsorbed as quickly as possible once the organs are healed, since the remaining material would give adverse effects to the surrounding tissues.

The bioabsorbable polymer we have selected is polylactides. This is because they are readily molded into products of different shapes with relatively high mechanical strengths and the rate of bioabsorption can be altered over a wide range by changing the molecular weight and the composition of the copolymers.

Some examples of the surgical applications of polylactides will be presented from our recent works below. Most of them are currently in the stage of animal experiments.

1. Fibers

As is well known, the polylactide that is most commonly used in clinics is polyglycolide(PGA), which is applied as suture. The tensile strength of the PGA suture decreases to half of the original value upon implantation for about two weeks and about three months is required for complete disappearance of the mass when it is subcutaneously implanted. In an attempt to obtain a fiber with a much lower bioabsorption rate, we carried out melt-spinning of poly-L-lactide with $\bar{M}w$ of 3.6×10^5. When the melt spinning was performed at 200°C and the fiber drawing and annealing were done at 160 °C, a fiber was obtained which had the tensile strength of 70 $kg \cdot mm^{-2}$. This fiber exhibited no significant degradation in phosphate buffer saline(PBS) at 37 °C up to six months. When implanted in the dorsal muscle of rabbit, the poly-L-lactide fiber showed a

detectable decrease in tensile strength after the 5th month implantation and 20 % decrease at 9th month implantation, but no weight loss was observed.

A hemostatic effect of a PGA fiber was compared with that of commercially-available oxycellulose (Oxycel TM) by applying it to the incised liver of rabbit. The oxycellulose fiber stopped bleeding more quickly than the PGA fiber, but the bioabsorption rate of the PGA fiber was higher than that of the oxycellulose.

2. Fabrics

A non-woven fabrics, prepared from our PGA fiber, was cut into a pledget of 3 x 8 mm^2 size and experimentally used for tracheal anastomosis of dogs. As a control was employed a Teflon pledget which is frequently applied for this operation. Results of the animal experiment showed that the Teflon pledget was encapsulated to result in scar formation or fell down in the tracheal lumen followed by granulation to the dog's death. On the other hand, neither falling-down of the pledget nor stenosis at the anastomotic site was observed for our bioabsorbable pledget. It was entirely absorbed at 3rd month postoperation.

Marlex meshes made of polyethylene have been widely used for the reconstruction of removed chest walls, but permanently remain even after regeneration of the new chest wall. In order to try to use a bioabsorbable support for the chest wall reconstruction, we have prepared a mesh from the PGA fiber by tricot braiding and implanted it in a dog. The implanted mesh was observed to be penetrated by tissues after 2 weeks and almost entirely replaced by newly-formed tissues after 2 months. No significant inflammatory reaction was observed for our bioabsorbable mesh, in contrast with the Marlex mesh.

3. Sheets

Postoperative adhesion of tissues sometimes causes severe problems. Therefore, several techniques have been attempted to prevent tissue adhesion, for instance, by applying viscous aqueous solutions of polymer to protect the tissue. Our method is to insert a bioabsorbable sheet between the tissues where adhesion will possibly take place. For this purpose, a soft, flexible sheet was prepared from a copolymer of D,L-lactide and ϵ-caprolactone. The caprolactone monomer was copolymerized so as to reduce the softening temperature of the sheet. The biodegradation rate of the sheet is important in addition to the flexibility. L-Lactide-caprolactone copolymers of 65:35 and 88:12 (by mole) showed 100 % weight loss after 20 and 24 weeks, respectively, when immersed in PBS at 37 °C. To examine the effectiveness of our bioabsorbable sheet *in vivo*, the pericardium

and the parietal pleura of the same dog was partially ablated and the bioabsorbable sheet with a size of $4 \times 8\,cm^2$ was fixed in between. Inspection at 3rd month post-operation revealed no inflammation and no symptom of adhesion of the surrounding tissues.

Also, a study was undertaken to examine the possibility of prevention of the scar formation after lumbar laminectomy by use of poly-D,L-lactide sheet containing elastase that would prevent the growth of collagen fibrils. Experiments on rabbits showed that the sheet containing elastase more effectively suppressed the scar formation than the sheet without elastase.

