SEGMENTED POLYURETHANES

FOR BLOOD CONTACT

STUDIES OF SEGMENTED POLYURETHANES FOR BLOOD CONTACTING APPLICATIONS

By

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ABSTRACT

A series of segmented polyurethanes (SPU's) potentially suitable for blood contacting applications were synthesized. Various soft segment monomers (polypropylene glycol, PPG, MW 1000; PPG 2000; polyethylene glycol, PEG, MW 1500) and chain extenders (ethylene diamine; 1,3 diamino hydroxy propane; and 4,5 dihydroxy-m-benzene disulphonic acid disodium salt, Tiron®) were used to prepare polymers with a range of chemical and physical characteristics. Several of these polymers were novel with respect to the presence of functional groups in the hard segment. The principal objective was to assess the effect of these groups on the physical properties, and to some extent on the blood compatibility of SPU's.

Initially the SPU's were characterized to determine the course of the novel polymerizations. Nuclear magnetic resonance (NMR) was used to determine if the hydroxyl group of the chain extender 1,3 diamino hydroxy propane remained unreacted. Although the lack of model compound studies made the results inconclusive, it was estimated, using ^{1}H NMR, that about 87% of the hydroxyl groups remained unreacted. Sulphur analysis of sulphonate-containing SPU's, formed using Tiron®, showed very low sulphur contents compared to the expected values, suggesting that the repeat units of the SPU's were different from those based on simple stoichiometry. Low angle laser light scattering (LALLS) was used to

determine $\bar{M}w$ but did not always produce interpretable results. Electron spectroscopy for chemical analysis (ESCA) was performed on cast films of the polymers to determine chemical composition at the surface. The ESCA data obtained at varying take-off angles showed that the soft segment domains were enriched at the surface. The nitrogen content expected of several of the SPU's was twice that found by ESCA. Again this suggests that the repeat unit of these SPU's is different from the ideal repeat unit based on the stoichiometry used.

Mechanically the polymers behaved as expected in terms of stress-strain data. PPG 2000-based SPU's had greater extensibility but lower tensile strength compared to the corresponding PPG 1000-based SPU's. PEG-based polymers had very low mechanical strength and this was attributed to the absorption of water from the environment by these hydrophilic materials. PPG 1000-based polymers showed the best overall mechanical performance from a biomaterial perspective.

As a means of assessing the response of blood to these materials, the adsorption of fibrinogen on film coated tubes was studied, both from single protein solutions and from plasma. Fibrinogen "capacity" of the polymer surfaces obtained from the single protein data was strongly dependent on soft segment type and was in the order PPG 1000>PPG 2000> PEG 1500. As with most other materials previously studied, adsorption of fibrinogen from plasma was transient (Vroman effect). This effect was evident as peaks in curves of adsorption versus plasma concentration. The peak heights were found also to be in the order PPG 1000>PPG 2000>

PEG 1500. These peak heights are in general also lower than for other, more thrombogenic materials, and may indicate the affinity of the surface for fibrinogen relative to other proteins in plasma. From these observations it is tempting to associate thromboresistance with minimal fibrinogen adsorption.

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CHAPTER 1

INTRODUCTION AND OBJECTIVES

1.1 INTRODUCTION

Current research continues to address the problems associated with synthetic materials implanted in the body. In particular, materials used as blood contacting surfaces in cardiovascular assist devices are subject to extreme mechanical stresses as well as surface interactions with blood components.

The interaction of the surface of the implant with the blood components triggers the complex clotting mechanism which leads ultimately to thrombus formation. The possibility of this localized thrombus causing vessel occlusion or breaking free of the surface and becoming an embolus represents an extremely dangerous situation for the patient. The use of systemic anticoagulants which interfere with normal blood clotting is generally required to prevent thrombosis. However at the present time, the exact mechanisms that initiate thrombosis at a foreign surface have not been completely elucidated.

The major constituents of blood are cells, proteins, electrolytes and water. The interactions of blood components with a foreign surface are similar to those involved in the normal hemostatic mechanism (Hirsh

and Brain, 1983). A simplified scheme of the normal hemostatic mechanism consists of platelet adhesion to subendothelial structures followed by platelet aggregation and blood coagulation. A more detailed explanation of blood coagulation is presented in Chapter 2.1.

The adverse response of the blood to a foreign contacting material is the major concern in the design of blood-compatible materials. In particular the composition of the surface of a synthetic material will be responsible for the events leading to clotting and thrombosis. The surface of a material (which determines the material's effect on coagulation) may have a very different chemical composition from the bulk material. Factors such as surface hydrophilicity and hydrophobicity, the incorporation of charged species or the binding of anticoagulants like heparin on the surface are therefore vital considerations in the design of antithrombogenic materials.

The use of segmented polyurethanes (SPU) for blood contacting devices has become increasingly important. This is due mainly to the vast number of possible polyurethanes that can be synthesized, each with unique mechanical properties, surface properties and chemical structure. By tailoring the composition of the polyurethane it may be able to correlate surface properties with the degree to which clotting occurs. At the present state of knowledge, surface variables do not correlate well with observed antithrombogenic activity.

1.2 OBJECTIVES

Segmented polyurethane elastomers possess the type of mechanical

behaviour needed for a stress-bearing blood-contacting environment as well as exhibiting a degree of biocompatibility. The objectives of this thesis were to synthesize and characterize a series of novel segmented polyurethanes suitable for blood contacting applications. Molecular weights, chemical composition and surface properties were investigated. Mechanical properties were also investigated to determine the effect of both the novel chain extenders and the polyethers used to prepare the SPU's. Finally a study of the adsorption of fibrinogen (a key blood protein in thrombosis) onto the polymers was carried out in order to try to correlate polymer properties with blood plasma response.

1.2.1 Synthesis and Characterization

It was desired to synthesize a series of SPU's that would maintain the already good mechanical properties of conventional SPU's but potentially provide a more antithrombogenic surface. For this reason the polymers were prepared from components known to give good elastomeric polymers. The modified polymers were obtained by using chain extenders with pendant side groups. The two pendant side groups chosen were hydroxyl and sulphonate.

The polymers were prepared using a two step synthesis. The first step involves the reaction of a polyether with a stoichiometric excess of diisocyanate to form a prepolymer. The prepolymer is then reacted in stoichiometric proportions with a diol or diamine (chain extender) to create the polyether urethane. The polyurethane synthesized consists of two thermodynamically incompatible components denoted as the hard and soft segments. The soft segment represented by polyether gives the

polyurethane a rubbery phase responsible for its elastomeric behaviour. The hard segment represented by the urethane and urea linkages created by the reaction of an isocyanate with a hydroxyl or amine group acts as a filler/reinforcement phase for the soft segments.

The chain extender of the SPU is present in the hard segment phase of the polymer. Various studies (Lyman et al, 1975; Merrill et al, 1980, 1982; Sa Da Costa et al, 1980, 1981) have shown that the hard segment is probably responsible for high rates of platelet adhesion on SPU surfaces in contact with blood. It was hoped that the addition of hydroxyl or sulphonate groups through the chain extender would allow the study of several properties of the polymer associated with the hard segment:

1) Using electron spectroscopy for chemical analysis (ESCA), the amount of hard segment present in the surface could be determined.
2) It could be determined whether the presence of these pendant side groups significantly affects the mechanical performance of the polymers.
3) It could be determined whether the presence of these pendant side groups in the hard segment leads to any improvement in blood compatibility.

In addition to varying the chain extender, the type of soft segment was also varied. The soft segment has been found to predominate in the surface region of SPU solids (Lyman et al, 1975; Sung et al, 1978). The soft segment "monomers" chosen varied in degree of hydrophilicity and in chain length. Polyethylene glycol (PEG) and

polypropylene glycol (PPG) were examined, with PEG providing a more hydrophilic surface than PPG. By using polyethers with different hydrophilicity and molecular weight it was hoped to study the properties of the polymer associated with the soft segment:

1) Using ESCA the possible surface enrichment of the soft segment could be examined.
2) The effect of both the polyether type and molecular weight of the polyether could be examined in relation to the stress-strain behaviour of the SPU.
3) It could be determined if polyether type (degree of hydrophilicity of PEG versus PPG) or molecular weight of the polyether (enrichment of soft segment in surface greater for higher molecular weight polyethers) can be correlated with blood compatibility.

After the polymers were synthesized they were characterized by various techniques. These techniques allowed the determination of the degree of incorporation of the novel chain extenders. Secondly they provided information about the bulk and surface properties of the SPU. These properties can then potentially be correlated to both solid state behaviour and antithrombogenic tendencies. The characterization techniques and purpose are listed below:

1) Nuclear Magnetic Resonance (NMR) - both ^{13}C and ^{1}H NMR was performed to examine pendant OH incorporation in the hard segment of the hydroxyl series.
2) Sulphur Content Analysis - using a combustion technique performed by Guelph Chemical Laboratories, SO_3^-

incorporation in the hard segment of the sulphonate series was examined.

3) Low Angle Laser Light Scattering (LALLS) - using both a differential refractometer and a low angle laser light scattering photometer an absolute weight average molecular weight, $\bar{M}_w$, was determined for certain polymers.

4) Contact Angle Measurements - using a goniometer telescope, the degree of hydrophilicity of the various polymer films was determined from water contact angles.

5) Electron Spectroscopy For Chemical Analysis (ESCA) - performed at University of Washington, Seattle. ESCA studies gave information on the composition of the surface which impacts on the biomedical evaluation of the polymer.

1.2.2 Mechanical and Biomedical Evaluation

The SPU's synthesized were tested with respect to their mechanical properties and plasma interactions. Mechanically the elastomeric properties and high yield strengths of SPU's result from phase separation of the hard and soft segments. Important variables such as degree of phase separation and molecular weight of the polymer will impact on the stress-strain behaviour. Phase separation for the two segments was not examined in this thesis. However it may be possible to infer degree of phase separation based on the components of the SPU. Molecular weight data obtained from LALLS experiments were also related to the mechanical behaviour of the SPU.

The polymers were cast into films and their stress-strain

behaviour studied using an Instron tester. Tensile stress-strain curves along with ultimate strengths for the different polymer series were obtained. Relationships among polymers which incorporated different chain extenders and among polymers which incorporated different soft segments were studied. It was an objective that the stress-strain behaviour not be detrimentally affected by the addition of the novel chain extenders.

The various materials were evaluated from a blood interaction standpoint by studying the adsorption of fibrinogen from plasma. As will be discussed later, fibrinogen is a key component in the clotting mechanism. The adsorption of this blood protein onto SPU's, which are considered fairly biocompatible in relation to other surfaces, could be examined. Also the effect of both the soft segment and hard segment of the various SPU's synthesized could show trends in fibrinogen adsorption that might be correlated to blood compatibility.

Radioactively labelled fibrinogen was added to plasma as a tracer thereby allowing the quantitative study of adsorption behaviour. Initial studies examined preferential adsorption of radiolabelled fibrinogen versus cold (unlabelled) fibrinogen. This experiment also gave information on the fibrinogen adsorption "capacity" of the various surfaces. Fibrinogen adsorption from plasma at 5 minutes was examined using various plasma dilutions. The information gathered on fibrinogen adsorption on the polymer surfaces may allow the correlation of the SPU structure to overall blood response.

CHAPTER 2

LITERATURE REVIEW

2.1 BLOOD/SURFACE INTERACTIONS

The use of synthetic materials for blood contacting devices has been hampered by the phenomena of thrombosis and blood coagulation. It is the blood's response to a foreign surface that triggers the formation of thrombus through a complex sequence of events. The clotting mechanism which forms part of this sequence has been the subject of an extensive amount of research and the particular role of the surface in clotting is of specific interest in understanding blood-material interactions. A basic understanding of these phenomena should allow a more rational approach to the challenges in the design of blood compatible materials.

2.1.1 The Clotting Mechanism

The behaviour of blood components in contact with a foreign surface follows a series of defined reactions leading to surface coagulation. It has been shown that blood components, in particular plasma proteins, start to organize at the interface within seconds of initial contact (Baier, 1977; Vroman et al, 1977). Cellular components arrive at the surface after the proteins due to their larger size and

smaller diffusion coefficients (Brash, 1981). Subsequent events in blood-material interactions include platelet adhesion and aggregation, fibrin formation and entrapment of red blood cells (red thrombus). All the above occurrences can be demonstrated within the first few minutes after blood contact (Baier, 1977).

Surface activated coagulation is a result of the response of a group of plasma proteins, known as clotting factors, to the foreign surface. The activation of the clotting mechanism can follow either an intrinsic or extrinsic pathway, the extrinsic pathway being a much faster process (Hirsh and Brain, 1983). The two pathways are illustrated schematically in Figure 2.1. The intrinsic pathway is triggered by the surface activation of Factor XII also known as Hageman Factor. The extrinsic pathway is initiated with the activation of Factor VII by tissue thromboplastin (extracts of various tissues) which forms a complex with Factor VII in the presence of Ca^{++}.

It has been reported that in simple mixtures of the three most abundant plasma proteins, fibrinogen is preferentially adsorbed over albumin and ɣ-globulin (Brash and Davidson, 1976; Kochwa et al, 1977; Brash and Uniyal, 1979). Vroman et al (1980, 1982) believe that in plasma, fibrinogen dominates the protein layer in the initial 1 to 2 seconds of contact and then is replaced by high molecular weight kininogen (HMWK). This replacement facilitates propagation of the "contact" or initial phase of intrinsic coagulation. Factor XII, Factor XI, plasma prekallikrein and HMWK are considered the four plasma proteins responsible for contact activation (Griffin, 1981). These proteins interact in a complex manner, not entirely understood, to

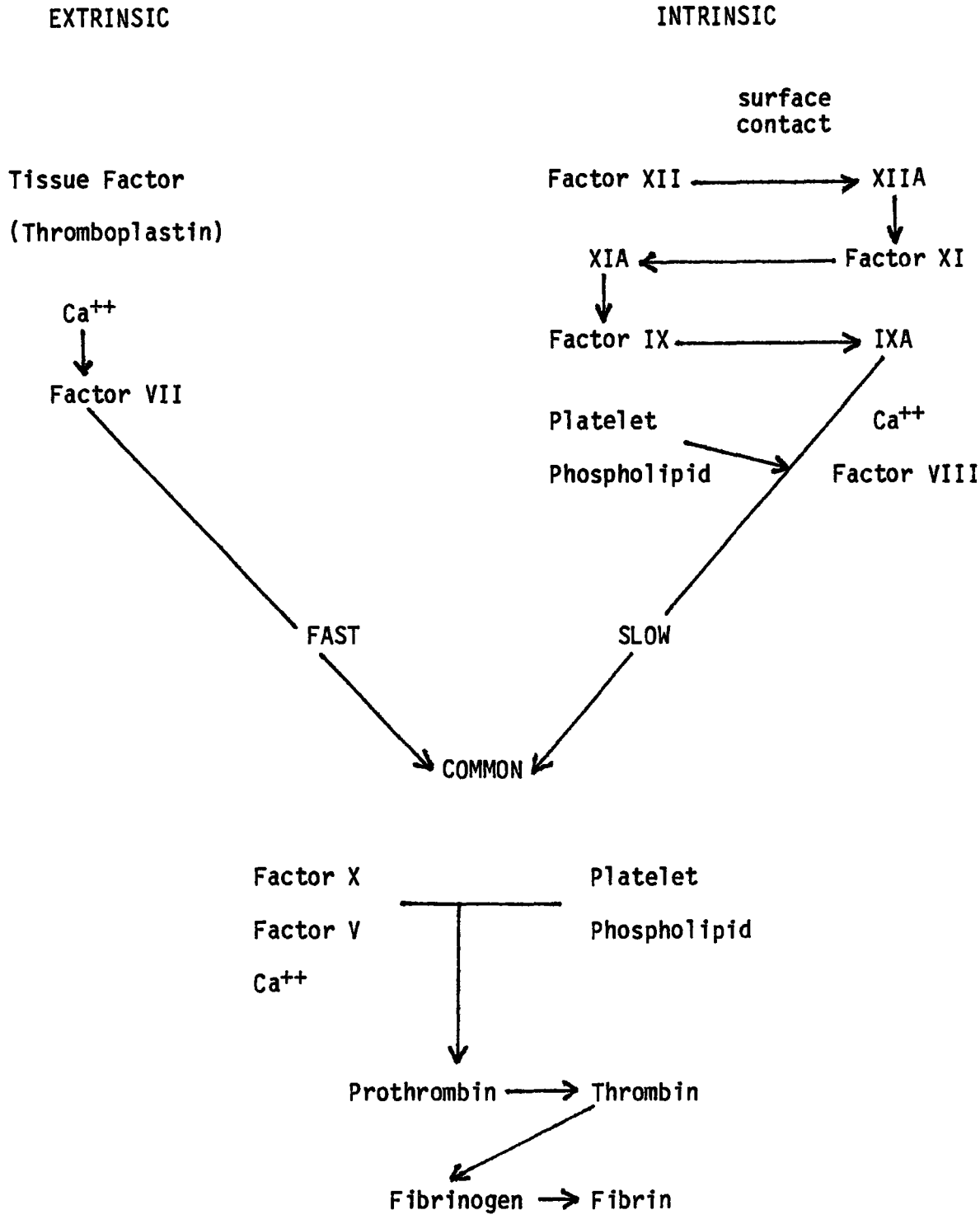

Figure 2.1 EXTRINSIC AND INTRINSIC CLOTTING PATHWAYS
(Hirsh and Brain, 1983)

produce Factor XI_a, the end product of the contact system. A possible model for these interactions has been presented by Griffin (1981) and is shown in Figure 2.2. In Figure 2.2 Hageman Factor (HF) is bound to a negative surface where it is susceptible to proteolytic attack by kallikrein (Kal) to form activated αHF_a. Factor XI and HMWK are also bound to the negative surface via HMWK. αHF_a activates Factor XI to form surface bound Factor XI_a. The rate at which fibrinogen is replaced by HMWK varies for the type of surface and is faster for more "active" surfaces (Brash and ten Hove, 1984). Therefore it appears that fibrinogen replacement may give an indication of the contact activation activity of the surfaces. It is for this reason that the adsorption of fibrinogen from plasma to polyurethanes was examined in this study.

2.1.2 Thrombus Formation

The initial adsorption of protein in the first few seconds after contact will have a dramatic affect on subsequent thrombotic events. At this point the surface charge, texture and chemistry are dependent on the layer of protein that has been adsorbed (Baier, 1977). Therefore the response of platelets that adhere to this surface may be altered significantly.

The competitive adsorption of plasma proteins is expected to involve mainly albumin, γ-globulin and fibrinogen. Albumin has been shown to have an inhibitory effect on platelet adhesion and release and Lyman and Kim (1974) have proposed that a preadsorbed albumin protein layer has antithrombogenic properties in short term applications. Fibrinogen and γ-globulin have been shown to enhance the

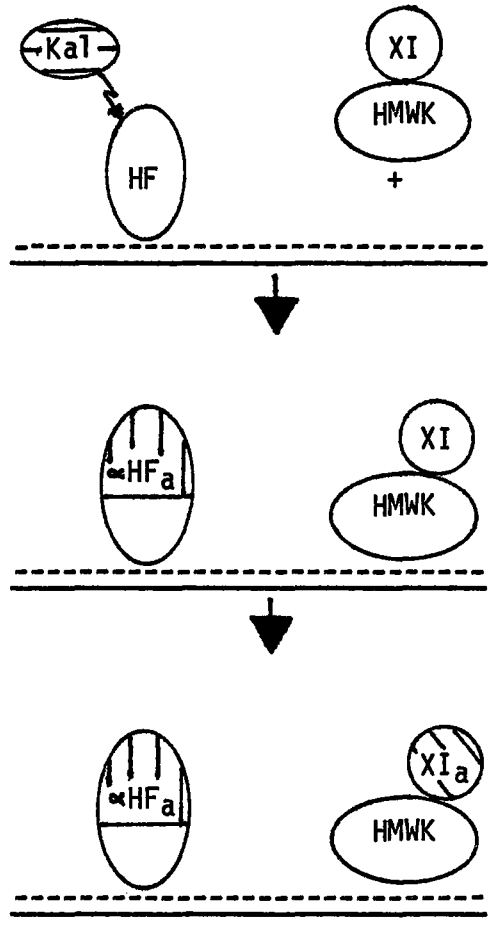

Figure 2.2 CONTACT ACTIVATION OF INTRINSIC COAGULATION (Griffin, 1981)

release from adherent platelets (Whicher and Brash, 1978). The release of adenosine diphosphate (ADP) and thromboxane A_2 from adhering platelets further stimulates platelets to aggregate resulting in the formation of platelet aggregates (Hirsh and Brain, 1983).