4. Rods

Materials currently used for fixation of fractured or cut ribs are metallic wires, plates or ceramic pins. All of them are not biodegradable. Rib fixation pins newly prepared in our laboratories are composed of poly-L-lactide and hydroxyapatite. The hydroxyapatite powder that is widely accepted to be bioactive was mixed with poly-L-lactide in order to improve the poor mechanical property of the polymer rod. Indeed, the tensile strength of the rod was increased by addition of the inorganic powder. Intramedullary implantation of this pin (20 mm length and 2 mm ϕ) containing hydroxyapatite by 10 wt% into a dog rib showed that the fractured ribs were satisfactorily healed without any significant slip and inflammation.

5. Plates

The plate-type implant that is most commonly used is perhaps the metallic bone plate. It has been pointed out that this metallic plate has two disadvantages; one is the requirement of re-operation to remove the implanted plate after reunion of the fractured bone and the other is the poor mechanical properties of the healed bone due to high modulus of the supporting metal implant compared with that of bones. Therefore, an attempt has been made by some research groups to overcome these drawbacks by using biodegradable bone plates from polymers but any clinically-applicable plate has not yet been developed because of low mechanical strength of the polymeric plates. We also are currently trying to develop a biodegradable bone plate from polylactides, but we are not yet successful to produce such a polymer plate that is high enough in mechanical strength. However, it should be noted that the biodegradable plates have some useful applications in osseous surgery even if their mechanical properties do not meet the demand as a fixation plate for big bones.

One of the examples is to use the bioabsorbable plate as a support for fractured thoraces. We have prepared H-type plates from poly-L-lactide and applied them for therapy of deformed thoraces with success. Another application is as a bone filler to replace cancellous bones where a high mechanical strength is not required but the bone filler should be replaced by newly formed host bone tissues. To this end a composite was prepared from polylactides and hydroxyapatite at different mixing ratios. For instance, a 1:1 composite from poly-L-lactide with $\bar{M}w$ of 7,200 and a hydroxyapatite powder with a size less than 90 μm had the impact strength of 1.5 $kg \cdot cm \cdot cm^{-1}$ and the compressive strength of 4 $kg \cdot mm^{-2}$. This compressive strength is lower than that of compact bones (14-17 $kg \cdot mm^{-2}$), but higher than that of vertebra (0.7-1.1 $kg \cdot mm^{-2}$).

6. Tubes

Bioabsorbable tubes of small size are useful as splints for non-suture or one-knot anastomosis of blood vessels and intestines. We have studied the above cases for the applicability of polylactide splints and obtained a very promising result. The splint we have most extensively investigated is to be used for the microvascular anastomosis. To apply for the one-knot anastomosis between the carotid artery and the jugular vein of rats, a tubular splint was prepared from D,L-lactide-glycolide (80:20) copolymer to have a size of 0.85-1.0 mm i.d., 1.0-1.2 mm o.d., and 2-3 mm length. When this was used as an external splint, the patency rate at the anastomotic site was found to be 100 % (33/33). The time required for the anastomosis was approximately 5 min and the time required for complete bioabsorption of the splint was 3 months.

J-1

THE INTERACTION OF POLYMERIC MATERIALS WITH BLOOD CONSTITUENTS AND CELLS

Prof.dr. A. Bantjes (Lab. of Materials and Biomaterials Technology, Twente University of Technology, Enschede, The Netherlands)

Introduction

Polymers are widely used in modern medicine for a wide variety of applications, varying from the membranes of the artificial kidney and the oxygenator to materials and devices for surgical reconstruction such as the artificial heart. With many of these applications there will be contact between the polymeric surface and blood. This generally leads to platelet adhesion and activation of the intrinsic clotting system and finally to the formation of bloodclots, red thrombi. Polymers which would eliminate this problem could open the way to new vascular prostheses and smaller blood treatment devices, useable over much longer periods than now which could be even implanted and used continuously.
Several approaches have been used towards this end:

a) The development of inert polymers, showing minimal or no interaction with blood constituents.
b) The development of polymers interacting specifically with the factors of the intrinsic clotting system (heparin-like polymers).
c) The development of polymer surfaces allowing the adhesion and overgrowth of human vascular endothelial cells.