The adhesion of platelets is believed to be achieved via the protein monolayer or the proteinaceous bridging layer (Salzman et al, 1969; Vroman, 1972). Fibrinogen and γ-globulin as already indicated have been implicated as the bridging cofactors. Therefore the adsorption of these plasma proteins on the surface can alter the thrombogenic characteristics of the material.

These platelet aggregates further assist in the coagulation process. Coagulation factors attach to the platelet surface where activation occurs. Activated Factor IX, Factor VIII and Factor X form activated Factor X. Factor X complexes with Factor V and Factor II (prothrombin) to cleave prothrombin to thrombin. Thrombin released from the platelet surface converts fibrinogen (Factor I) into fibrin (Hirsh and Brain, 1983). The fibrin platelet aggregate further traps and destroys red blood cells (hemolysis) and interrupts blood flow (Baier, 1977).

Therefore fibrinogen and γ-globulin when preadsorbed to the surface are postulated to be highly thrombogenic (Packham et al, 1969; Whicher and Brash, 1978). A simple model of blood-material interactions is illustrated in Figure 2.3.

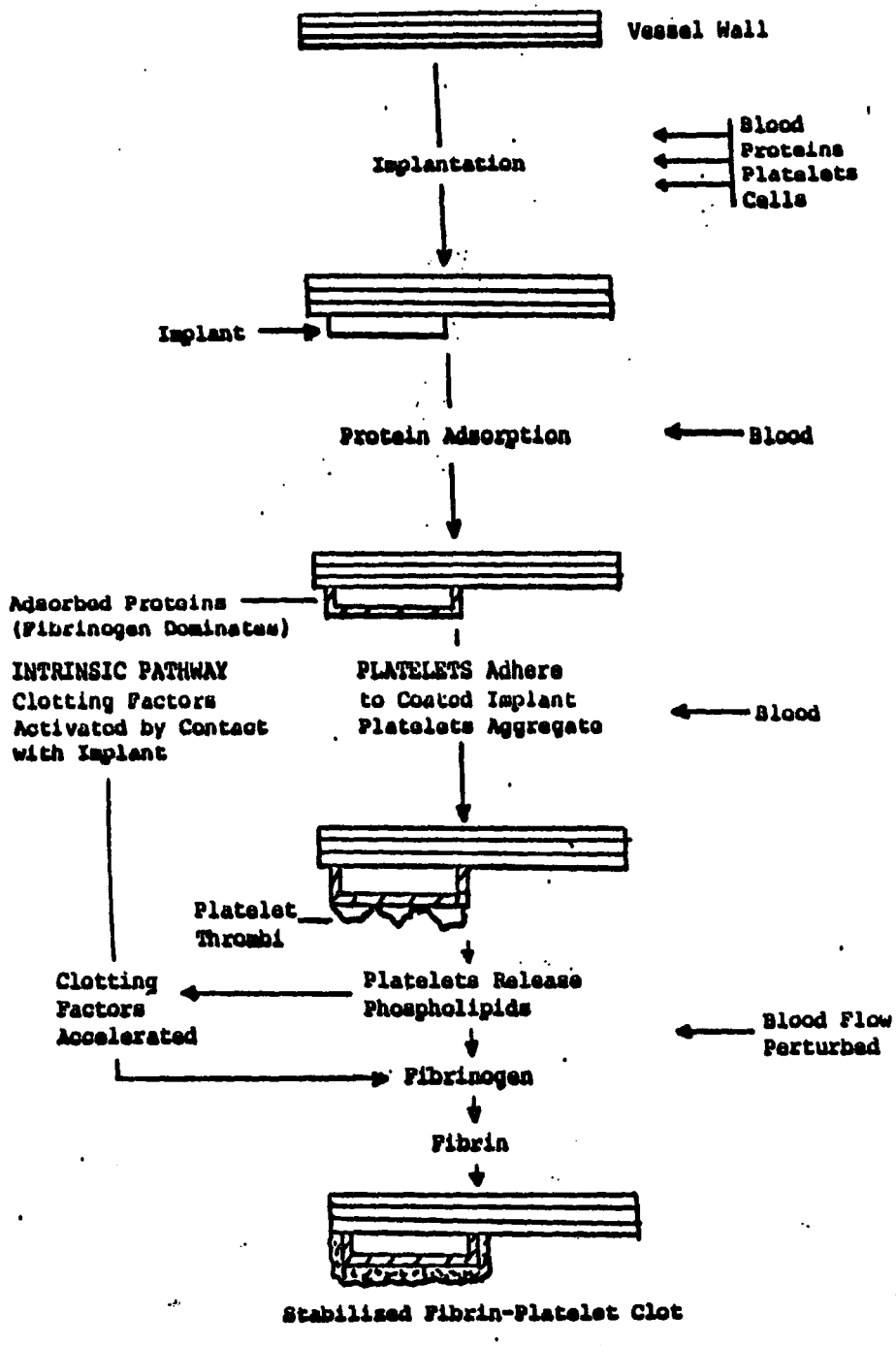

Figure 2.3 BLOOD-MATERIAL INTERACTION EVENTS (Coury et al, 1984)

2.1.3 The Effect of Synthetic Surface Properties on Thrombosis

The surface properties of a synthetic polymer will determine the thrombogenic potential of the material in contact with blood. For example, as noted by Hoffman (1980), there are several characteristics of the polymer surface that are very important in the control of blood coagulation.

1) Water sorption.
2) Surface chemical composition.
3) Surface roughness and porosity.
4) Crystalline/amorphous structure of the surface.
5) Distribution of surface chemical "domains".

Hydrogels are polymeric materials which at equilibrium contain large quantities of water. They therefore have a strong physical resemblance to living tissue. Furthermore since blood is an aqueous fluid one would expect a relatively low energy interface between blood and a water-bearing material. Although it is believed that the hydrated surface will constantly provide a fresh foreign interface and cause high thrombogenic potentials, it is also believed that the lower interfacial free energy created by the water swollen polymer more than counteracts this effect making this type of polymer suitable for implants (Hoffman, 1980).

The surface free energy of a synthetic material has been used as a surface parameter to correlate with blood compatibility. In this connection it has been shown that the critical surface tension, $_c$, related to surface free energy of hydrophobic polymers with uniform

molecular composition and no hydrogen or ionic bonding capabilities, correlates well with certain aspects of blood/surface interactions (Baier, 1977). However the critical surface tension is not always a good indication of the eventual performance of a polymer-blood implant.

A possible reason for lack of correlation is that, as already noted, materials in contact with blood quickly become "coated" with adsorbed protein and this layer may "mask" the underlying surface. It has been suggested by Baier (1970) that materials showing moderate biocompatibility generally, have γ_c values in the range of 20 - 30 dyne/cm.

The texture of the surface is also considered important in determining certain aspects of blood-surface interactions. For example, surface irregularities of a micrometre or less have been found to be tolerable in allowing complete wetting (Baier, 1977). The complete wetting of the surface prevents the adverse thrombus-initiating events of protein adsorption and the entrapment of gas bubbles (Baier, 1977). However as protein is adsorbed to the surface, the texture of the surface will change accordingly. Also on rough surfaces, the contact angle measurement in determining γ_c is compromised since the surface is no longer smooth and homogeneous (Neumann et al, 1975).

Perhaps the most important surface property with regard to blood compatibility is surface chemical composition. For example the presence of charged species, polar groups and hydrophobic groups are known to affect the thrombogenic potential of the material (Brash and Lyman, 1969; Kaeble and Moacanin, 1977; Ratner et al, 1979; Coleman et al, 1982).

The effects of hydrophilic, polar groups and hydrophobic, apolar

groups have been investigated with respect to protein adsorption. Work by Kaeble and Moacanin (1977) showed that a surface with a high dispersive force component of γ_c and low polarity favours protein film adhesion while a low dispersive force component, highly polar surface weakly holds plasma proteins and may result in an embolus. In tests by Brash and Lyman (1969) the adsorption of proteins on both hydrophilic and hydrophobic surfaces was examined. It was found that the adsorption of proteins occurs at both types of surfaces to varying degrees. The adsorption of proteins was greater on hydrophobic surfaces and was irreversible. In contrast, adsorption to hydrophilic surfaces was lower and reversible (Brash and Lyman, 1969).

Nyilas et al (1975) proposed that surface properties are related to thrombogenicity. They concluded that thrombogenicity increased as the polar contribution to the surface free energy increases. The work of Ratner et al (1979) proposed an extension of the polar/dispersion model for the adsorption of proteins to a polymer surface suggested by Nyilas (1975). According to this proposal an optimum value of the polar to dispersion force is needed for "suitable" proteins to be adsorbed irreversibly to the surface. The ratio at which a marked sensitivity to increased adsorption occurred was found to be approximately 1.3 (Coleman et al, 1982). It was noted that a polymer surface in which the dispersion forces begin to dominate over polar forces has better antithrombogenic properties (Coleman et al, 1982).

In multiphase polymers, the presence of phase "domains" in the surface can affect the thrombogenic potential. Multiphase polymers, such as segmented polyurethanes, are block copolymers where microphase

separation or domain formation occurs due to thermodynamic incompatibilities of the different blocks. These materials will be discussed in more detail in the next section. Although the reasons for the antithrombogenic potential of these polymers is unknown, it has been pointed out that the normal vascular endothelium itself is composed of microphase separated domains of hydrophilic and hydrophobic areas (Sawyer et al, 1964).

The initial phase of blood coagulation has been shown by Okano et al (1981) to be suppressed by polymers that contain microdomains of hydrophilic and hydrophobic blocks. They found that albumin was selectively adsorbed to the hydrophilic domains and γ-globulin and fibrinogen were selectively adsorbed to the hydrophobic domains. It was hypothesized that the organized surface protein layer on the two domains of the copolymer was the basis of anticoagulant behaviour of these materials. In the work of Whicher and Brash (1983) on platelet reactivity with multiphase polymers it was proposed that thrombus propagation but not thrombus initiation was affected when the domain size was similar to the platelet size.

The presence of negatively charged or anionic groups in the surface has been studied as a potential antithrombogenic characteristic. In early studies by Sawyer (1964) it was suggested that net negatively charged surfaces were antithrombogenic. This suggestion seems reasonable since blood proteins, platelets and the vascular endothelium all carry net negative charges at normal blood pH. Therefore one would expect proteins and platelets to be repelled from the blood vessel wall or from any other negative surface.

However not all negative surfaces are antithrombogenic and in some cases they actually promote thrombosis (Srinivasan et al, 1979). Ratnoff (1977) has found that some negative surfaces, particularly glass, can activate Factor XII thereby initiating the clotting cascade mechanism.

Inability to correlate consistently negative charge with antithrombogenicity was accounted for by Leonard (1969) in terms of spatial distribution of the surface charge. According to this hypothesis the spatial distribution of charge on a surface can either promote or suppress the adhesion of platelets. If pairs of negatively charged sites on the surface are separated appropriately so that calcium ions can bridge the two to form a ring (i.e. chelate) then there is no free calcium ion to form a bond between the platelet and polymer. However if this ring cannot be formed with the Ca^{++}, platelet adhesion can occur (Leonard, 1969), see Figure 2.4.

Proteins can also adsorb to a negative surface even though they have a net negative charge. There are specific cationic sites on the protein that may form electrostatic bonds with the negative charged surface sites (Brash, 1981).

As already noted, negative charge in a surface has been shown in some cases to impart a degree of blood compatibility (Leonard, 1969; Srinivasan et al, 1979). Sulphonate groups, carboxylate groups and glutamic acid in particular have been shown to impart antithrombogenic properties (Srinivasan et al, 1979; Cottonaro et al, 1982; Helmus et al, 1984). Therefore the incorporation of negative charges via sulphonate and hydroxyl groups in a polymer may improve blood compatibility. This

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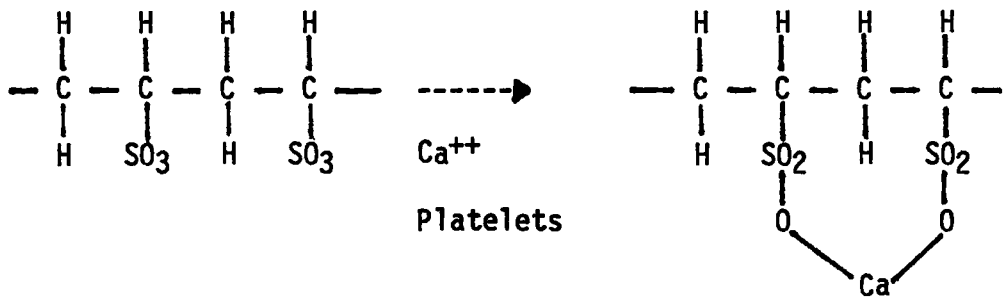
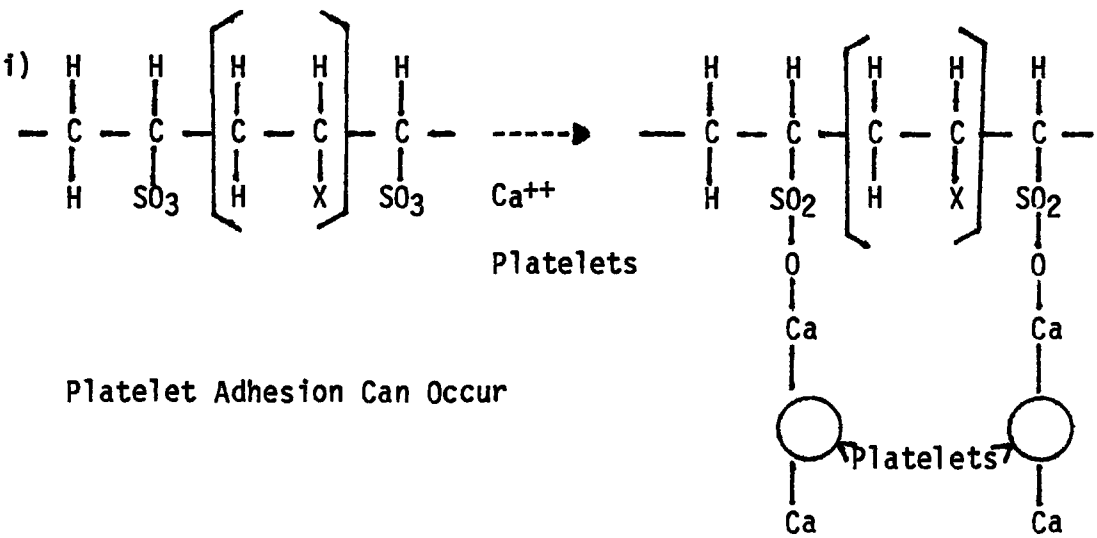


Platelet Adhesion Does Not Occur

ii)



Platelet Adhesion Can Occur

Figure 2.4 PLATELET ADHESION TO A NEGATIVE SURFACE (Leonard, 1969)

notion is examined in the present thesis. Again it should be stressed that it may be the spatial distribution of charge more than the charge itself that is responsible for improved antithrombogenic properties.

2.2 SEGMENTED POLYURETHANES

Segmented polyurethanes (SPU's) are members of a family of polymers that contain the characteristic urethane linkage, -N(H)-C(=O)-O-. The polymer needs only to have this group within the repeat structure to be classified as a polyurethane. Polyurethanes may have a variety of other groups incorporated in the polymer chain. This variety leads to great diversity in the mechanical properties and uses of these polymers. The ability to tailor the properties of polyurethanes has led to applications ranging from gum-like materials, to foam products to elastomers to rigid polymers.

One of the recently found uses of polyurethanes is in the biomaterials field. Their excellent elastomeric properties (high tensile strength, tear resistance, elastomeric recovery) combined with a reasonable degree of biocompatibility has led to the use of SPU's in many blood contacting devices. Examples of current devices in which SPU's are used include vascular grafts (Lyman et al, 1978), intra-aortic balloon pumps (Brash, Fritzinger, and Bruck, 1973), heart assist devices (Brash, Fritzinger, and Loo, 1970), artificial kidneys (Lyman and Loo, 1967), pacemaker wire insulation and artificial heart valves. Of course one of the higher profile uses of SPU's is in blood contacting areas of the Jarvik artificial heart first implanted in Barney Clark on December 2, 1982.

Brief reviews of the chemistry of polyurethane synthesis, the solid state properties that give rise to their mechanical behaviour and their performance in biomedical applications will now be presented.

2.2.1 Polyurethane Chemistry

Polyurethanes are prepared by step-growth polymerization involving either addition or condensation reactions. Commercially, the use of addition reactions is the usual method of preparation (Wright and Cumming, 1969) and is the method used in the present work. The addition reaction is between a diisocyanate and a diol to create the urethane linkage. The isocyanate group is the one most often involved in the formation of polyurethane structures. Isocyanates will react with any group having an active hydrogen (Saunders and Frisch, 1962). Thus a wide variety of reactions, some undesirable, is possible during polyurethane synthesis. The following discussion of isocyanate chemistry is intended to briefly illustrate some of the possible reactions that may occur. Knowledge of these reactions should provide a basis for control of undesired side reactions (Saunders and Frisch, 1962).

2.2.1a Reactions of Isocyanates

OH Groups

$$RNCO + R'OH \longrightarrow RNHC(=O)OR' \quad \text{(urethane)}$$

The reaction of an isocyanate with an OH group is the basis of polyurethane formation. All compounds with a hydrogen linked to an oxygen will react under appropriate conditions unless sterically hindered. The reaction with an alcohol produces a urethane linkage (also known as a carbamate linkage). Primary alcohols are the most reactive, readily reacting at 25-50°C. Secondary and tertiary alcohols are less

reactive with respective rates about 0.3 and 0.005 that of primary alcohols.

These reactions are strongly catalyzed by mild and strong bases and metals, and are weakly catalyzed by acids.

Compounds Containing the N-H Group

$$RNCO + R'NH_2 \longrightarrow RNHCONHR' \quad \text{(urea)}$$

Compounds containing N-H groups are capable of reaction with isocyanates to create a urea linkage. Reactivity correlates well with basicity unless steric hindrance is great. The reaction of isocyanates with amines forms ureas. Primary aliphatic amines are very reactive even at 25°C; reactivity is lower for secondary aliphatic and primary aromatic amines.

Other nitrogen compounds such as ammonia and hydrazine also react readily with isocyanates. The respective reactions are:

(ammonia) $RNCO + NH_3 \longrightarrow RNHCONH_2$

(hydrazines) $RNCO + H_2NNHR' \longrightarrow RNHCONHNHR'$

Water

$$RNCO + H_2O \longrightarrow [RHNCOOH] \longrightarrow RNH_2 + CO_2$$

(carbamic acid)

The reaction of an isocyanate with water does not yield a stable urethane linkage but gives an amine and carbon dioxide. The intermediate product is an unstable carbamic acid derivative.

$$RNCO + RNH_2 \longrightarrow RNHCONHR$$

The amine produced reacts more readily than the water with the isocyanate to create a urea linkage. Therefore two moles NCO are consumed per mole urea linkage formed with one mole of CO_2 produced.

The reaction with water can be modified in the presence of strong acids and bases. For more information on the reaction of isocyanates with water the reader is referred to Saunders and Frisch (1962).

Ureas and Urethanes

$$\underset{\text{(Urea)}}{RNCO + R'NHCONHR''} \longrightarrow \underset{\text{(biuret)}}{R'N(CONHR)CONHR''}$$

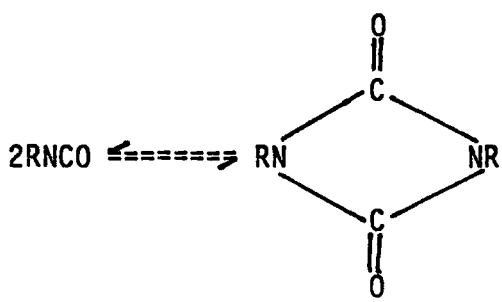
The urea formed by an amine and isocyanate may further react with an isocyanate to give a biuret linkage. This reaction normally requires temperatures in excess of 100°C.

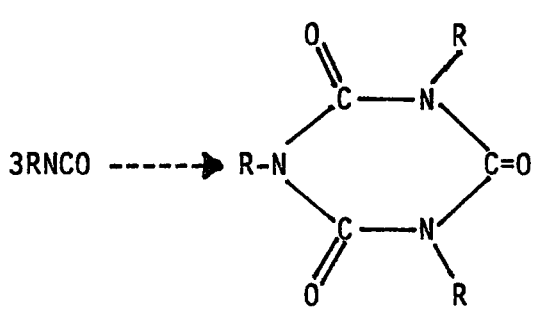
$$\underset{\text{(Urethane)}}{RNCO + R'NHCOOR''} \longrightarrow \underset{\text{(allophanate)}}{R'N(CONHR)COOR''}$$

The urethane formed by reaction between an alcohol and an isocyanate may further react with an isocyanate to give an allophanate linkage. Urethane is less reactive than urea and requires temperatures between 120-140°C to proceed at a moderate rate.

These two reactions lead to branched and crosslinked polyurethanes but again are relatively slow at normal polymerization temperatures.

Isocyanates





Isocyanates can react with themselves to produce dimers and trimers. These reactions are catalyzed strongly by phosphines and weakly by tertiary amines. Also certain aromatic diisocyanates such as

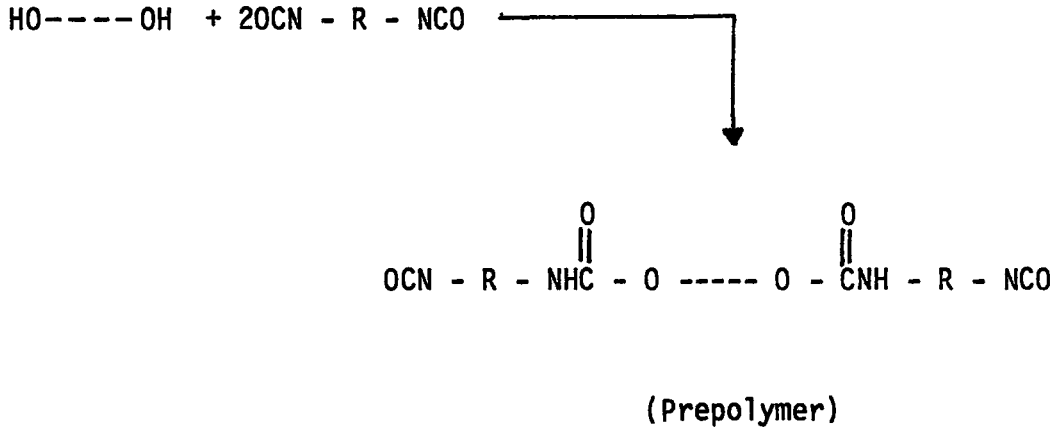
4,4' diphenylmethane diisocyanate (MDI) can dimerize slowly on storage, thereby reducing the effective diisocyanate content. Care should therefore be taken when using diisocyanates with long storage times.

2.2.2 Synthesis of Segmented Polyurethanes

The synthesis of segmented polyurethanes can be achieved in a one-step or two-step process. The two step method is the major production route to SPU's (Solomon, 1972). The initial step is the end capping of a low molecular weight hydroxy-terminated polymer (diol) with a diisocyanate. A stoichiometric excess of diisocyanate over diol is used in this end capping step. In the second step the "prepolymer" is chain extended using either a diol or a diamine to create a high molecular weight polymer. Peebles (1974) reported that the two step method of SPU synthesis leads to a narrower distribution of diisocyanate-chain extender (hard segment) lengths providing the first isocyanate reaction occurs at a faster rate than the extending reaction. The reaction scheme for the two-step preparation is shown in Fig. 2.5.

In the one shot method the prepolymer stage is omitted and diisocyanate, macrodiol and diol and/or diamine are mixed in approximately equivalent stoichiometric ratios. This method however has a major drawback in the balancing of reactivities of the components (Wright and Cumming, 1969). In a diisocyanate-diamine-diol system, the diamine is more reactive than the diol. This leads to a non-uniform polymer unless the diisocyanate-diamine reaction is inhibited or the diisocyanate-diol reaction is catalyzed. Systems consisting of diisocyanate and diamine or diisocyanate and diol should not give this

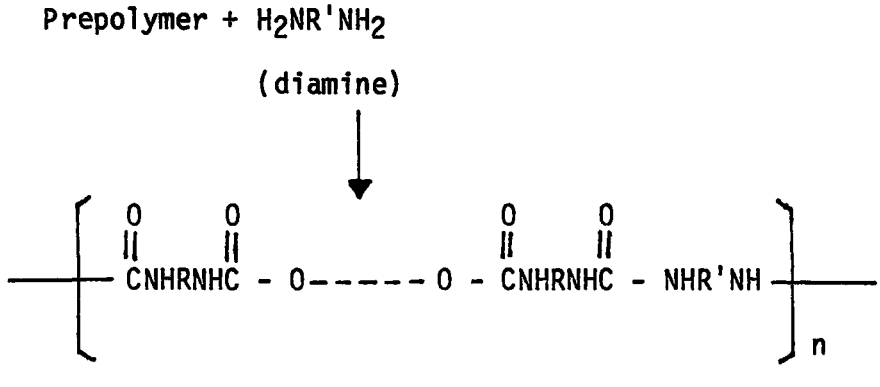
1. PREPOLYMER FORMATION



(Prepolymer)

2. CHAIN EXTENSION

(Chain extender either diamine or diol)



(Polyurethane urea)

Figure 2.5 TWO STEP SYNTHESIS OF SEGMENTED POLYURETHANES

type of complication.

Synthesis of elastomeric polyurethanes is usually carried out in solution using highly polar solvents like dimethyl formamide (DMF) and dimethyl sulphoxide (DMSO). In solution polymerizations careful control is needed to prevent various side reactions involving the isocyanate group. The absence of water is crucial since water reacts with NCO as described previously. Formation of allophanate and biuret linkages producing a branched or crosslinked polymer is also generally not desired. These side reactions must be controlled, usually via temperature, in order to obtain reproducible high molecular weight linear polyurethanes.

For this study a two step solution polymerization was carried out to prepare the various SPU's. In the prepolymer stage the polyether (hydroxy-terminated):MDI ratio was maintained at 1:2. In the chain extension step stoichiometrically equivalent amounts of prepolymer and chain extender were used.

2.2.3 Solid State Properties of Segmented Polyurethanes

Segmented polyurethanes contain alternating blocks of two dissimilar materials classified as hard and soft segments. The hard segment consists of the urea or urethane linked units and the soft segments are low molecular weight polyethers or polyesters. In segmented copolymers the dissimilarity of the two units results in microphase separation or "domain" formation. The soft segments form domains or microphases which are rubbery and amorphous. The hard segments, usually comprising 30 to 70% of the material and consisting of urea and

urethane-linked chain units (isocyanates and diols or diamines), form domains which act as multifunctional crosslinks and as reinforcing filler for the soft domains. In segmented polyurethanes the segments tend to be much shorter than in other block copolymers such as styrene-butadiene, resulting in a greater number of hard-soft segment interactions (Chang and Wilkes, 1975). It is this phenomenon that gives segmented polyurethanes their unique and useful properties.

The solid state morphology is of major importance because the formation of separate domains based on hard and soft segments affects the ultimate properties of the polymer. The effect of variables such as hard segment content, type of hard segment, type of chain extender and type and molecular weight of soft segment on degree of phase separation will also be discussed.

2.2.3a Morphology of Segmented Polyurethanes

The elastomeric properties of segmented polyurethanes depend not only on the relative concentrations of hard and soft segments but also on the degree of phase separation. It is because of the thermodynamic incompatibility of the two segments that domain formation occurs. Thermodynamically the free energy change of domain mixing is positive and there is also a positive surface free energy associated with the interfaces of the units promoting domain growth (Van Bogart, Lilaonitkul and Cooper, 1979). Entropy loss occurs in two ways during phase mixing. The first is the confinement of block joints to the interface and secondly by trying to maintain a constant overall polymer density by reducing the number of available conformations (Van Bogart, Lilaonitkul

and Cooper, 1979). These thermodynamic considerations of free surface energy and entropy promote domain growth and also determine the size and shape of the domains.

The mechanism of nucleation and growth of these domain regions is illustrated in Figure 2.6 (Chang and Wilkes, 1975). The steps of this process are as follows (refer to Figure 2.6):

I. Nucleation between chain segments C and D.

II. Hydrogen bonding compatibility joins hard segments together.

III. Growth of the nucleus starts domain formation. Hard segments radiate outwards.

IV. Segments of other molecules join structure to create larger hard segment domains.

V. Possibility of hard segments domains not being crystalline shown by irregular bending in hard segments.

The resulting morphology for these partially crystalline systems is said to resemble fringed micelle domains (Chang and Thomas, 1979).

2.2.3b Effect of Composition Variables on Phase Separation

The morphology of segmented polyurethanes is dependent on the numerous chemical constituents available for the synthesis of the polymer. The type of soft segment, molecular weight of soft segment, type of chain extender and content of hard segment have all been found to affect phase separation.

Clough and Schneider (1968) investigated the effect of type of soft segment on phase separation by examining polyether and polyester

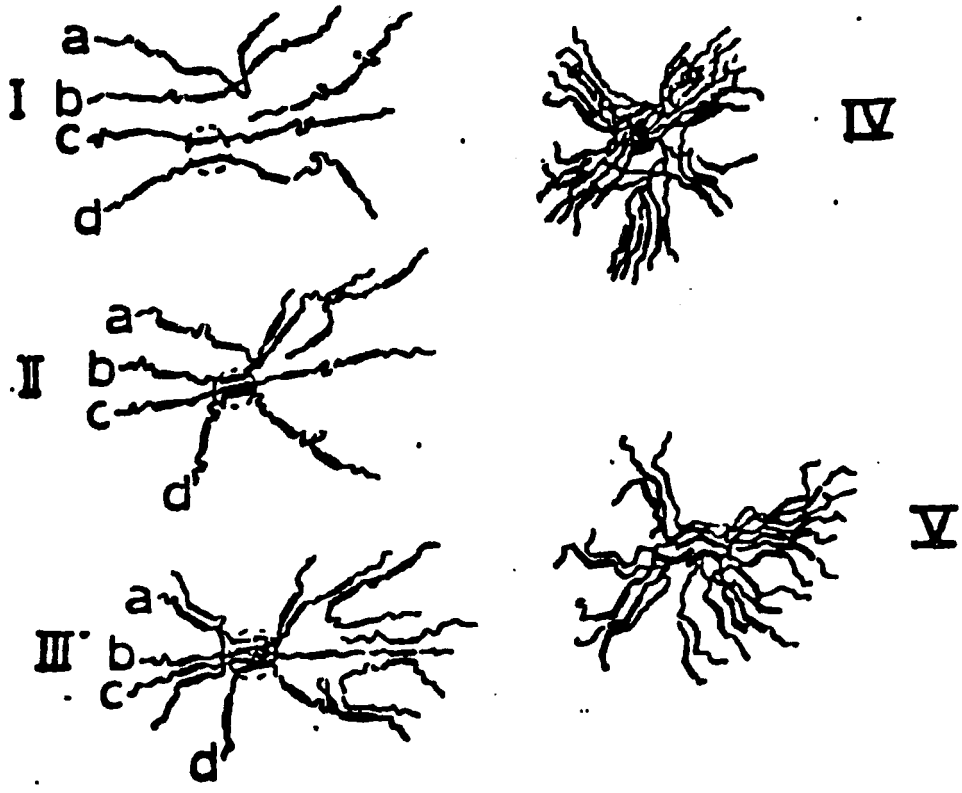


Figure 2.6 NUCLEATION AND GROWTH OF DOMAIN REGIONS
(Chang and Wilkes, 1975)

based polyurethanes. Differential scanning calorimetry (DSC) was used to identify three transition temperatures, the first temperature, T_1, corresponding to the onset of rotation in the polyester and polyether chains (the glass transition); the second T_2, relating to the hydrogen bonding between urethane N-H groups and ester carbonyl groups or ether oxygen and the third T_3, to inter-urethane hydrogen bonding. The transition temperature T_3 was found to be higher than T_2 (Clough and Schneider, 1968). Therefore hydrogen bonds within soft segments will dissociate before inter-urethane bonds as the temperature is raised. These inter-urethane hydrogen bonds contribute strongly to domain formation. There is also evidence of more extensive inter-urethane hydrogen bonding in polyether than in polyester urethanes. Perhaps for this reason, polyether based urethanes show greater phase separation of hard and soft segments (Clough and Schneider, 1968).

Differences in phase separation due to type of soft segment have also been seen for various types of polyether-based urethanes. Chang and Wilkes (1975) studied the phase separation of polyurethanes based on polyethylene oxide (PEO) and polypropylene oxide (PPO). Although PEO and PPO are similar with respect to intermolecular dispersion forces, dipole-dipole interactions and H-bonding tendencies, PPO shows greater domain growth. This is explained by the fact that PPO is more aliphatic and has a slightly lower H-bonding tendency than PEO, making it more incompatible with the hard segment (Chang and Wilkes, 1975).

It was also observed by Hu and Ward (1982) that the higher the molecular weight of the soft segment of a given type the higher the crystallinity. Therefore phase separation increases with increasing

molecular weight of the soft segment due to a decreased tendency for phase mixing (Hu and Ward, 1982).

The effect of type of chain extender on domain formation is based on the symmetry, hydrogen bonding and rigidity of the hard segments. Chain extenders that lack symmetry such as m-methylene diphenylamine (m-PDA) show poorer phase separation than symmetric extenders (Chang and Wilkes, 1975). The chain extender p-PDA showed greater phase separation than m-PDA because it is more symmetric and also since it has a lower tendency for intramolecular H-bonding.

The aliphatic structure of chain extenders such as 1,6 hexane diamine and ethylene diamine resemble the soft segment of the polyurethane. Therefore phase mixing is promoted and the formation of domains is decreased. However aromatic chain extenders are less compatible with the soft segments and phase separation occurs more readily (Hu and Ward, 1982). Aromatic chain extenders show larger degrees of crystallinity because of this incompatibility of hard and soft segments.

Blackwell et al (1982) have postulated that the number of carbons contained in the chain extender will influence the degree of phase separation. Chain extenders with an even number of carbons gave polymers with greater phase separation than those using a chain extender with an odd number of carbons. Yoon and Ratner (1986) have also found that the odd carbon number chain extenders produce polymers with more hard segment at the surface. This was attributed to the poorer phase separation resulting from using a chain extender with an odd number of carbons versus one with an even number of carbons. Similarly Takahara et al (1985) found phase mixing of the hard and soft segments more predominant

for SPU's chain extended with diamines that contained an odd number of methylene groups.

Sung, Hu and Wu (1980) found that polyurethanes extended with a diamine show better phase separation than those extended with a diol. It was postulated that three dimensional hydrogen bonding involving one carbonyl and two NH groups created this difference.

2.2.3c Dynamic Mechanical Properties

Dynamic mechanical measurements can also give information on the degree of phase separation and thermal transitions of the polyurethane. Various characterization methods that can be used to study phase separation include thermal transition temperature measurements, modulus-time and modulus-temperature measurements. The modulus-temperature behaviour of SPU's will be discussed.

The modulus-temperature behaviour of several types of polymer structure is shown in Figure 2.7. At temperatures below T_g all polymer systems are in the glassy state. As the temperature increases through the glass transition region all polymer systems respond as expected, except segmented polyurethanes which show unusual elastic behaviour above T_g (Cooper and Tobolsky, 1966; Huh and Cooper, 1971; Illinger, Scneider and Karasz, 1972; Van Bogart, Lilaonitkul and Cooper, 1979). There are two defined transitions indicated by the steep drops in modulus. These transitions should correspond to the T_g and T_m of the individual segments (Van Bogart et al, 1979). It is known however that the sample composition, segmental lengths and method of preparation (solution or cast) all influence phase separation which will affect the temperature

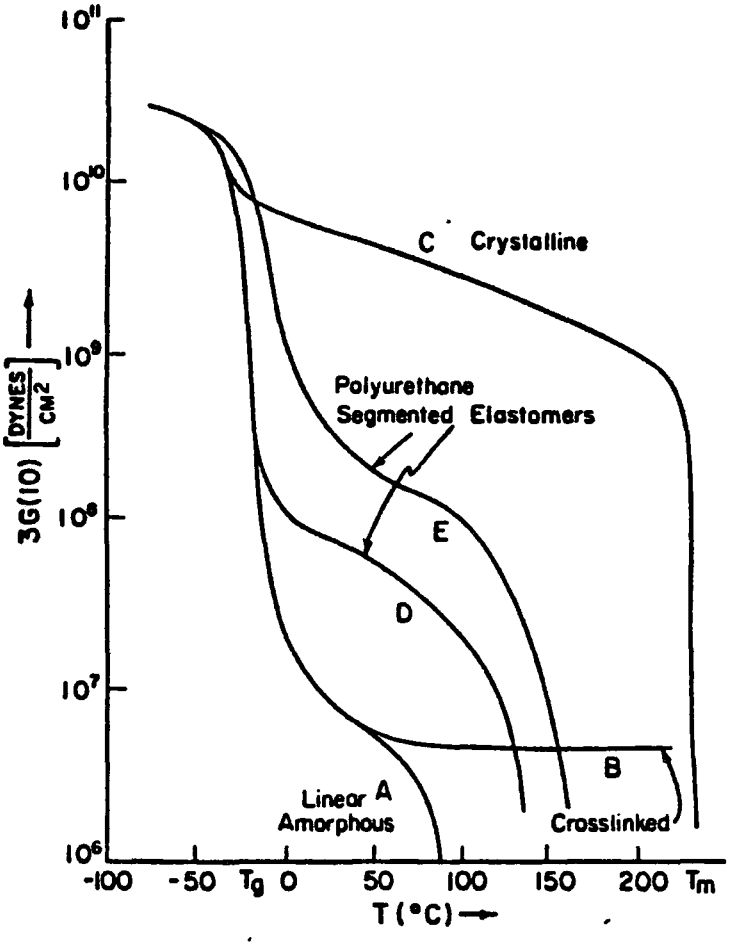


Figure 2.7 STORAGE MODULUS vs. TEMPERATURE CURVES

(A) Linear Amorphous Polymer

(B) Crosslinked Polymer

(C) Semi-crystalline Polymer

(D) PTMO/MDI/BD SPU (32% MDI by wt.)

(E) PTMO/MDI/BD SPU (38% MDI by wt.)

(Van Bogart, Lilaonitkul and Cooper, 1979)

locations of the transition points (Van Bogart et al, 1979).

2.2.3d Stress-Strain Behaviour

The ultimate properties of segmented polyurethanes are very important from a practical standpoint. The stress-strain behaviour and ultimate strength of the SPU will determine its applicability to perform in various blood contacting situations. Stress-strain measurements and ultimate properties were examined in this thesis.

The stress-strain behaviour of a typical polymer is found in Figure 2.8. The initial straight line portion of the curve (stress is approximately proportional to strain) is a measure of the rigidity of the material. The ratio of stress to strain for this section is known as the "modulus of elasticity" or "Young's modulus". The point A in the curve is known as the yield point of the material. The elongations before the yield point are recoverable and are a measure of the elastic deformation of the polymer. After the yield point, the polymer cannot immediately recover and is said to have a measure of plastic deformation. The stress at the breaking point is known as the ultimate tensile or breaking strength.