Moreover, the specific interaction of polymers with blood constituents such as pathological or rare proteins can offer new therapeutic treatments or methods for the isolation of useful proteins or cells from the blood.

Blood-Polymer Interactions[22]

The first event taking place with polymer-blood contact is the adsorption of proteins from the blood onto the material surface. Protein adsorption phenomena are important for both the triggering of the intrinsic coagulation and for the adhesion of platelets. For instance surfaces to which fibrinogen or γ-globulin is adsorbed show a pronounced adhesion of platelets as compared with surfaces coated with albumin. In view of the kinetic and thermodynamic factors that govern the adsorption phenomena and in view of the pronounced time dependant competitive aspects of the adsorption of different proteins from blood it is necessary to study these effects with protein mixtures and preferably with bloodplasma or whole blood. This may be done with radioactively labeled protein mixtures[1] or with an enzyme immunoassay, utilizing specific antibodies for the detection of proteins adsorbed to the surface of the polymer[2].

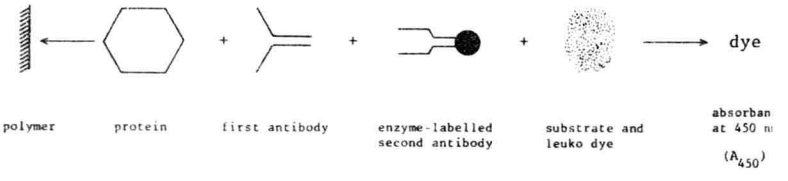


Fig. 1. Schematic representation of the applied EIA.

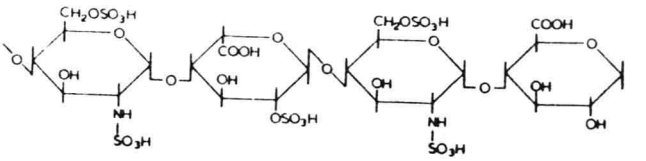
From the measurements of protein adsorption it can be concluded that neutral hydrophilic surfaces of minimal interfacial energy show minimal or no protein adsorption and also minimal activation of factor XII. This then would eliminate the two possible pathways to thrombus formation: initiation of the intrinsic clotting cascade and the thrombus formation through the platelet adhesion and aggregation. One can speak here of inert polymers.

Inert Polymers

Hydrogel-type materials prevent both platelet adhesion and clotting activation. The class of acrylate- and methacrylate hydrogels has been widely investigated by Hofman and others[3,4].
Sa da Costa[5] investigated the relationship between platelet adhesion and the amounts of polyether segment in copolyetherurethanes and found a reduced platelet adhesion with increasing polyether content. Polyethylene oxide (PEO) was reported to be most active in suppressing platelet adhesion as compared to polypropylene oxide (PPOX) and polytetramethylene oxide (PTMO).
We therefore studied the possibility of combining these materials as network systems: PEO as the hydrophilic and most bloodcompatible component, and PPOX or PTMO as the slightly less compatible, but stronger and more hydrophobic component. High molecular weight amorphous PPOX (M_w 250 - 450 . 10^5) was prepared by polymerization of propylene oxide with a catalyst obtained from $[(CH_3)_2N(CH_2)_3]_2Zn$ and Ph_2 SnS. Crosslinking of the two components was accomplished by incorporating dicumylperoxide and UV irradiation at 50°. A 90/10 crosslinked blend of PPOX/PEO showed very good mechanical properties, similar to natural bloodvessels and it was shown by Fourier Transform Infra Red measurements that the surface of films and fibers consisted for ~60% of PEO. It was possible to construct porous vascular prostheses by cospinning a solution of the two polymers in methylene chloride in the presence of DCP from a linearly moving spinneret onto a rotating thin rod with an internal diameter of 1.3 mm. These vascular prostheses are currently evaluated in test animals.
In vitro evaluation for bloodcompatibility involved platelet adhesion testing, Kallikrein generation and APTT testing. Especially the blood platelet adhesion gave very low values, but also the Factor XII activation and clotting times were low.
Currently we are also preparing blockcopolymers of PEO and PTMO by coupling segments (M_w 2000 - 5000) in solution, by treatment first with sodionaphtalene and in a second step with methylenebromide, in a joint program with the Nankai University, Tianjin. These blockcopolymers are strong, clear, rubbery materials, suitable for film and fiber formation.

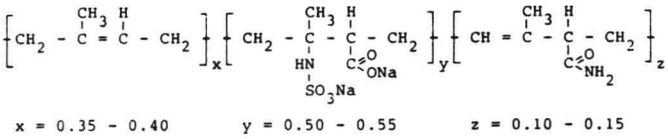
Heparin-like Polymers

Heparin, a mucopolysaccharide of the structure indicated below has strong anticoagulant properties and is widely used in medical blood treatment and surgical procedures to prevent clotting.



Its most important effect is the catalysis of the formation of inactive complexes of the clotting factors thrombin and antithrombin and factor Xa-antithrombin. Many attempts have been made to imitate the activity of heparin in synthetic polymers[8,9]. In view of the special sulfamate groups in heparin,

which are required for its anticoagulant action we have made polymers with these groups and amide groups by reaction of polyisoprene with isocyanate sulfonyl chloride:



x = 0.35 - 0.40 y = 0.50 - 0.55 z = 0.10 - 0.15

This polyelectrolyte showed similar anticoagulant activity as heparin[10]. In attempts to improve the bloodcompatibilities of different materials this heparinoid was linked to various materials by ionic coupling, hydrogel formation by irradiation and by irradiation grafting on silicone rubber, PVC and PS[11,12]. In vitro evaluation of the bloodcompatibility indicated a much reduced tendency to adhere platelets and a minor activation of factor XII[13].

Endothelial Cell Overgrowth on Polymer Surfaces

In atherosclerotic patients pathological aortic bloodvessels are routinely replaced by woven Dacron polyester tubing; however, when small diameter bloodvessels are replaced in this manner (< 4 mm diameter) clotting will take place. Natural vessels do not show clotting, when undamaged, due to the presence of an internal lining with a continuous layer of endothelial cells, which excrete a.o. prostacyclin, a powerfull inhibitor of platelet adhesion. If it were possible to provide an artifical bloodvessel prosthesis with a layer of these cells a solution for the replacement of small diameter bloodvessel prostheses would be available. With this in mind we have investigated the adhesion and cellular overgrowth of human endothelial cells (HEC) on various polymeric surfaces[14,15]. The endothelial cells were obtained by culture of umbilical cord endothelial cells at 37° in a special culture medium. A series of polymers varying in wettability, expressed by the contact angle, were contacted with a suspension of these cells at 37° in closed and sterilized cylindrical containers containing a polymer film as the bottom. The parameters investigated were the adhesion and proliferation of the cells as a function of time. Polystyrene and polyethyleneterephtalate treated by glow discharge or by oxidative acids to lower the wetting angle as a result of the introduction of oxygen containing groups (TCPS and TCPETP) showed the best properties and a confluent layer of cells could be obtained here after 6-8 days incubation. Another way to obtain similar results with other polymers is the preadsorption of the bloodproteins fibronectin or fibrinogen of which the first is generated also by the proliferating cells. It can be stated that for optimal adhesion and overgrowth of these cells a moderate wetting angle of ~40° is required. Hydrophobic polymers adsorb inhibiting (lipo)proteins from the culture medium. Albumin, immunoglobulin and high density lipoprotein are such inhibitors. Neutral hydrophilic polymers show insufficient adsorption of fibronectin or fibrinogen from the medium to allow adhesion. A series of neutral, positively and negatively charged copolymers of methylmethacrylate (MMA), hydroxyethyl methacrylate (HEMA), trimethylaminoethyl-methacrylate (TMAEMA) and methacrylic acid (MAA) were prepared by radical copolymerization. In the series HEMA/MMA the best adhesion was found again with the composition 25 HEMA/75 MMA (wetting angle 39°). In the polar series 85 HEMA/15 TMAEMA showed a strong adhesion and overgrowth of cells; also the 85 MMA/15 MAA and the 85 MMA/15 TMAEMA showed this phenomenon, indicating the positive effects of ionic groups. With this knowledge we now are developing polymers with the right properties suited for the preparation of cell covered small diameter vascular prostheses.