Several segmented polyurethanes have been shown to exhibit this type of behaviour. Examples of this stress-strain behaviour in relation to two groups of segmented polyurethanes are shown in Figures 2.9 and 2.10 (Chang and Wilkes, 1975). Figure 2.9 represents SPU's synthesized from a range of molecular weights for the soft segment monomer, PEO, and chain extended with methylene diphenylene amine (p-PDA). Figure 2.10 represents a similar series of SPU's chain extended

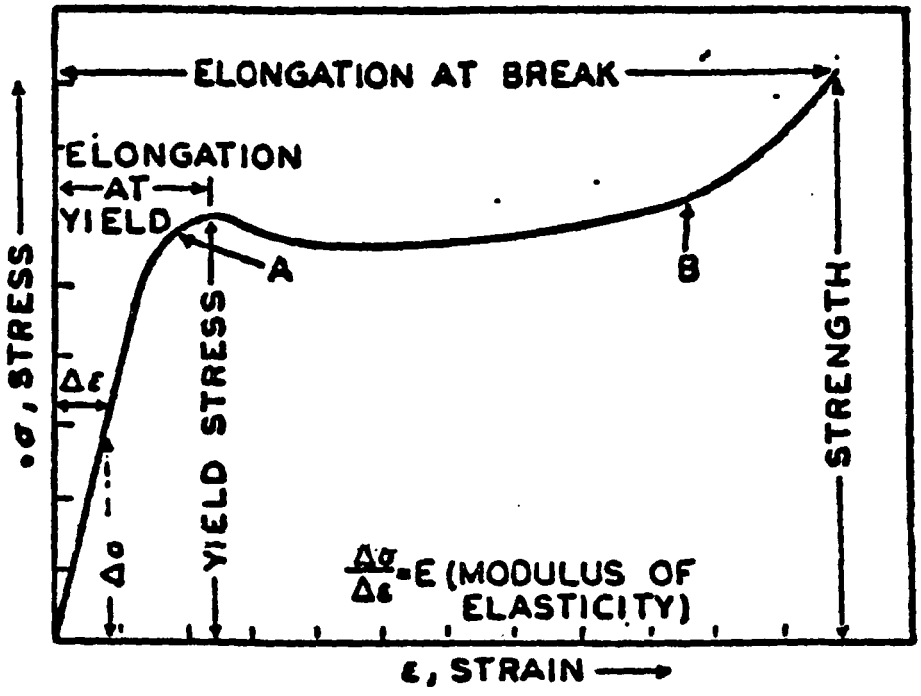


Figure 2.8 STRESS-STRAIN BEHAVIOUR OF A TYPICAL POLYMER

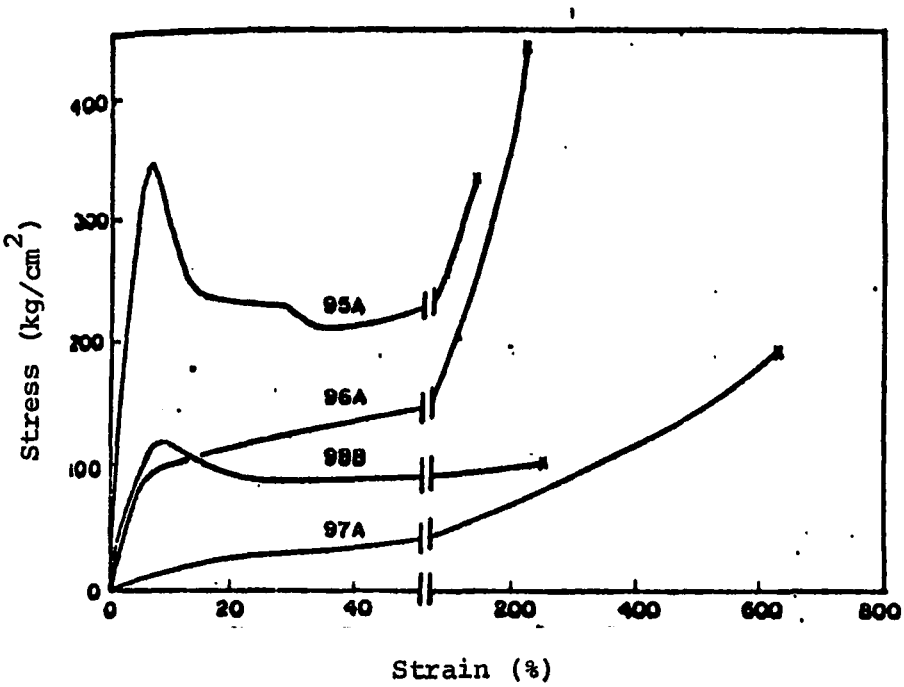


Figure 2.9 STRESS-STRAIN DATA FOR VARIOUS PEO BASED SPU'S EXTENDED WITH p-PDA (Chang and Wilkes, 1975)

p-methylene diphenylene amine

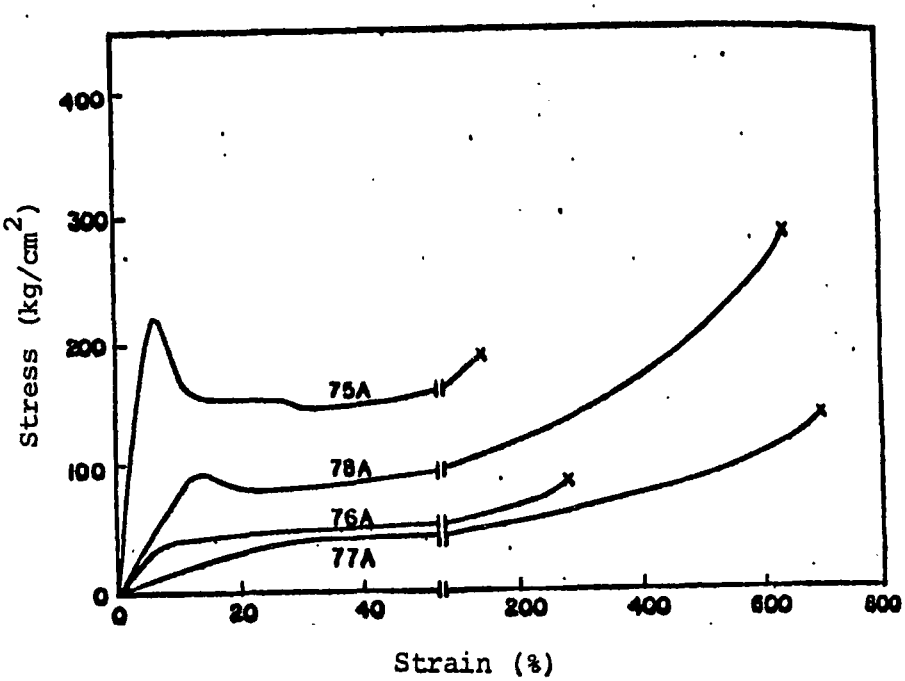


Figure 2.10 STRESS-STRAIN DATA FOR VARIOUS PEO BASED SPU'S EXTENDED WITH ED (Chang and Wilkes, 1975)

ethylene diamine

with ethylene diamine (ED). From these Figures it can be seen that the moduli of elasticity for SPU's are high in the initial portion of the curve indicating a fair degree of rigidity. It should also be noted that this initial rigidity occurs for strain values up to 20%. However the final elongations of the SPU's at ultimate failure occur at over 600% strain.

The effect of the molecular weight of the soft segment on the ultimate properties of the SPU can be seen from Figures 2.9 and 2.10. In both Figures the number average molecular weight of the PEO increases in the series 95A to 97A and 75A to 78A (98B represents a different casting condition). The trend with increasing soft segment molecular weight (corresponding to decreasing hard segment content) shows decreases in modulus and greater extensibilities. The high modulus and yielding behaviour of 78A is explained by Chang and Wilkes (1975) as being due to a change in morphology as a result of the crystallization of the PEO soft segment material. Sung and Smith (1980) have made similar findings on the effect of the molecular weight of the soft segment.

The difference in ultimate properties as a result of the chain extender can be explained by the phase separation of the hard and soft domains (Chang and Wilkes, 1975; Sung and Smith, 1980). In Figures 2.9 and 2.10 it can be observed that the 95A series is higher in both modulus and breaking strength than the 75A series. The 95A series was chain extended with p-methylene diphenylene amine (p-PDA), an aromatic chain extender, and the 75A series extended with ethylene diamine, an aliphatic chain extender. It has already been discussed that the lesser compatibility of an aromatic chain extender with the soft segment results

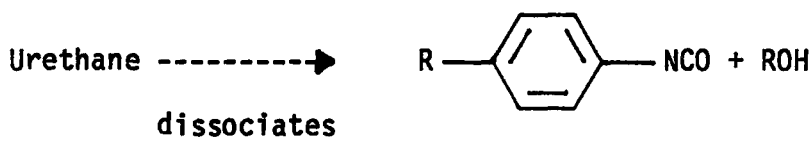
in increased phase separation. It is therefore believed that increased phase separation results in higher breaking strength and modulus (Chang and Wilkes, 1975; Sung and Smith, 1980).

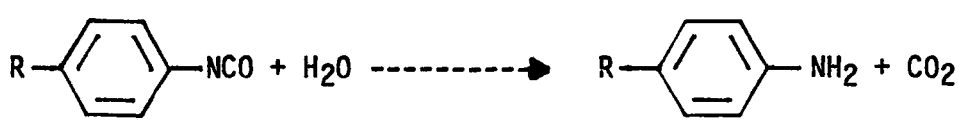
2.2.4 Segmented Polyurethanes as Biomaterials

Segmented polyurethanes are presently among the materials most extensively used for blood contacting situations. The potential diversity in surface properties of these materials along with their excellent elastomeric properties led to extensive research that began in 1967 (Boretos and Pierce, 1967). The first polyurethanes synthesized for biomedical applications were polyester based polyurethanes (Boretos and Pierce, 1967). It was quickly found, however, that these polymers are unsuitable for in vivo applications due to rapid hydrolytic degradation (Boretos, 1980). Polyether urethanes, on the other hand, are hydrolytically stable making them suitable for long term implants. These materials are therefore the segmented polyurethanes of choice for biomedical applications.

The hard segment (urethane or urea) for most biomedical polyurethanes is based on an aromatic diisocyanate. Specifically 4,4' diphenylmethane diisocyanate (MDI) is the basis for many biomaterials in use today. Compared to other diisocyanates, MDI presents fewer problems from a safety/toxicity point of view due to its low vapour pressure (0.0075 mm Hg). In addition it gives polymers having excellent resilience, abrasion resistance and hydrolytic stability (Boretos, 1980). However concerns have increased recently about the possible carcinogenic degradation by-products of MDI based polyurethanes (Ward, 1984). In the

molding or extrusion of SPU's, the relatively high temperatures cause the urethane group to dissociate to hydroxyl and isocyanate. If water is present at this point aromatic amines or aniline compounds may be formed, some of which have been found to be carcinogenic (Ward, 1984):





Therefore some researchers (Szycher et al, 1977) have developed polyether based SPU's based on an aliphatic diisocyanate. Tecoflex HR® is an example of this type of SPU and has been found by Szycher et al (1977) to be acutely non-toxic and to perform mechanically as well as other biomedical SPU's.

As mentioned previously the thermodynamic incompatibility of the hard and soft segments of SPU's results in microphase separation. Furthermore since SPU's are not homopolymers the bulk composition of the polymer solid state has the potential to be different from that of the solid surface. These two factors are very important in determining the biocompatibility of these polymers.

For example, this difference in composition between the surface and the bulk phase appears to be important in determining the rates of platelet adhesion during blood contact. It has been shown that the hard segment phase is more reactive to platelets than the soft segment phase (Lyman et al, 1975; Merrill et al, 1980, 1982; Sa Da Costa, 1980, 1981). Merrill et al (1980, 1982) found typical platelet retention index values of p = 0.8 (the platelet retention index is defined for a particular experiment as the fraction of platelets in whole citrated blood that are retained on the test surface). In contrast they found that the soft segment phase has platelet retention values of about 0.2 to 0.3. Using X-ray photoelectron spectroscopy (XPS) to measure the content of hard and soft segment phases in the surface, it was found that the surfaces with the highest fraction of ethereal carbon (carbon 1s signal) had the lowest platelet retention indices (Merrill et al, 1980). Ethereal carbon can be used as measure of the soft segment phase of polyether-based SPU's. The hard segments of SPU's are therefore believed to be platelet reactive. Stupp et al (1977) have shown that aromatic rings in the hard segment give lower platelet adhesion indices than aliphatic chains. It is hypothesized that the peptide-like bonds in the aromatic segment have weak interactions with the surface of the platelet (Stupp et al, 1977). However, the concentrations of hard segment phase in the surface region using appropriate fabrication techniques can be kept relatively low compared to the soft segment.

The majority of recent research on polyurethane biocompatibility concerns the soft segment. The three main soft segments studied for use in biomaterials are polytetramethylene oxide (PTMO), polypropylene oxide

(PPO) and polyethylene oxide (PEO). Results from Merrill et al (1980) and Sa Da Costa et al (1981) show that platelet adhesion increases in the order PEO < PPO < PTMO. Merrill et al (1980) also found that certain combinations of PEO-PPO gave platelet retention indices of approximately 0.04. This low value was explained by the molecular disorder resulting from the mixed soft segment (Merrill et al, 1980).

Since PEO soft segments provided the surface with promising behaviour in relation to platelet adhesion, researchers have concentrated considerable effort on the testing of this material. Table 2.1 illustrates the low platelet retention indices for various PEO based materials. Typical values of 0.80 for polymers containing only the hard segment of SPU and 0.30 for polymers containing only the soft segment of SPU are also found in Table 2.1. The segmented polyurethanes containing both segments also show a trend of lower platelet retention values with increasing molecular weight of the soft segment (increasing C-1s fraction).

Another factor contributing to the low platelet retention of PEO is its high water capacity. Merrill et al (1980) suggest that swelling of the PEO segment phase with water might further mask the hard segment beneath the surface. Whatever the reasons, the long chain PEO segments in SPU's seems to confer unique surface properties and their use in biomedical devices shows promising results.

The distribution of two distinct phases in the surface of SPU's has been reported to depend on the method of fabrication (Lyman et al, 1975; Sung et al, 1978). As indicated in the above discussion it seems to be desirable to have enrichment of the soft segment in the surface of

XPS. CHARACTERIZATION AND PLATELET RETENTION

	Polymer Surface	ϕ, fraction C_{1s} as ether C-O-C	$\bar{\rho}$, Platelet Retention Index
A)	Model Compounds		
	HSA[1]	0	~ 0.80
	PEG 8000[2]	1.00	0.30
B)	Segmented Polyurethanes Based on PEG and CHDI[3]		
	PEG 600	0.75	0.045
	1000	0.85	0.067
	1500	0.9	0.053
	3500	1.00	0.042
C)	Segmented Polyurethane Based on PEG, TDI and MDI[4]		
	PEG 1000	0.6	~ 0.06

[1]Alternating copolymer of CHDI and ED
[2]The α,ω diol of PEO, MW about 8000
[3]By the synthesis outlined in this paper (2 step)
[4]Synthesized from TDI (tolylene diisocyanate),
MDI (4,4'diphenyl methyl diisocyanate),
PEG 1000 and ED by 3 step process[7,8]

Table 2.1 XPS CHARACTERIZATION AND PLATELET RETENTION (Merrill et al, 1982)

the implant. Fabrication factors such as the type of solvent, percent polymer in solution, drying temperature, rate of drying and interfacing material (air side versus mold side) are important in determining the surface composition (Lyman et al, 1975). Sung et al (1978) investigated the effect of the mold surface for two commercial polyurethanes, Biomer® and Avcothane®. Biomer® is a SPU consisting of soft segments derived from PTMO and a hard segment from MDI and a diamine. Avcothane® (now known as Cardiothane®) is reported to be a polyurethane/poly (dialkyl-siloxane) block copolymer (Sung et al, 1978). It was found generally that there was a higher concentration of the soft segment in the air side of the film. Therefore this surface would be desired as the blood contacting surface since hard segments of the SPU increase platelet retention.

2.2.4a Surface Modifications of SPU's for Biomaterials

Modification of the surface of SPU's has been investigated as a means of reducing their thrombogenic potential. Heparin bonding to the surface of the SPU is one such modification (Esquivel et al, 1983; Heyman et al, 1985). Esquivel et al (1983) bonded heparin to the surface via a glutaraldehyde-stabilized complex. It was found that thrombus formation was significantly reduced on these SPU's and platelet retention was lessened in relation to non-heparinized surfaces. Heyman et al (1985) immobilized heparin to the surface of the SPU via an alkyl "spacer arm" (H_2N-(CH_2)-NH_2). The stable bond formed had no effect on the interaction between the heparin and the coagulation factors (inactivation of thrombin and Factor X_a). These heparinized SPU's again displayed

significant reduction of thrombus formation when compared to non-treated surfaces (Heyman et al, 1985).

Jansen and Ellinghorst (1985) have modified the SPU surface by radiation induced grafting of various hydrophilic polymers like poly-2-hydroxyethyl methacrylate (P-HEMA) and polyacryramide. As indicated previously, crosslinked hydrophilic polymers or hydrogels are known to have good biomedical properties but poor mechanical behaviour when water swollen. The materials found by grafting these polymers onto a SPU, which is both hydrolytically stable and possesses good mechanical properties, were further chemically reacted to introduce functional groups such as hydroxyl, carboxyl and sulphonic acid (Jansen and Ellinghorst, 1985). These groups are thought to be potentially important for the antithrombogenic properties of the material.

Sharp et al (1971) introduced carbon black on the surface of the polyurethane by dipping or coating vascular grafts and artificial heart diaphragms. The resulting highly negative surface charge gave good results in experimental animals. Recent work by Lelah et al (1984) has investigated the antithrombogenic potential of polyurethane zwitterionomers and anionomers. Polyurethane zwitterionomers and anionomers were found to be more antithrombogenic than uncharged polyurethanes. This is accounted for by the high concentration of the ionic sulphonate group at the surface (Lelah et al, 1984). It is the presence of these functional groups and the resulting strong negative charge in the surface that have been related to improved antithrombogenicity.

CHAPTER 3

EXPERIMENTAL METHODS

3.1 POLYMER SYNTHESIS

This section deals with the synthesis of the eight segmented polyurethanes used for further testing and study along with other experimental polyurethanes that did not possess adequate mechanical properties to be useful as materials. Although all polymers were prepared by the same general procedure, reaction conditions were changed in some cases to obtain polymers suitable for mechanical testing. These changes will be identified for each polymer system as it is discussed.

3.1.1 Materials

A list of the compounds used in the synthesis and post processing of the SPU's is given in Table 3.1.

3.1.2 Solvent Distillation

Dimethyl sulphoxide and dimethyl formamide were both distilled to remove water prior to use in polymer synthesis (dimethyl sulphoxide is hygroscopic). The solvents stored in the presence of a "drying agent" (Molecular Sieves, Type 4A) were used in polymer synthesis within two

TABLE 3.1 CHEMICAL LIST

	CHEMICAL	SOURCE
1)	Dimethyl Sulphoxide (DMSO)	Caledon Labs, BDH Chemical
2)	Dimethyl Formamide (DMF)	Caledon Labs, BDH Chemical
3)	Polypropylene Glycol 1025 (PPG 1025)	BDH Chemical
4)	Polypropylene Glycol 2025 (PPG 2025)	BDH Chemical
5)	Polyethylene Glycol 1500 (PEG 1500)	Union Carbide, Aldrich
6)	Ethylene Diamine (ED)	Aldrich
7)	1,3-Diamino-2-hydroxypropane (DHP)	Aldrich
8)	4,5 Dihydroxy - 1,3 benzene disulphonic acid disodium salt monohydrate (Tiron®)	Aldrich
9)	N-Methyldiethanolamine (MDEA)	Aldrich
10)	4-4' Diphenylmethane Diisocyanate (MDI)	Mobay
11)	Stannous Octoate	Sigma
12)	Molecular Sieves (Type 4A, beads)	Aldrich

days of distillation.

The distillation apparatus is schematized in Figure 3.1. One litre of solvent was distilled for each run (approximately 700 ml of solvent was used for a polymerization). The solvent was poured into the 2 litre round bottom flask and the vacuum apparatus set-up. The temperature was controlled at between 60 and 70°C using the rheostat and heating mantle. The vacuum was controlled at between 1 and 2 mm Hg using a manostat.

The initial fraction (25-50 ml) which contains any water, was discarded. The remainder of the distillate was collected and placed in a dry container with a small amount of molecular sieves (Type 4A, beads).

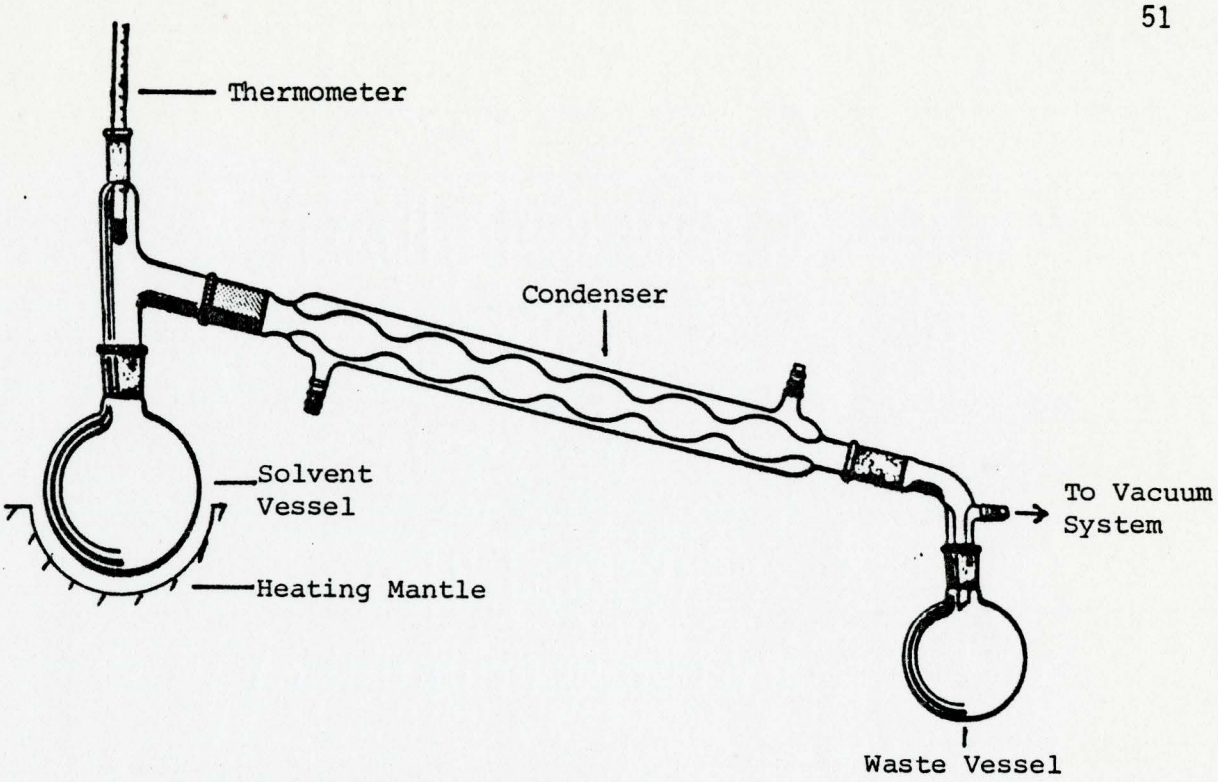
3.1.3 Polyether Degassing

The polyethylene glycol and polypropylene glycol were both degassed prior to use in polymer synthesis. The apparatus is shown in Figure 3.1.