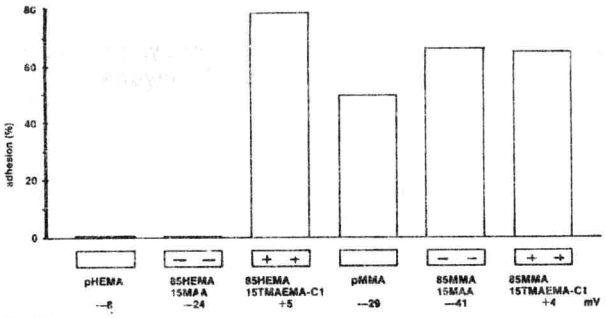


Fig. 2
Adhesion of HEC in CMS to methacrylate (co)polymers varying in surface charge, measured after 2 hours.

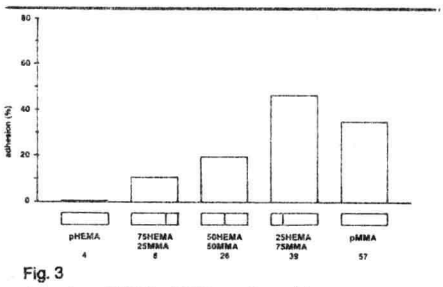
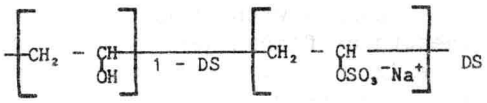


Fig. 3
Adhesion of HEC in CMS to methacrylate (co)polymers varying in surface wettability, measured after 2 hours.

Specific Polymeric Sorbents for Biomedical Application

For detoxification of blood various methods are at our disposal, such as the artifical kidney for the removal of urea and other metabolites. Sorbents are used for the regeneration of the dialysate. In a cartridge urea can be converted by urease to ammoniumcarbonate, from which the ammonium ions can be bound by zirconium phosphate. Recently a new method for the direct binding of urea by ninhydrinegroup containing synthetic polymers will allow soon the oral treatment of uremia patients[16].
Active carbon and microporous polystyrene resins have been used as nonspecific sorbents for the detoxification of blood. The particles have to be coated with a polymeric permeable membrane to prevent damage of the bloodconstituents and/or the loosening of fine carbon particles towards the bloodstream. In this area we have developed processes for the coating of these particles[17,18].

Ionic hydrogels have been developed by us for the specific binding of bloodproteins. With the availability of membrane plasmaferesis it is now possible to remove pathogenic bloodconstituents on line from the separated bloodplasma with special sorbents, after which the treated plasma can be returned to the patient.
In hypercholesteremia patients the bloodlevels of Low Density Lipoprotein (LDL) is elevated. This can lead to serious cholesterol deposition in the arteries and a drastically reduced lifespan due to the occurrence of cardiovascular disease. It has been known that heparin can form soluble complexes with LDL. In view of the heparin structure we have investigated the reaction of LDL with various polyelectrolytes containing respectively sulfamate, sul-



fate and carboxylate groups. Of these only the poly(vinylsulfate), prepared by reaction of poly(vinyl alcohol) with $ClSO_3H$ and pyridine, showed a strong complexing capacity for LDL. The complexation takes place through ionic interaction between the sulfate groups and the apoprotein B surrounding the cholesteric and triglyceridic core of the LDL. Conversion of the watersoluble Na salt of poly(vinylsulfate) into a hydrogel with an equilibrium water content of 95% is possible by irradiating a water solution with Co^{60} gamma irradiation (55 - 110 KGy). This hydrogel in particulate form was able to remove in 10 minutes 95% of the LDL present in the plasma, while HDL, the lipoprotein present in the blood for cholesterol transport to the intestines for removal, was not bound by this gel[19,20,21].

We have also prepared and studied aminogroup containing hydrogels for the isolation of clotting factor VIII, the haemophilia factor. Patients lacking this factor suffer from the "bleeding sickness". They can lead a normal life with a weekly injection of a small dose of this protein, which is present in the plasma in exceedingly low concentration. Cryogenic precipitation methods used up to now give a low recovery of only 15 - 20%. By coupling diamines with varying chain length to a hydrogel substrate we have been able to optimize the recovery. All of the factor VIII can be bound to the sorbent from plasma and 75% can be recovered by salt solution elution, with a purification degree of 40x.