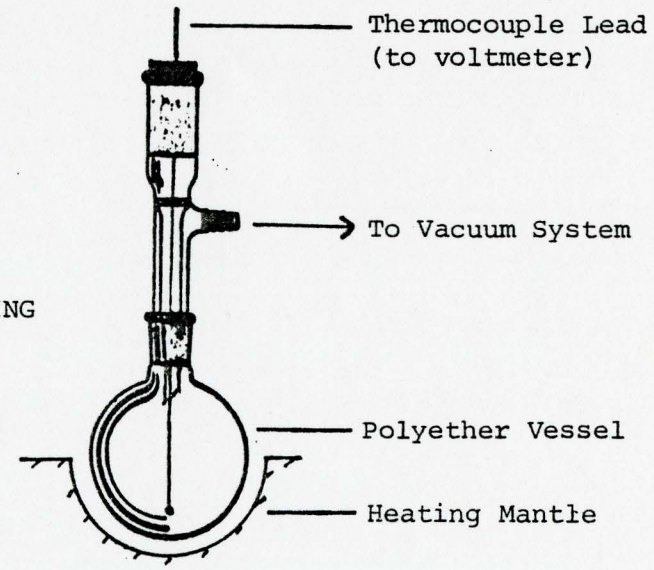
The glycols in slight excess of the amount required for the polymerization were placed in a 500 ml round bottom flask and attached to a vacuum apparatus. The temperature was controlled at approximately 50°C under a vacuum of 1-2 mm Hg. Degassing was performed for at least 16 hours and the glycols used immediately in polymer synthesis.

3.1.4 Polyurethane Synthesis

SPU synthesis was performed in the apparatus schematized in Figure 3.2. All SPU samples were synthesized using a two step process, the first step being prepolymer formation and the second step chain



SOLVENT DISTILLATION APPARATUS



POLYETHER DEGASSING
APPARATUS

Figure 3.1 SOLVENT DISTILLATION AND POLYETHER DEGASSING APPARATUS

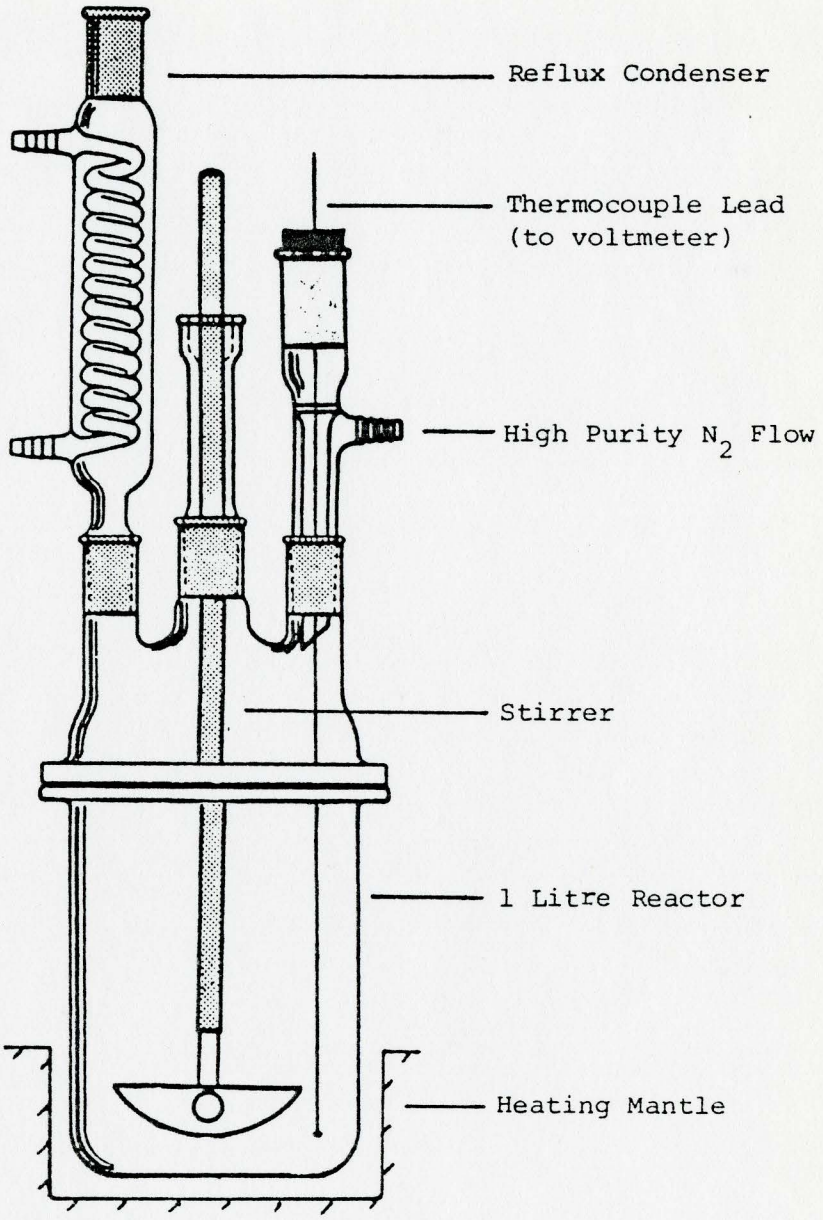


Figure 3.2 POLYURETHANE SYNTHESIS APPARATUS

extension. Details of the two step mechanism can be found in the literature survey section.

The synthesis of the polymers did not proceed under the same reaction conditions in all cases. However for the different polymer series based on chain extender, the reaction conditions were similar. Therefore each of these series will be described individually. The chain extenders used for the three series are:

a) ethylene diamine (ED)

b) 1,3 diamino-2-hydroxypropane (DHP)

c) 4,5 dihydroxy-1,3 benzene disulphonic acid disodium salt monohydrate (Tiron®)

A fourth series in which N-methyldiethanolamine (MDEA) was used as a chain extender will also be briefly discussed. Unfortunately polymers with adequate mechanical properties were not obtained for this series; however, the attempted synthesis is worth noting.

3.1.4a Ethylene Diamine (ED) Extender

The synthesis of segmented polyurethanes using ethylene diamine as a chain extender is straightforward. These materials may be described as "classical" SPU's. The procedure used to prepare this series of polymers is as follows:

In the prepolymer step, the molar ratio of diisocyanate to polyether was maintained at 2:1. The polyether (0.1 moles, previously degassed) is placed in the reaction kettle. The MDI, which is in flake form, is then added (0.2 moles or 250.0 g to the nearest 0.1 g). Finally 500 mL of distilled DMSO is added to the monomer mixture. The reaction

kettle is then sealed as quickly as possible and a flow of high purity N_2 is started.

The temperature of the mixture is raised to between 80 and 90°C (temperatures in excess of this may lead to allophanate and biuret formation). The temperature is monitored using a thermocouple immersed in the mixture. Once the desired temperature is reached the reaction is allowed to proceed for 3 hours. During this time the mixture is constantly stirred and solvent is refluxed back into the system.

After the 3 hour reaction period the contents are allowed to cool to approximately 30°C. At this point the chain extender is added. The amount of chain extender is calculated on the basis of a 1:1 molar ratio with the theoretical amount of prepolymer formed in the first step (0.1 mole). The ethylene diamine is mixed with 200 mL of distilled DMSO before it is added to the prepolymer. The reaction between the ethylene diamine and the prepolymer is very rapid as indicated by a sudden, large increase in the viscosity of the mixture. Stirring is maintained for 30 minutes to ensure complete conversion even though the reaction is essentially complete within the first minute (Brash et al, 1970).

The polymer is then precipitated in distilled water. It is washed thoroughly with distilled water to remove DMSO. The washed polymer is then chopped in a Waring blender and dried initially in a conventional forced air oven at 70°C. The polymer is then dried to constant weight at 50°C in a vacuum oven. This final drying step typically lasts at least 48 hours.

3.1.4b 1,3 Diamino-2-hydroxypropane (DHP) Extender

The nature of this extender resulted in reaction conditions identical to those for ethylene diamine. Both extenders have reactive amine groups attached to a short chain aliphatic residue. The major difference is the pendant -OH- group at the 2-position. As stated previously a hydroxyl group can react with an isocyanate. However since urea formation is generally much faster than urethane (Saunders and Frisch, 1962) it was assumed that the -OH- group would not be involved in the chain extension reactions. This was verified by ^{13}C and ^{1}H NMR measurements (see below section 3.2.4).

3.1.4c 4,5 Dihydroxy-1,3 benzene disulphonic acid disodium salt monohydrate (Tiron®) Extender

In this series prepolymer formation was performed in a fashion identical to the procedure already outlined. The major difference for this series was in the chain extension step.

Tiron® is an aromatic compound that has two reactive hydroxyl groups for chain extension of the prepolymer. The sulphonate groups also have the potential to react with isocyanate but since they are much less nucleophilic than hydroxyl it is assumed that the chain extension proceeds through the hydroxyl groups. Hydroxyl groups, particularly phenols, are not as reactive as the aliphatic amine groups of either ED or DHP. Therefore the chain extension had to be catalyzed and carried out over longer periods of time to obtain polymers of reasonable molecular weight and mechanical properties. In the chain extension step using Tiron®, 0.15 wt% (based on total reaction mixture) stannous

octoate is added as catalyst along with the Tiron® (0.1 mole) dissolved in 200 mL of DMSO. The reaction mixture did not show a sudden increase in viscosity as in the first two series and the reaction was continued for about 2 hours before precipitating the polymers. However there was an exception to this general behaviour. The PEG 1500-based polymer immediately polymerized to a solid gel-like mass after a few seconds of chain extension with Tiron®. The resulting polymer was precipitated and dried but could not be redissolved in solvent. It was obvious that this polymer was highly crosslinked.

3.1.4d N-methyldiethanolamine (MDEA) Extender

A series of polymer syntheses using MDEA as chain extender was attempted to try to incorporate a quarternary amine group in the hard segment. The synthesis was performed using the reaction scheme given by Hwang et al (1981) and Miller et al (1983). In this reaction the MDI was initially dissolved in dimethyl formamide (DMF) at a concentration of 30% by weight. The soft segment monomer (PEG or PPG) and stannous octoate catalyst were also dissolved in DMF at about 30% and 0.15% by weight respectively.

These solutions were reacted for 3 hours under N_2 at 60-70°C. MDEA was then added in stoichiometric proportions to the theoretical amount of prepolymer formed and reacted for an additional 2 hours. (It should be noted that Hwang et al (1981) and Miller et al (1983) used PTMO as a soft segment monomer).

The chain extension of these polymers did not proceed in the same manner as in the other series. Stirring was continued for 4 hours after

addition of the chain extender without a noticeable change in viscosity. The polymers that precipitated from the mixture were extremely gummy and the films formed were mechanically weak. Several attempts to synthesize this series of polymers failed to produce mechanically acceptable elastomeric polyurethanes.

3.2 CHARACTERIZATION

Several characterization methods were performed to give quantitative information on the polymer samples. They included low angle laser light scattering (LALLS) for absolute determination of weight average molecular weight, water contact angle measurements to determine relative hydrophilicity of the polymer film surfaces, electron spectroscopy for chemical analysis (ESCA) to give surface chemical composition, elemental sulphur analysis to determine sulphur content of the Tiron® series and nuclear magnetic resonance (NMR) spectrometry to determine free hydroxyl content of the DHP series. These various methods as applied to the SPU's synthesized in the present work are now described.

3.2.1 Low Angle Laser Light Scattering (LALLS)

Low angle laser light scattering was performed on each polymer sample to give an absolute value of $\bar{M}_w$. Since the polyurethane samples are novel in some respects a measure of dn/dc, the refractive index increment used in LALLS calculations, had to be obtained for each system. In this work dimethyl formamide (DMF) was used as solvent.

Solution preparation for light scattering and dn/dc measurements were performed as follows:

1) polyurethane samples were first dissolved in DMF, reprecipitated in water to remove impurities and dried to constant weight;

2) approximately 0.5 g of these polymer samples were weighed (precision of $\pm$ 0.002 g) and placed in a 100 mL volumetric flask;

3) DMF was then added, the polymer dissolved and solvent added to the mark;

4) dilutions of approximately 4/5, 3/5, 2/5, 1/5 of the original solution were used to make a series of polymer solutions for LS measurements.

The initial concentration found to be suitable for the DHP and the Tiron® series was 0.5 g/100 mL. However difficulties arose with this concentration for the ethylene diamine series and it was found that for these polymers about 1/10 of this concentration was suitable.

dn/dc was measured using a KMX-16 laser differential refractometer (He-Ne laser operating at 633 nm). The refractive index of the polymer solutions was measured relative to the solvent itself. A value of n (refractive index) was determined for the various concentrations by multiplying together two machine parameters: 1) $k = 1.33843 \times 10^{-7}$ (fixed instrument parameter); 2) a value (L-R)sample determined by subtracting (L-R)solvent from (L-R)solution (varies for each concentration). A plot of n versus concentration allows calculation of dn/dc by measuring the slope.

Light scattering measurements were performed using a KMX-6 low angle laser light scattering photometer. A schematic representation of a low angle laser light scattering photometer is shown in Figure 3.3. The cell windows must first be carefully cleaned. Typical cleaning procedure involves washing in succession with acetone, methanol and detergent, then

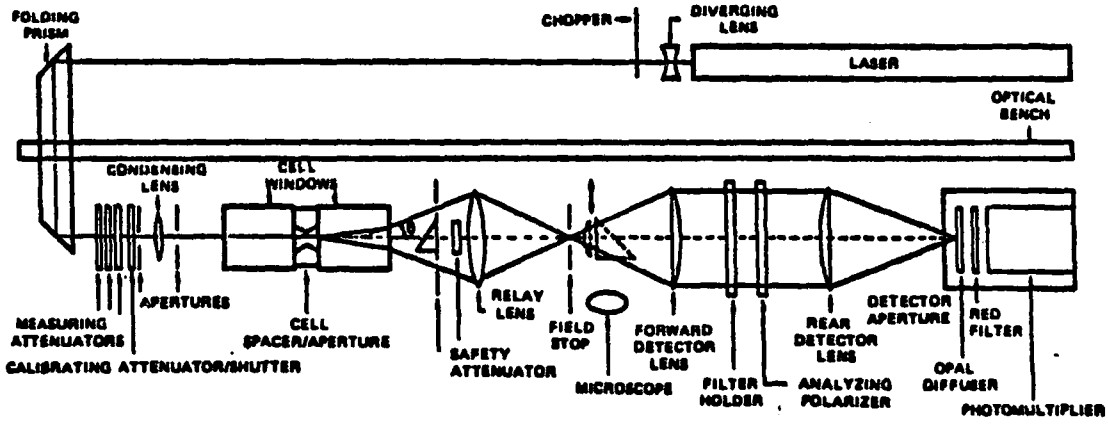


Figure 3.3 LOW ANGLE LASER LIGHT SCATTERING PHOTOMETER (Yau, Kirkland and Bly, 1979)

rinsing with deionized water and drying over isopropanol vapours. Distilled methyl ethyl ketone (MEK) was used for quick cell cleaning with lens tissue. The clean cells were then assembled in the cell holder making sure that they were properly seated (etched arrows on sides of cells point to each other) and the spacer bar inserted between the cells.

The solvents and solutions were introduced to the cell using a syringe pump and a gas tight syringe. The solutions were passed through two filters; one at the tip of the syringe, the other at the inlet hole of the spacer. To check for gas bubbles, the cell was removed from the compartment and examined. If gas bubbles were seen they were removed by increasing the flow rate to 1.0 mL/min. or by gently tapping the cell on the bench. The flow rate was then returned to 0.3 mL/min. and the cell placed back into the compartment.

Light scattering data were collected for the solvent and subsequent solutions beginning with the lowest and ending with the highest concentration. Initially the beam is centered to obtain a small bright red dot when viewed through the microscope. The scattered light is defined by an annular ring (thin red ring around centre dot). If the background is not black the cell is dirty and must be cleaned. Measurements can now be made using different combinations of attenuators to get readings of G_0 and G_θ (machine parameters used in calculation of molecular weight).

The molecular weight was calculated using the following equations:

$$R_O = \frac{G_\theta}{G_O} * (\sigma' \chi)^{-1} * D$$

G_O, G_θ machine parameters

$(\sigma' \chi)^{-1}$ is a function of solid angle, field stop and refractive index of solvent. In our measurements the solid angle was 6-7 and field stop 0.2.

D is a function of the attenuating filters.

R_θ polymer = R_θ solution - R_θ solvent

$$\frac{KC}{R_\theta} = \frac{1}{M_w} + 2A_2C$$

The value K is obtained using the following equation:

$$K = 408 \times 10^{-8} * (n_D)^2 \times (dn/dc)^2$$

c = concentration (g/mL)

n_D = refractive index of solvent

KC/R_θ versus concentration was then plotted. The inverse of KC/R_θ at c = 0 gives the weight average molecular weight ($\bar{M}w$) of the polymer and the slope is twice the second virial coefficient.

3.2.2 Contact Angle Measurements

Water contact angles on polymer films were measured using a goniometer telescope. The water used was four times distilled. Polymer films were prepared on glass microscope slides. Polyurethane solutions of approximately 10 wt% in DMF were spread on clean slides and dried in a vacuum oven at 50°C for at least 48 hours prior to contact angle measurements.

The water was delivered to the polymer surface using a thin diameter glass pipette. The angle the water made in contact with the polymer surface was then measured by lining up the cross hairs of the telescope with the slope of the water droplet. The angle was then read from the goniometer. At least six measurements of water contact angle were performed on each polymer surface. An illustration of the measurement is shown in Figure 3.4.

3.2.3 Electron Spectroscopy for Chemical Analysis (ESCA)

ESCA or X-ray Photoelectron Spectroscopy (XPS) is used to determine all elements except hydrogen and helium in the first 50 Angstroms or so of the surface. Atomic concentrations can be determined with a relative accuracy of 10%. ESCA is based on X-ray induced photoelectron emissions. Photoelectron energies identify elemental species present and their bonding environment and photoelectron intensities give information on atomic concentrations.

ESCA was performed at the University of Washington, Seattle by Ratner and McElroy (1985) using a Surface Science Labs SSX-100 spectrometer. The spectrometer utilizes a monochromatic aluminum X-ray

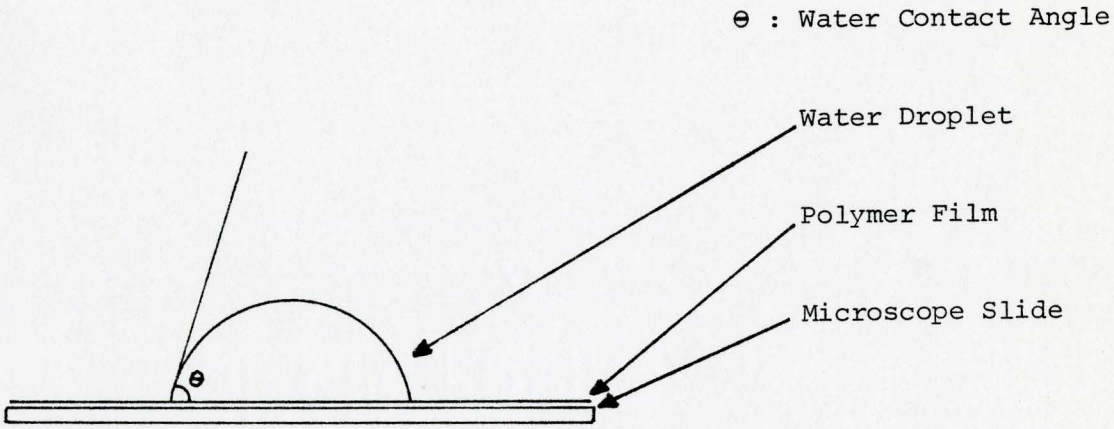


Figure 3.4 WATER CONTACT ANGLE MEASUREMENT

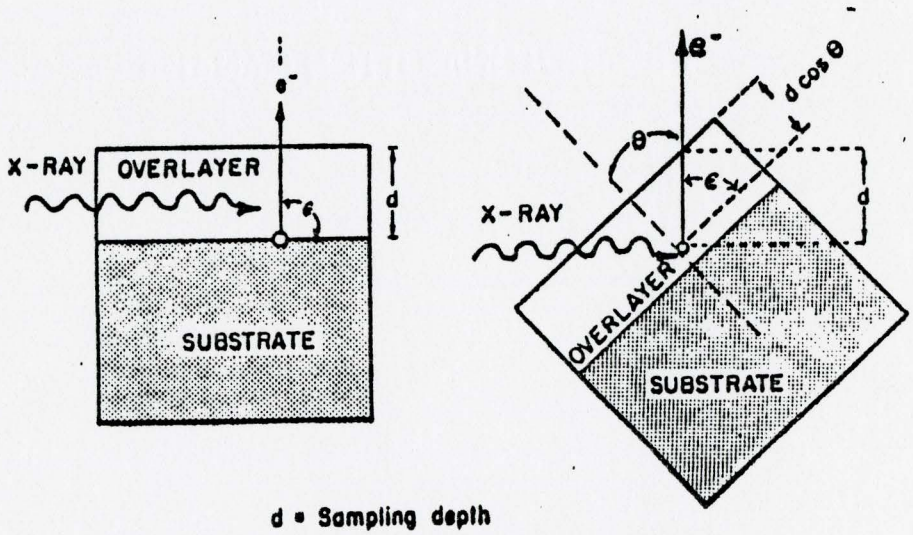


Figure 3.5 ESCA ANGULAR EMISSION GEOMETRY
θ = Take-off Angle ϵ = Sample Angle
(Ratner and McElroy, 1985)

source of variable spot size (150-1000 μm diameter).

ESCA measurements (Ratner and McElroy, 1985) were performed as a function of take off angle to determine if a compositional gradient exists near the surface. Figure 3.5 illustrates how a high take-off angle (grazing angle) gives information on the top most surface layer and a low take-off angle (normal surface angle) contains a large contribution from the deeper bulk layers.

A low resolution/high sensitivity spectrum of each element was obtained at 20 degree angular intervals. Intermediate resolution spectra of the carbon 1s peak indicated the presence or absence of carbamate and hydroxyl/ether groups. A high resolution carbon 1s peak was also obtained at grazing and normal angles.

3.2.4 Nuclear Magnetic Resonance Spectrometry (NMR)

NMR was performed at McMaster University, Dept. of Chemistry by Storer-Folt (1985). The ^{1}H NMR spectra were obtained on a WP80 Bruker FT NMR spectrometer at 80.03 MHz with a 45° pulse width (6.0 μs) and an aquisition time plus time delay of 5 sec for 16 scans. ^{13}C NMR spectra were obtained at a frequency of 20.115 MHz with a 45° pulse width (6.3 μs) using an inverse pulse sequence with a 5 second scan cycle for 17,000 scans.

The two polymer series examined by this method were the ED series and the DHP series. It was hoped that the hydroxyl of the DHP could be determined using the ED series as controls. All polymers samples to be examined by NMR were dried at 60°C for 24 hours and then dissolved in deuterated DMSO at a concentration of 15 w/v% and filtered into a 5mm

O.D. NMR tube (10 mm O.D. for ^{13}C).

3.2.5 Sulphur Content

Sulphur analysis was performed by Guelph Chemical Laboratories for the "Tiron®" series. It was accomplished by burning the sample in an oxygen flask with hydrogen peroxide and water. The resulting sulphur dioxide was absorbed in solution and titrated with barium perchlorate to determine sulphur content.

3.3 MECHANICAL TESTING

Tensile stress versus strain behaviour of the SPU's was measured with an MTS material testing system (Dept. of Mechanical Eng. at McMaster University). Films of the polyurethane samples were prepared from a 10 wt% solution in DMF. The solutions were centrifuged at 3000 rpm for 15 minutes to remove any undissolved polymer. The solutions were cast on a 1/4" thick flat Teflon plate. To produce films with enough mechanical strength for the load cell conditions of the test, multiple layers of the polymer solution were used. The films were all dried in a vacuum oven at 50°C for at least 48 hours after initially drying in a forced air oven at 60°C. Samples for mechanical testing were cut using an ASTM dumbbell die (width 0.125 inches).

Polymer samples were placed in the grips of the test apparatus to give the shortest possible gauge length (0.100 inches) so that maximum elongations would be possible. Using this gauge length the upper limit of elongation was about 3000% of the original sample length. The crosshead speed was set at 1 inch/min. The maximum scale setting for polyurethanes based on PPG 2000 or PEG 1500 was set at 1 lb. maximum. For PPG 1000 based polymers the scale was set for 5 lb. maximum.

3.4 FIBRINOGEN ADSORPTION STUDIES

3.4.1 Tube Preparation

In these studies glass tubing segments of 2.5 mm I.D. and 19 cm long were used as substrates for SPU coatings. The glass tubes were first soaked in chromic acid cleaning mixture (Chromerge) for 3 hours and then washed in distilled water. The tubes were then dried overnight at 70°C in a vacuum oven.

The polymer solutions used for coating were prepared in the same manner as for mechanical testing. The clean tubes were dipped in the polymer solution and then placed vertically in a drying rack. This first coat was dried for 3 hours in a vacuum oven at 50°C. The tubes were then inverted and again dipped in the polymer solution. This second coat was dried for at least 24 hours in a vacuum oven at 50°C. This two-dip technique was used for polymers based on PPG.

Polymers based on PEG are hydrophilic and tend to absorb water. Thus if such polymers are coated directly onto glass, subsequent water absorption when placed in contact with an aqueous fluid will cause peeling of the coating. Hence such coatings could not be used in studies involving contact with blood plasma such as the adsorption studies performed in the present work. To overcome this difficulty the tubes were coated as before with a PPG based polymer. Two additional dips were then performed using the PEG based polymers. In this way the PEG-based polymer is bonded to the PPG-based polymer and water absorption in the former does not cause delamination. Clean microscope slides were prepared in the same manner as the tubing segments and contact angle

measurements made to check the hydrophilicity of the coating.

3.4.2 Fibrinogen Adsorption

The materials used for the fibrinogen adsorption study were as follows: i) Pooled human platelet poor plasma from blood collected in CPD anticoagulant was obtained from the Canadian Red Cross, Ottawa; ii) Human fibrinogen - Grade L was from Kabi, Stockholm.

Fibrinogen was radiolabelled with ^{125}I using the ICl method (Uniyal and Brash, 1982). This material was added to the plasma as a tracer in amounts ranging up to 10% of normal plasma fibrinogen concentration. The experiment performed is based on previous studies in this laboratory (Uniyal and Brash, 1982; Brash and ten Hove, 1984) and consists of determining the quantity of fibrinogen adsorbed during 5 minutes of contact from plasma diluted to various extents with isotonic Tris buffer, pH 7.4. From this data a "5-minute isotherm" can be constructed, the characteristics of which give an indication of the response of the plasma to the contacting surface.

A schematic diagram of the experimental set-up is illustrated in Figure 3.6. All experiments were performed under static conditions at room temperature. The tubes were equilibrated overnight with isotonic Tris buffer (pH 7.4), which was then displaced by the plasma, using about 20 tube volumes. The adsorption time for all isotherms was 5 minutes. When adsorption was complete, the plasma was displaced by buffer, again using 20 tube volumes, and leaving the buffer in contact for 10 minutes. Two additional 20 tube volume rinses with a 10 minute interval between were performed. After the third rinse the tubes were drained.

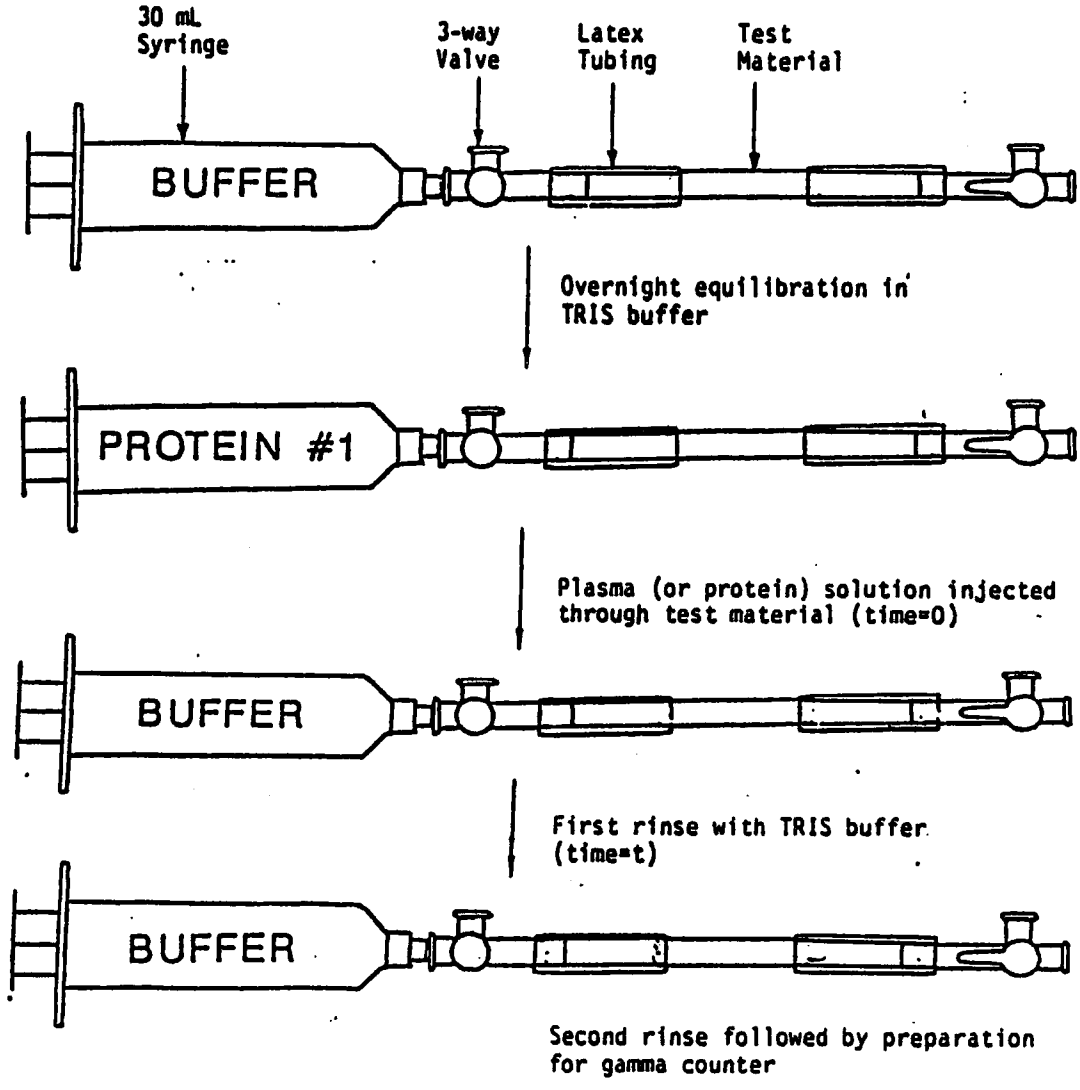


Figure 3.6 FIBRINOGEN ADSORPTION EXPERIMETNAL SET-UP (Wojciechowski, 1986)

A 1.5 cm piece was cut off each end of the tubing segment and the rest of the tube was then cut into 4 sections of 4 cm each. These were counted in a Beckmann Biogamma Counter for 10 minutes. At the same time a solution count was done using 0.1 mL of the labelled solution and 0.9 mL buffer.

The fibrinogen concentration in the plasma pool was determined by the coagulation lab of the McMaster Medical Centre and reported to be 2.9 g/L.

The surface area was calculated from accurate length and inner diameter measurements and the surface concentration of adsorbed fibrinogen was calculated using the following equation:

$$\text{Adsorption } (\mu g/cm^2) = \frac{\text{net surface count (CPM)}}{\text{surface area } (cm^2)} \times \frac{\text{plasma fibrinogen concentration (mg/mL)}}{\text{solution count (CPM/mL)}} \times 1000$$

The net surface count is obtained by subtracting the background from the total surface count and multiplying by a geometric counting factor for the glass tubing segments (determined to be 1.06).

Prior to determining the isotherms, each surface was checked for preferential adsorption of labelled fibrinogen versus unlabelled fibrinogen. This was done by preparing three solutions of pure labelled fibrinogen in isotonic Tris buffer (pH 7.4) all with concentration of 1 mg/mL, but containing 90%, 50% and 10% labelled fibrinogen respectively. The procedure was identical to that followed for the plasma isotherm experiments, except that the adsorption time in this case was 2 hours, to allow for equilibrium adsorption.

CHAPTER 4

RESULTS AND DISCUSSION

4.1 CHARACTERIZATION

Characterization of polymers is important if any attempt is to be made to obtain a correlation between physical/chemical and biomedical properties. Due to the variation in both the soft segment monomers and the chain extenders used in the preparation of the SPU's for this thesis, the individual polymers were characterized using techniques that would indicate the course of the various polymerizations. Even though some of the characterization techniques provided questionable results, important information was obtained on the suitability of these procedures in relation to SPU's. Eight polyurethanes were studied. Three chain extenders, ethylene diamine (E), 1,3 diamino hydroxy propane (O), and 4,5 dihydroxy-m-benzene disulphonic acid or Tiron® (T) and three polyethers, PPG 1000 (1), PPG 2000 (2), and PEG 1500 (3), were used. A polymer coded PUO2 therefore indicates a PPG 2000 based SPU extended with 1,3 diamino hydroxy propane. Table 4.1 indicates the tests performed on each polymer system.

POLYMER	NMR	SULPHUR CONTENT	LALLS	CONTACT ANGLE	ESCA	STRESS-STRAIN BEHAVIOR	FIBRINOGEN ADSORPTION
PUE1			**	*	*	*	*
PUE2			**	*	*	*	*
PUE3			**	*	*	*	*
PU01	*		**	*	*	*	*
PU02			*	*	*	*	*
PU03			**	*	*	*	*
PUT1		*	*	*	*	*	*
PUT2		*	*	*	*	*	*

* Test Performed

** Only dn/dc values obtained, LALLS results could not be interpretered.

TABLE 4.1 SPU'S SYNTHESIZED AND CHARACTERIZATIONS PERFORMED

4.1.1 Nuclear Magnetic Resonance (NMR)

Nuclear magnetic resonance (NMR) was used to characterize the 1,3-diamino hydroxy propane (DHP) extended series of SPU's. It was assumed in this series, that the reaction in the chain extension step would proceed through the amine groups and not the pendant hydroxyl group of DHP. This was thought to be the case since amine groups are much more reactive with isocyanates than hydroxyl groups as stated previously in Chapter 2.2.1. PUE1 (chain extended with ethylene diamine) was used as a "conventional" or "control" SPU since it contains only amine end groups and its NMR spectra should be useful for interpretation of the PUO1 NMR. Both ^{1}H and ^{13}C NMR were utilized to obtain a measure of the hydroxyl groups in DHP that remained unreacted. The following discussion is based on a report given by Storer-Folt (1985).

Figure 4.1 shows ideal repeat units with the assignments for ^{1}H and ^{13}C NMR. Tables 4.2 and 4.3 show the ^{1}H NMR data for PUE1 and PUO1 respectively. The sequence length distributions of the narrower units (diisocyanate-diol and diisocyanate-extender) were calculated using a method outlined by Suzuki (1971) and compared to similar polymerizations. It was found that the sequence lengths of PUE1 and PUO1 were greater than those found by Suzuki (1971) and this is most likely due to the presence of short crosslinks. Any grossly crosslinked species would be removed from the solutions previously by filtration. Therefore the variable solubility in DMSO may have an affect on the results and should be examined separately.

The calculation of the free hydroxyl content of the chain extender is therefore not possible by this method. If the ^{1}H NMR

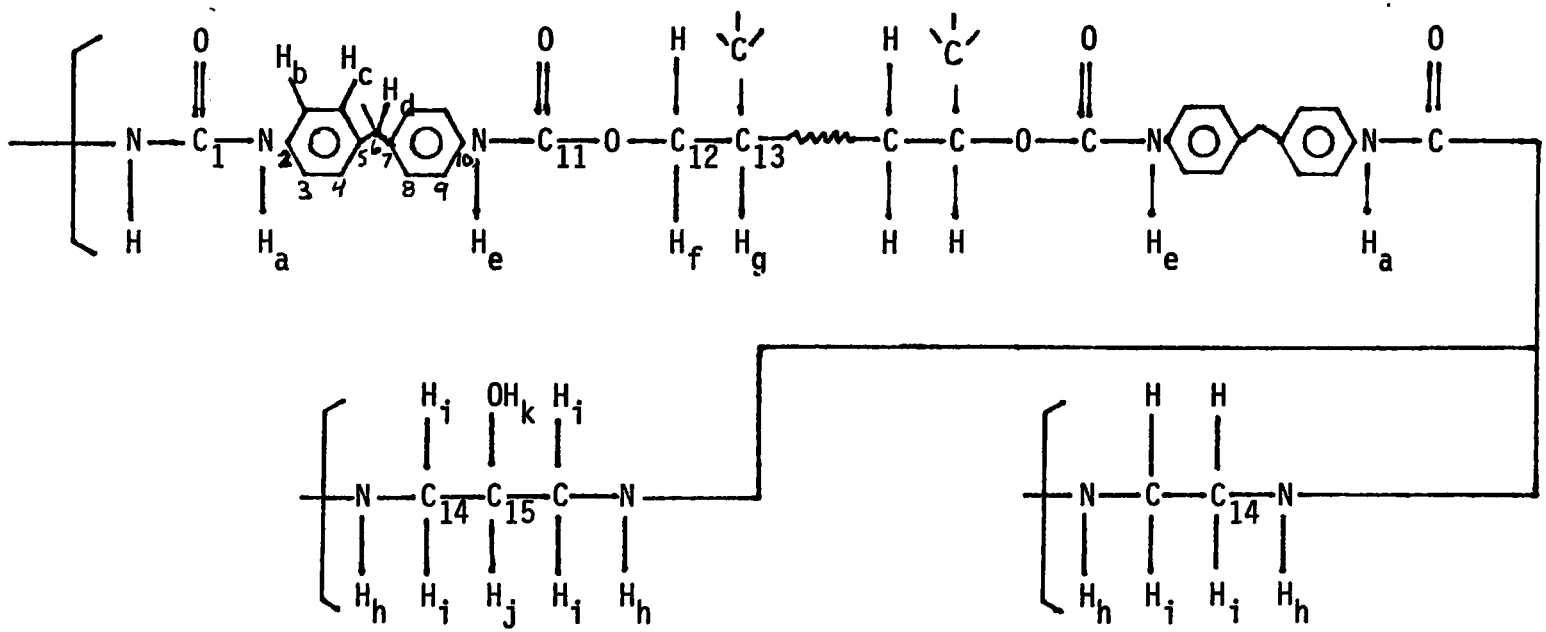


FIGURE 4.1 SCHEMATIC REPRESENTATION OF IDEAL REPEAT UNITS WITH NMR DESIGNATIONS FOR PUE1 AND PUO1 (SEE TABLES 4.2 - 4.4)

PEAK #	CHEMICAL SHIFT (ppm) (a)	ASSIGNMENT (b)	AREA	# OF C ATOMS (c)	RELATIVE AREA
1	8.6	N-H_a	5	2	2.5
2	7.55-7.46	MDI End Groups			
3	7.09	N-H_a	6.25	2	3.13
4	7.62-6.72	Same as Peak 5			
5	6.56-6.13	H_b, H_c	46.5	16	2.9
6	5.26	N-H_h	3.13	2	1.56
7	4.07	H_2O Impurity			
8	2.62	H_f			
9	2.49	DMSO			
10	2.40	H_a			
11	2.02	ED Impurity			
12	1.87	Unknown Impurity			
13	1.66	H_i			
14	1.51	H_d			
15	0.32	H_g			
16	0.16	H/PPG			

(a) Relative to DMSO (2.49 ppm)

(b) Based primarily on model compound chemical shifts

(c) Based on stoichiometric amounts if ideal polymerization

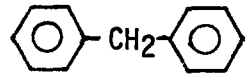
TABLE 4.2 ^1H NMR OF PUE1

CHEMICAL PEAK #	SHIFT (a)	ASSIGNMENT (b)	AREA	RELATIVE # OF C ATOMS (c)	AREA
1	8.57	$N\text{-}H_e$	7.5	2	3.75
2	7.64	$N\text{-}H_a$	7.5	2	3.75
3	6.54-6.12	H_b, H_c	66	16	4.2
4	5.3	$N\text{-}H_h$	5.5	2	2.75
5	4.2	H_k	3.0	1	3.0
6	3.94	H_2O+H_j	5.5	1	5.5
7	2.61	H_f			
8	2.49	DMSO			
9	2.2-2.4	H_d			
10	1.62	H_i			
11	1.22	H_d			
12	0.55	H_g			
13	0.15	H/PPG			

a,b,c - see Table 4.2

TABLE 4.3 ^1H NMR OF PUO1

assignments are correct, then it may be estimated that 87.4% of the hydroxyl groups remained unreacted. Due to the limited solubility of the polymer, solid state NMR may have been an alternative method worth exploring.