References

1. Lee, R.G.; Adamson, C.; and Kim, S.W.: Thromb. Res. 4, 485-490 (1974)
2. Breemhaar, W.; Brinkman, E.; Ellens, D.; Beugeling, T.; and Bantjes, A.: Biomaterials 5, 269-274 (1984)
3. Andrade, J.D.; Ed. "Hydrogels for Medical and related Applications" ACS Symp. Series no. 31, Am. Chem. Soc. Washington D.C. 1976.
4. Hofman, A.S.; Horbett, T.A.; Ratner, B.D.: Ann. N.Y. Acad. Sci. 283,372 (1977)
5. Sa da Costa, V.; Brier-Russell, D.; Trudel, D.; Waugh, D.F.; Salzman, E.W.; and Merrill, E.w.: J. Coll. Interf. Sci., 76, 596 (1980)
6. Bots, J.G.F.; van der Does, L.; and Bantjes, A.: in "Blood Compatible' Materials and their Testing", Eds. S. Dawids, A. Bantjes Meulenhoff Publ. Co., Dordrecht, Netherlands, pp 277-284 (1986)
7. Bots, J.G.F.; van der Does, L.; and Bantjes, A.: Biomaterials, in print (1986)
8. Fougnot, C.; Jozefonvicz, J.; Samana, H.; and Bara, L.: Ann. Biomed. Eng. 7, 429-441 (1979)
9. Sorm, M.; Nespurek, S.; Mrkvickova, L.; Kalal, J.: J. Polym. Sci., Polym. symp. 66, 349 (1979)
10. Sederel, L.C.; van der Does, L.; van Duyl, J.F.; Beugeling, T.; Bantjes, A.: J. Biomed. Mater. Res. 15, 819 (1981)
11. Sederel, L.C.; Kolar, Z.; Hummel, A.; van der Does, L.; and Bantjes A.: Biomaterials 4, 210-214 (1983)
12. Sederel, L.C.; van der Does, L.; Euverman, B.J.; Bantjes, A.: Biomaterials 4, 3-8 (1983)
13. Sederel, L.C.; Kolar, Z.; van der Does, L.; Bantjes, A.: Labelled Comp. and Radiopharmceuticals 19, 1251 (1982)
14. Van Wachem, P.B.; Beugeling, T.; Feijen, J.; Bantjes, A.; Detmers, J.P.; Van Aken, W.G.: Biomaterials 6, 403-410 (1985)
15. Van Wachem, P.B.; Beugeling, T.; Feijen, J.; Bantjes, A.; Detmers, J.P.; Van Aken, W.G.: Life Support Systems, J. of the Europ. Soc. for Artif. Organs, Vol. 2, Suppl. 1, pp. 98-102 (1984)
16. Smakman, R.: European Patent Appl. KEP 121,275,10 oct. 1984.
17. Tijssen, J.; Bantjes, A.; Van Doorn, A.W.J.; Feijen, J.; Van Dijk, B.; Vonk, C.R.; Dijkhuis, I.C.: Artificial Organs 3, 126-129 (1979)
18. De Koning, H.W.M.,; Chamuleau, R.A.F.M.; Bantjes, A.: Artificial Organs 6, 280-287 (1982)
19. Maaskant, N.; Bantjes, A.; Kempen, H.J.M.: in "Blood compatible Materials and their Testing: Martinus Nijhoff Publishers, Dordrecht, Boston, Lancaster, Eds. S. Dawids and A. Bantjes pp. 317-325 (1986)
20. Maaskant, N.; Bantjes, A.; Kempen, H.J.M.: Europ. Pat. 8,402,021, 27 June 1984.
21. Maaskant, N.; Bantjes, A.; Kempen, H.J.M.: Atherosclerosis, in press.
22. Feijen, J.; Beugeling, T.; Bantjes, A.; Smit Sibinga, C.Th.: Biomaterials and Interfacial Phenomena in. Adv. Cardiovasc. Physics, Vol. 3, pp. 100-132 (Karger, Basel 1979).

INVITED LECTURES

目　　录