^{13}C NMR was used to try to verify the assignments made in ^{1}H NMR. The results are given in Table 4.4. Peaks 1 and 2 were assigned to the two environments containing N since chemically equivalent species are known to fall in the region between 152-156 ppm. The distinction between the two N environments was made on the basis of linewidth, the broader linewidth referring to the environment with two N atoms as opposed to the environment with one N atom and one O atom. Peak 4 was assumed to be an end group because its linewidth is the same as that of the urethane and the net area was equivalent to that of urea. Difficulty arose in trying to assign the region between 75-68 ppm. Peaks 13-15 were assumed to be impurities in the system since they are not in proportion to the rest of the spectrum. The resonances assigned as peaks 16/17 and 18/19 could be NH_2CH and  respectively.

However a problem existed in trying to assign the CHOH peak of PUO1. There were differences in the spectra between PUE1 and PUO1. For example peaks 16 and 19 were resolved and peak 17 was shifted up field slightly in the PUO1 spectra. However the significance of these differences is not clear and could not be used as confirmation of the existence of the CHOH resonance. A specific model compound that could give chemical shift information at this level of resolution would be needed to verify the ^{13}C NMR results.

PEAK #	ASSIGNMENT (a)	CHEMICAL SHIFT (+ 0.05 ppm) (b)	
		PUE1	PU01
1	C_I (NH-C(=O)-NH)	155.38	155.44
2	C_{II} (NH-C(=O)-OR)	153.05	153.05
3	C_5	138.32	138.39
4	End Group	137.64	137.60
5	C_7	137.12	137.12
6		135.37	135.40
7	C_3, C_8	135.18	135.16
8		134.19	134.12
9		133.97	133.92
10	C_4 + C_8	128.62	128.65
11	C_{10}	118.30	118.27
12	C_2	117.80	117.75
13	(?)	74.52	74.51
14	(?)	72.33	72.36
15	(?)	72.17	72.20
16	C_{15} (?)	------	71.08
17	C_{12} (?)	70.85	70.88
18	C_6 (?)	69.54	69.48
19	C_{14}/C'_{14} (?)	69.38	69.16
20	CH_2/PPG	17.08/16.73	17.10/16.74

(a) Based primarily on model compound chemical shifts
(b) Relative to DMSO

TABLE 4.4 SUMMARY OF ^{13}C NMR DATA

4.1.2 Sulphur Content

Sulphur contents as determined by Guelph Chemical Laboratories for the Tiron® series are reported in Table 4.5. The values of 0.53% and 0.19% sulphur found for the polymers PUT1 and PUT2 are less than the sulphur contents expected on the basis of the ideal repeat units using a stoichiometry of 2:1:1 diisocyanate:polyether:chain extender.

Obviously the repeat unit obtained is different from that expected. At the prepolymer stage a stoichiometric ratio of 2:1 diisocyanate to diol was used. The resulting prepolymer should be an endcapped polyether. However no measure of residual MDI was made and therefore MDI could still be present which could react further in the chain extension step. Also the average number of molecules in the prepolymer may be higher than three thereby creating larger prepolymer species with no sulphur incorporation at this point.

The low percent sulphur in the final SPU is thought to be due mainly to the chain extension step. The reactivity of Tiron® is not known but is expected to be relatively low. The hydroxyls of Tiron® are phenolic and would react very slowly with isocyanate in comparison to aliphatic amine groups such as in ethylene diamine. For this reason longer reaction times and a catalyst were needed when Tiron® was used. This may have led to undesired side reactions (e.g. allophanate or biuret formation between prepolymers) creating larger chains with no incorporation of Tiron®.

Also Tiron® is supplied as a monohydrate. The H_2O present has the ability to react with isocyanate to form an amine which will react readily to form a urea linkage. Again such a reaction would consume

POLYMER	SULPHUR CONTENT FOUND (%)	SULPHUR CONTENT EXPECTED (%)	MOLECULAR WEIGHT OF THEORETICAL* REPEAT UNIT	MOLECULAR WEIGHT OF REPEAT UNIT TO ACHIEVE SULPHUR CONTENT FOUND
PUT1	0.53	3.5	1832	12075
PUT2	0.19	2.3	2832	33684

* Theoretical - calculated using a repeat unit containing one glycol molecule, two MDI molecules and one chain extender molecule.

TABLE 4.5 SULPHUR CONTENT OF TIRON® SERIES OF SPU'S

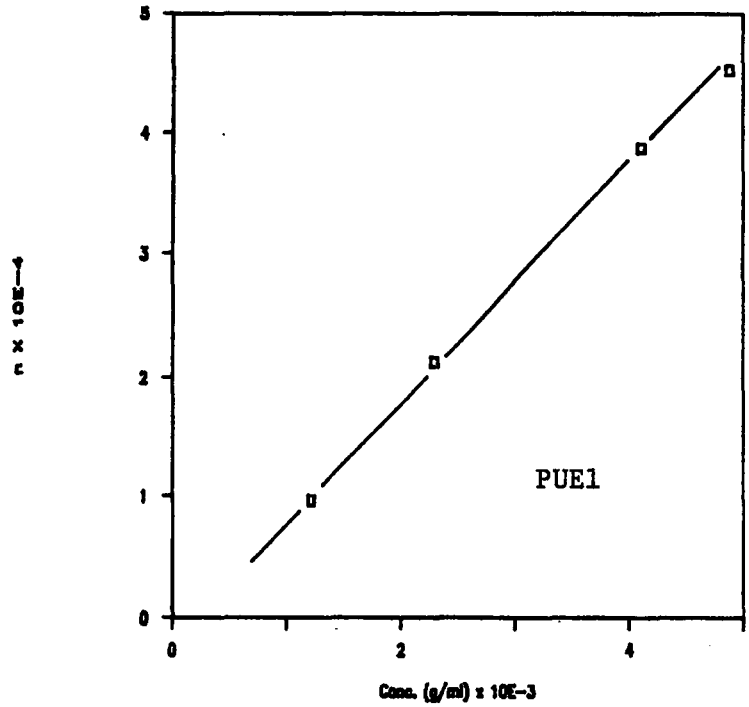
isocyanate without incorporating Tiron® into the polymer. A measure of the residual sulphur in the reaction media would have given additional information on the amount of Tiron® actually utilized in the reaction. This should be done in future work.

4.1.3 Low Angle Laser Light Scattering (LALLS)

Low angle laser light scattering (LALLS) was used to obtain absolute weight average molecular weights for the various SPU's synthesized. Considerable experimental difficulty was experienced in utilizing this technique. As a consequence, the data in most cases could not be interpretated to give estimates of the molecular weight. Only the data that did give reasonable results will be discussed. Possible reasons why LALLS did not produce meaningful results in the other cases will be indicated.

The differential refractive index or dn/dc had to be measured for each individual polymer system, since it could not be assumed that dn/dc for the various SPU's would be the same even in the same solvent due to the diversity of the constituents used to prepare the polymers. dn/dc plots for each polymer system are shown in Figures 4.2 to 4.9 and the results tabulated in Table 4.6.

dn/dc values were obtained by measuring the slope of n vs c plots. A measure of the correlation coefficient of each system, as shown in Table 4.6, indicates that this analytic method produced results that were valid. In every case the correlation coefficient was 0.99 or 1.00. dn/dc data for similar polymer systems in the appropriate solvent could not be found in the literature and therefore a check on the magnitude of



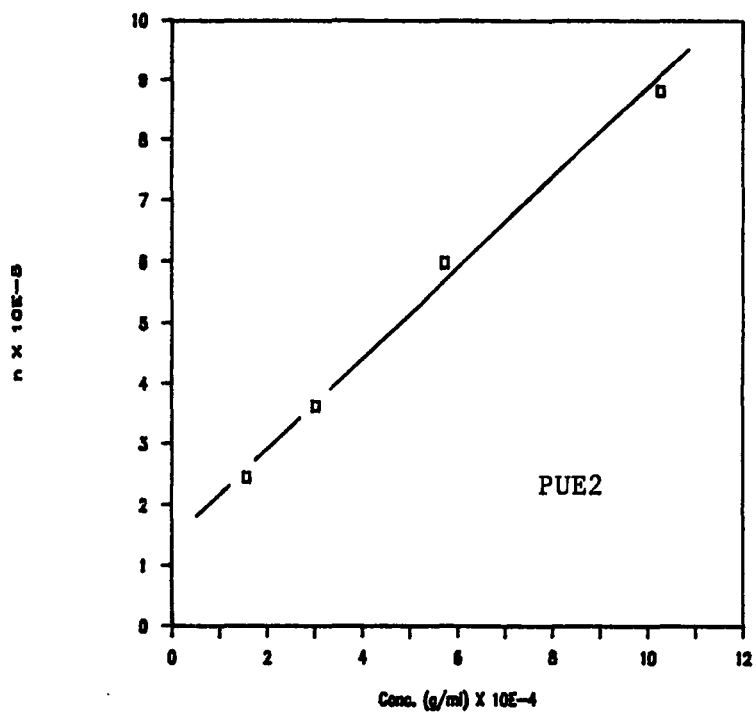
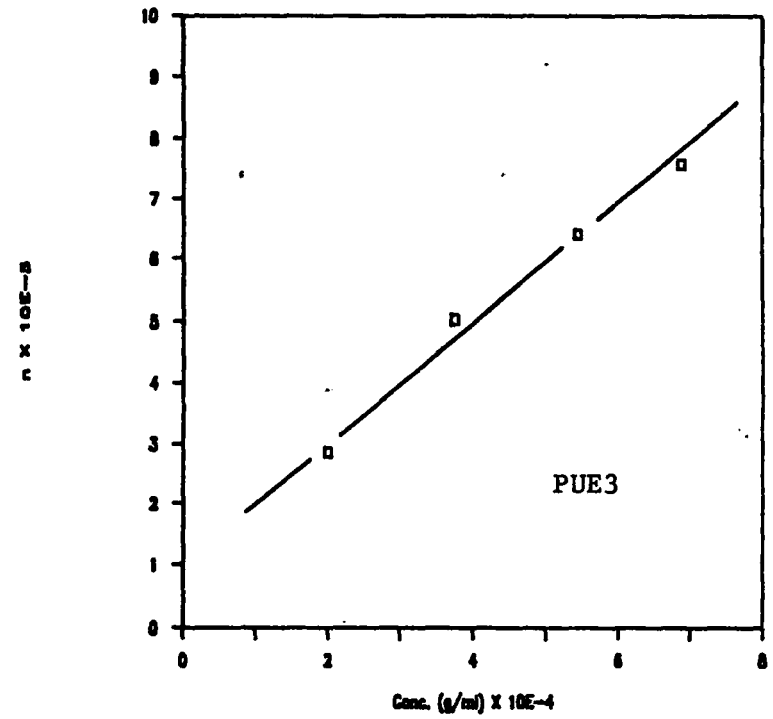


FIGURE 4.2 AND 4.3 REFRACTIVE INDEX INCREMENT PLOTS (DMF AT 25°C): PUE1 AND PUE2



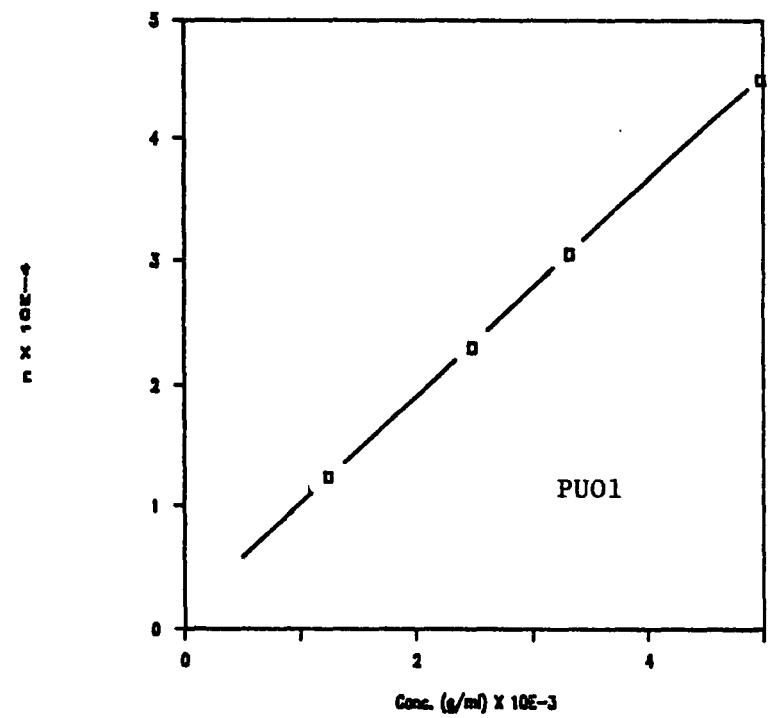
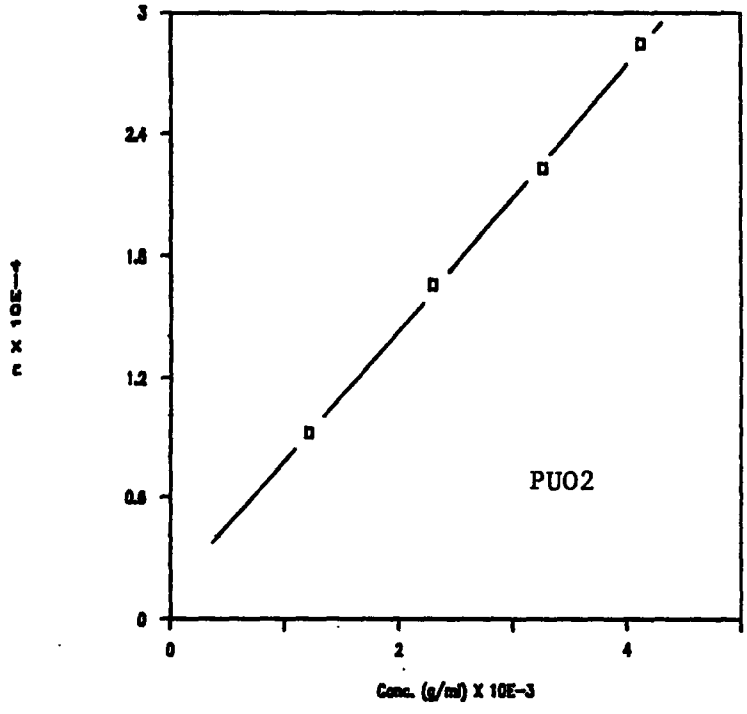


FIGURE 4.4 AND 4.5 REFRACTIVE INDEX INCREMENT PLOTS (DMF AT 25°C): PUE3 AND PUO1



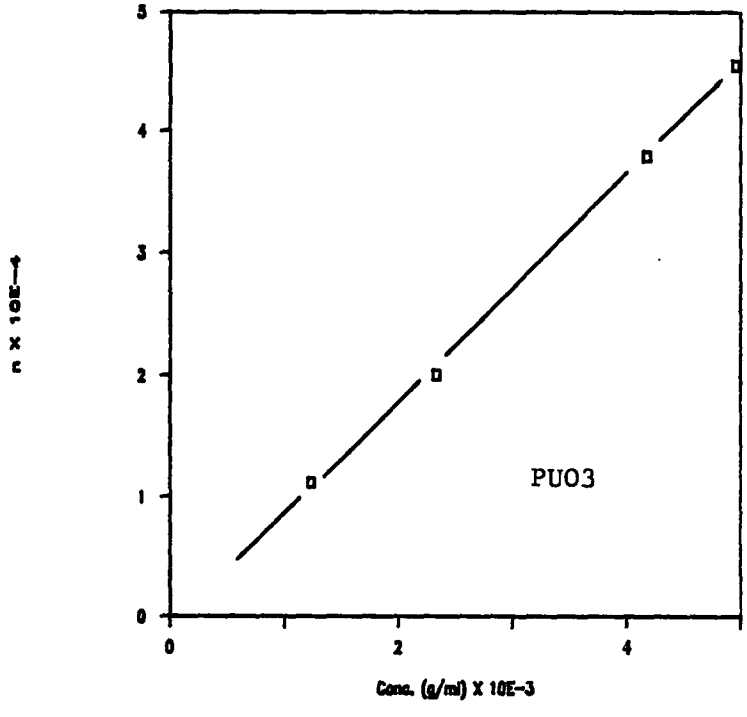
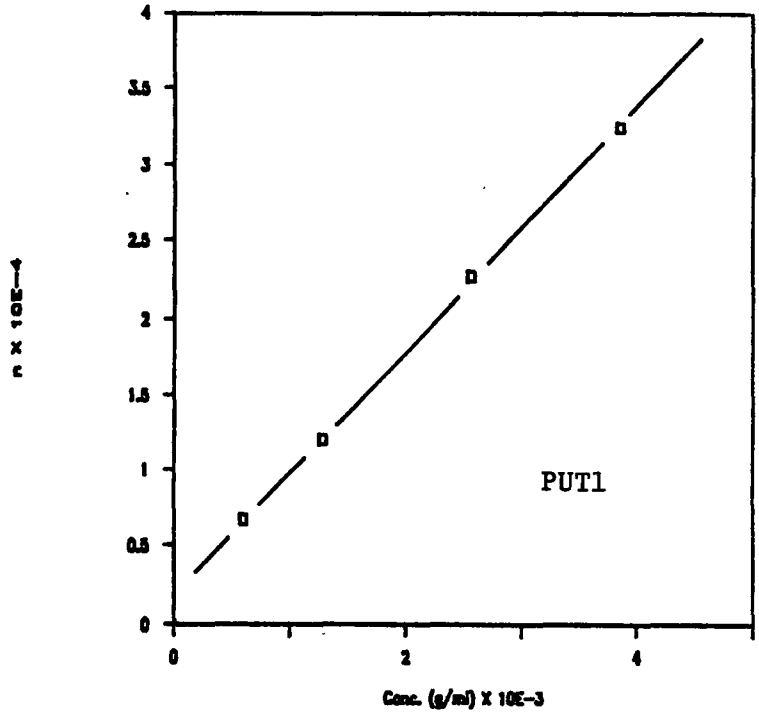


FIGURE 4.6 AND 4.7 REFRACTIVE INDEX INCREMENT PLOTS (DMF AT 25°C): PUO2 AND PUO3



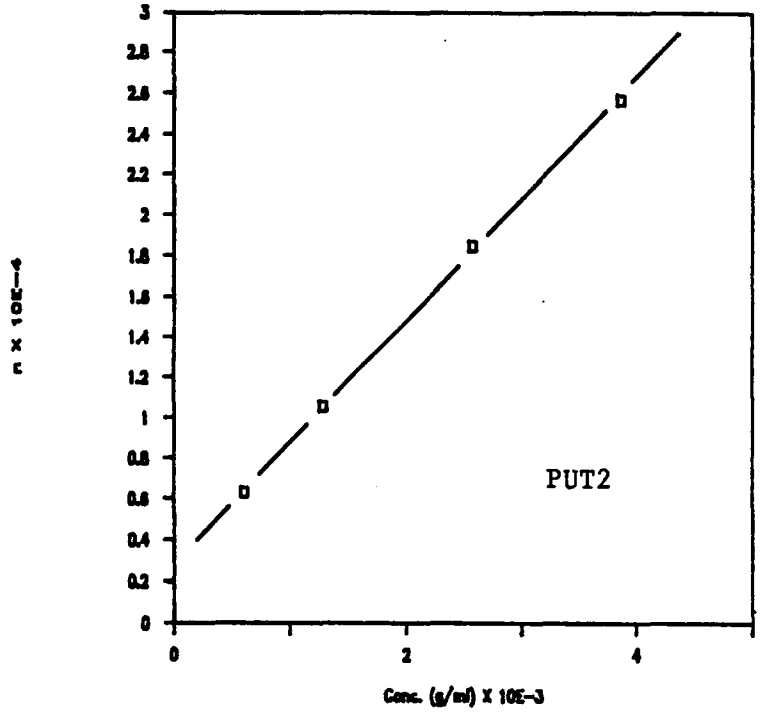


FIGURE 4.8 AND 4.9 REFRACTIVE INDEX INCREMENT PLOTS (DMF AT 25°C): PUT1 AND PUT2

POLYMER	dn/dc	CORRELATION COEFFICIENT
PUE1	0.09741	1.00
PUO1	0.08795	1.00
PUT1	0.07972	1.00
PUE2	0.07334	1.00
PUO2	0.06448	0.99
PUT2	0.05941	1.00
PUE3	0.09479	0.99
PUO3	0.09225	1.00

TABLE 4.6 dn/dc VALUES

the dn/dc values obtained was not possible.

Several trends can be seen with respect to dn/dc values. The dn/dc values are seen to vary with different chain extenders when the soft segment portion is constant. The dn/dc values decrease in the order ethylene diamine>1,3-dihydroxypropane>Tiron®. The largest dn/dc values were obtained for the PPG 1000-based polymers and decreased in the order PPG 1000>PEG 1500>PPG 2000.

Data from the LALLS photometer in many cases did not give useable data. Figures 4.10 to 4.12 show plots of scattering versus concentration for the only polymer systems that gave reasonable data. These three polymers, PUO2, PUT1 and PUT2 gave $\bar{M}w$'s of 74,000, 60,000 and 75,000 respectively. These values are comparable to those obtained by Sa Da Costa (1979) and Petrovic et al (1985) for similar polyurethane systems using gel permeation chromatography (GPC) with polystyrene standards. However the lack of success of LALLS with the other SPU's perhaps casts some doubt on the validity of these three results.

Several possibilities exist for the failure of LALLS with the polymer systems studied in this work. First of all, the application of LALLS to segmented polyurethanes in DMF seems to be relatively unexplored. A review of the literature showed that molecular weights of such polymers are more commonly measured using intrinsic viscosity or GPC. These techniques also have inherent problems associated with them such as the lack of established Mark-Houwink parameters and calibration using non polyurethane standards. However these methods are not as user sensitive as LALLS. Many problems can arise in using LALLS with any system. Dust and other contaminants are probably the most common source

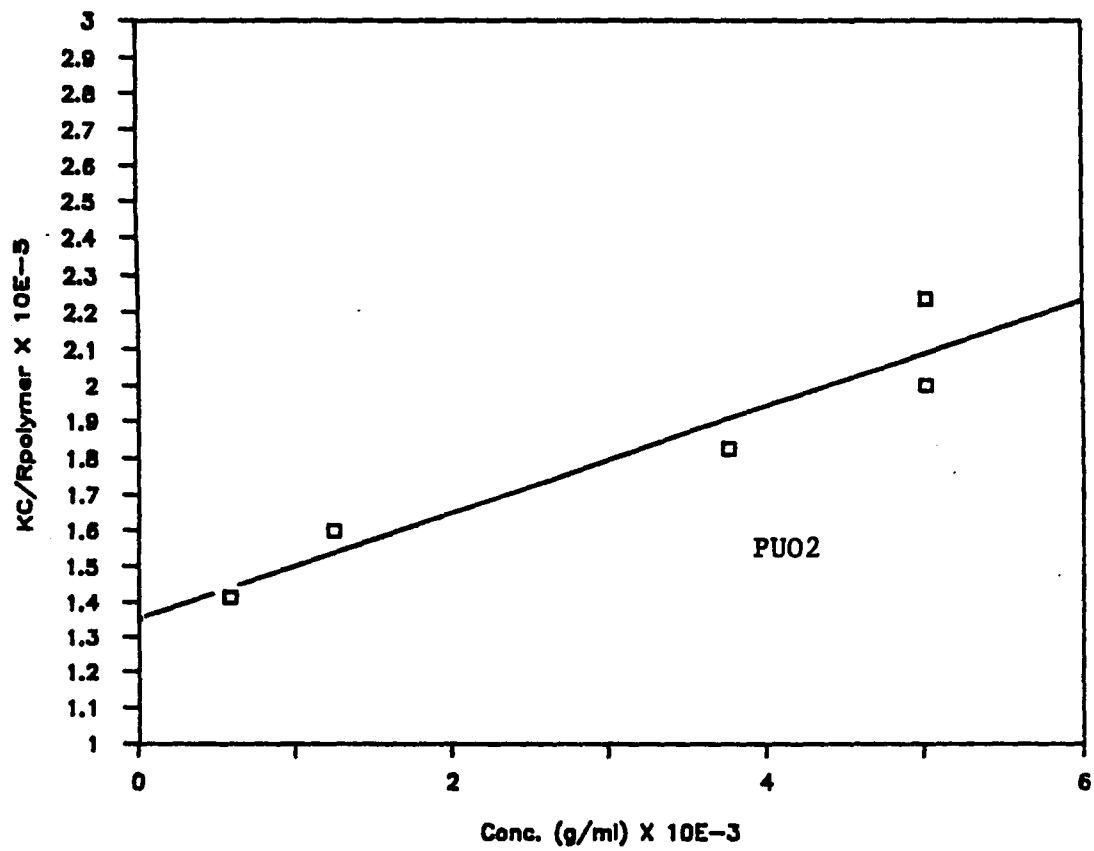


FIGURE 4.10 LALLS DATA FOR PUO2 (DMF AT 25°C): SCATTERING VERSUS CONCENTRATION PLOT

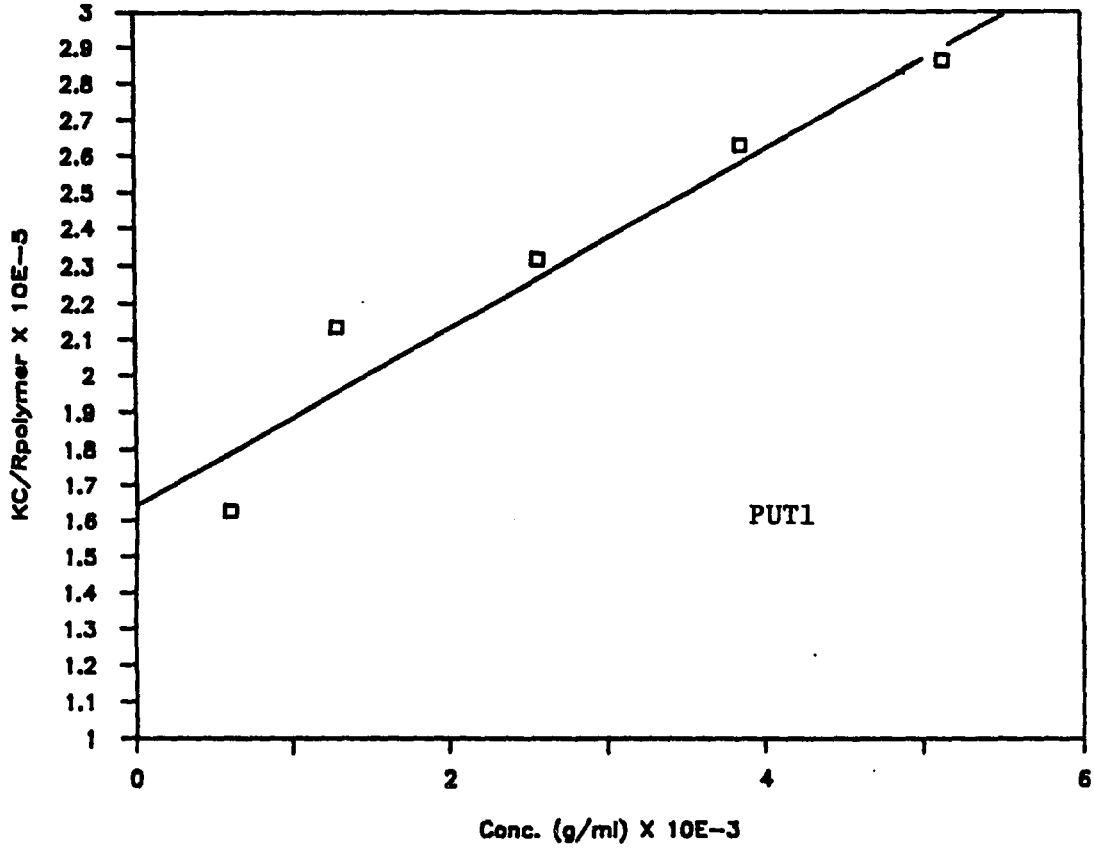


FIGURE 4.11 LALLS DATA FOR PUT1 (DMF AT 25°C): SCATTERING VERSUS CONCENTRATION PLOT

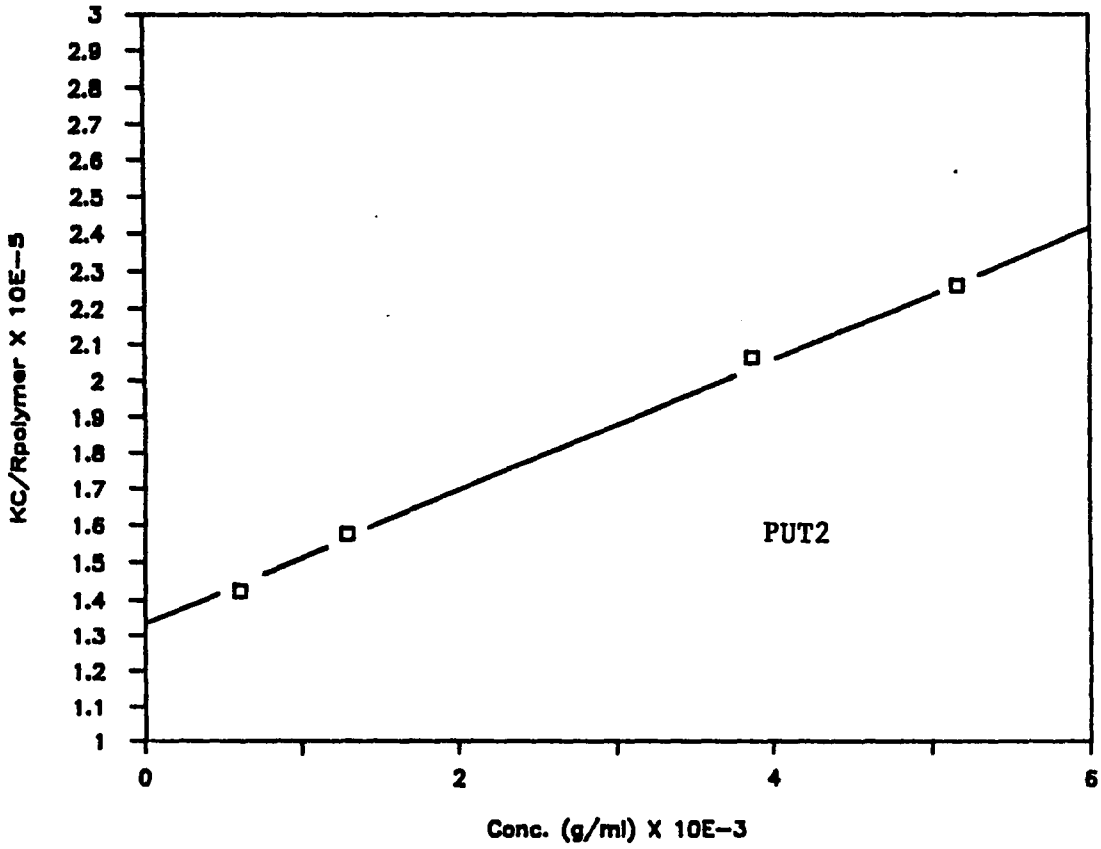


FIGURE 4.12 LALLS DATA FOR PUT2 (DMF AT 25°C): SCATTERING VERSUS CONCENTRATION PLOT

of error in LALLS measurements. The presence of dust can severely affect the scattering of light and extra precautions are needed to eliminate this type of impurity.

However the most probable cause of the difficulty in analyzing the present SPU systems is the presence of gel particles. These could result from crosslinked material created if allophanate or biuret linkages are formed in the polymerization. The presence of these gel particles is suspected since the on-line filters tended to clog and had to be replaced regularly. If gel particles were able to pass through the filter the light scattering measurements would be affected.

4.1.4 Electron Spectroscopy for Chemical Analysis (ESCA)

ESCA has become the dominant surface analysis technique used to study biomaterials for blood contacting devices. Ratner (1983) gives several reasons for the usefulness of ESCA in this regard: 1) ESCA examines a surface region ($\sim$ 50Å depth) relevant to surface biointeractions whereas other surface analysis techniques probe deeper into the specimen; 2) sample preparation is simple and non destructive; 3) ESCA is highly sensitive; and 4) ESCA has led to correlations between surface chemistry and blood interactions. In this thesis, ESCA was performed on the various polymers at the University of Washington by Ratner and McElroy (1985, 1986).

The results of this study are shown in Tables 4.7 to 4.9. Table 4.7 identifies the ESCA peak positions of the various carbon atoms found in polyurethanes. Table 4.8 summarizes the high resolution data of carbon 1s peaks for hydrocarbon, ether and urethane groups at grazing and

GROUP	PEAK POSITION (eV)	DESIGNATION
- CH Hydrocarbon	285.0	Peak A
- CN Amine	285.7 - 286.3	
- C-O Ether, Alcohol	286.5	Peak B
- $\overset{O}{\overset{\|}{C}}$- Ketone	288.0	
- $\overset{O}{\overset{\|}{C}}$-N- Amide	288.2	
- $\overset{O}{\overset{\|}{C}}$-O- Acid, Ester	288.8	
- N-$\overset{O}{\overset{\|}{C}}$-N- Urea	288.8	
- N-$\overset{O}{\overset{\|}{C}}$-O Urethane	289.3 - 289.7	Peak C

TABLE 4.7 C 1s ESCA PEAK POSITIONS FOR SOME CARBON ATOMS FOUND IN POLYURETHANES (Ratner and McElroy, 1985)

SAMPLE	GRAZING ANGLE (80° TAKE-OFF) RELATIVE AREA	NORMAL ANGLE (0° TAKE-OFF) RELATIVE AREA
PUE1		
peak A	42.2	45.6
peak B	54.2	49.5
Peak C	2.2	2.4
PUE2		
peak A	41.7	41.5
peak B	57.4	57.2
peak C	0.9	1.3
PUE3		
peak A	39.2	37.5
peak B	57.2	58.0
peak C	1.3	2.2
PUO1		
peak A	48.0	43.4
peak B	47.4	49.9
peak C	2.3	3.7
PUO2		
peak A	46.9	44.6
peak B	52.2	54.1
peak C	0.9	1.3
PUO3		
peak A	35.2	32.8
peak B	62.5	63.2
peak C	1.6	2.0
PUT1		
peak A	45.2	45.3
peak B	53.5	52.2
peak C	1.4	2.5
PUT2		
peak A	47.5	44.8
peak B	52.3	54.1
peak C	0.3	1.2

TABLE 4.8 HIGH RESOLUTION C 1s PEAK COMPARISON AT GRAZING AND NORMAL SAMPLE ANGLES

SAMPLE	TAKE-OFF ANGLE	ATOM %				
		C	N	O	Si	S
PUE1	0	73.5	3.8	22.7	ND*	ND
	20	73.2	4.2	22.7	ND	ND
	40	74.7	3.5	21.8	ND	ND
	60	74.6	2.9	22.5	ND	ND
	80	74.8	3.0	22.2	ND	ND
PUE2	0	76.0	1.7	22.2	ND	ND
	20	75.6	1.7	22.2	ND	ND
	40	74.6	2.4	23.0	ND	ND
	60	75.7	1.9	22.4	ND	ND
	80	77.4	1.4	22.2	ND	ND
PUE3	0	72.6	1.9	24.5	1.0	ND
	20	72.0	2.1	24.8	1.1	ND
	40	72.2	2.3	24.6	1.0	ND
	60	72.8	2.0	23.7	1.5	ND
	80	72.3	1.2	24.4	2.1	ND
PUO1	0	71.9	4.5	22.1	1.5	ND
	20	72.0	4.5	22.0	1.6	ND
	40	71.3	4.6	22.6	1.5	ND
	60	73.0	4.5	20.4	2.0	ND
	80	71.6	3.6	21.1	3.7	ND
PUO2	0	74.1	2.0	22.3	1.6	ND
	20	70.1	1.0	24.1	4.8	ND
	40	73.9	1.2	21.1	3.8	ND
	60	73.8	1.7	21.9	2.6	ND
	80	72.6	1.4	21.6	4.3	ND
PUO3	0	71.3	2.4	25.7	0.7	ND
	20	74.0	2.4	23.3	0.4	ND
	40	72.8	2.4	24.2	0.6	ND
	60	74.5	1.7	23.4	0.5	ND
	80	72.8	1.6	23.1	2.6	ND
PUT1	0	73.8	3.8	21.9	ND	0.5
	20	74.0	3.2	22.5	ND	0.5
	40	75.2	3.1	21.5	ND	0.5
	60	75.4	3.0	21.7	ND	BD**
	80	75.2	2.6	22.2	ND	BD
PUT2	0	73.5	1.1	23.0	2.5	ND
	20	73.4	1.1	22.6	2.6	ND
	40	74.5	1.4	21.4	2.6	ND
	60	73.9	1.3	21.6	3.1	ND
	80	72.3	0.9	21.5	3.3	ND

* ND = Element not detected
** BD = Sulphur is below detectability limit which is approx. 0.2 to 0.4% with experimental conditions used here.

TABLE 4.9 ELEMENTAL COMPOSITION IN ATOM % AT VARIOUS SAMPLE ANGLES

normal take-off angles. Table 4.9 shows the elemental concentrations in atom % at five different take-off angles. Both the C 1s peak for the urethane-carbonyl carbon (peak C) and the N 1s peak can be used to quantitatively estimate the hard segment concentration at the surface for conventional SPU's (Yoon and Ratner, 1986). It should be noted however that these two methods do have several drawbacks. Errors can arise in the peak area determination since both of these peaks are small. Difficulties also arise in determining the contribution of nitrogen to the soft segment as opposed to the hard segment (Yoon and Ratner, 1986), since it will contribute to both.

It has previously been reported that the soft segment is enriched in the surface of SPU's compared to the bulk. Lyman et al (1975) and Sung et al (1978) both found surface enrichment of the soft segment on the air side of a molded SPU film. Data from both Table 4.8 and 4.9 on the segmented polyurethanes of this study also indicate the possible surface enrichment of the soft segment. At a grazing angle of 80° the sampling depth is approximately 8.5 Å and at a normal angle or 0° take-off angle the sampling depth is approximately 50 Å. If we postulate that Peak C (Table 4.8) represents the hard segment content of the SPU, then it is seen that the relative area of Peak C for PUE3, PUO1, PUT1 and PUT2 increases significantly from grazing to normal take-off angle, indicating soft segment surface enrichment. The other SPU's also show increases in the urethane peak from the grazing to the normal take-off angle but these increases are probably not significant within the experimental error of the area measurement. In examining the N 1s peak of Table 4.9 and assigning it to the hard segment, surface gradients can

again be observed. Again the concentration of N is lower at the surface and increases into the bulk of the polymer indicating surface enrichment of the soft segment. Surface enrichment of the soft segment is also indicated in PUT1 on the basis that sulphur was not detectable in the surface but was found in the bulk polymer (sulphur would be present only in the hard segment of the Tiron® extended polymers).

The effect of the various chain extenders on the surface content of the hard segment is also apparent in Tables 4.8 and 4.9. Blackwell et al (1982) and Yoon and Ratner (1986) have found that chain extenders with an even number of carbons produce SPU's with a greater degree of phase separation, thereby increasing the soft segment content in the surface since surface enrichment is only possible to the extent that phase separation occurs. Two extenders in this study could be used to examine this hypothesis, namely ethylene diamine, which has an even carbon number, and 1,3 diamino hydroxy propane which has an odd carbon number. The data from the C 1s urethane peak and the N 1s do not indicate greater soft segment surface enrichment of the "E" series versus the "O" series. However it should be noted that the structure of the two chain extenders is not homologous due to the hydroxyl group in DHP and a comparison between the two corresponding polymers in this respect may not be possible.

The effect of the soft segment molecular weight for the three different monomers PPG 1000, PPG 2000, and PEG 1500 can also be viewed as the effect of hard segment concentration since the stoichiometry for all polymers is the same (differences in hard segment content do arise because of the different chain extenders but these are small). As shown

in Tables 4.8 and 4.9 the relative concentration of the hard segment in the surface decreases with increasing molecular weight of the soft segment. This result is reasonable as the soft segment concentration increases with soft segment molecular weight corresponding to a greater amount both in the surface and in the bulk. SPU's based on PPG 1000 exhibit a small angular dependence with respect to the N concentration, whereas those based on either PPG 2000 or PEG 1500 do not. Yoon and Ratner (1986) found that a decrease in chain length of the soft segment causes a decrease in surface enrichment of soft segment. Such an effect was not found in the present work.

The hard segment concentration at normal versus grazing angles of PUE1 and PUE2 do not show any significant differences. However polymer PUO1 shows an increased surface enrichment of the soft segment at a grazing take-off angle as compared to PUO2. These results may be explained as a novel effect of the different chain extenders and may not be related to the chain length of the soft segments.

The concentration of sulphur was also found using ESCA and can be compared with sulphur content found by elemental analysis (Table 4.5). The ESCA results for sulphur found in Table 4.9 confirm those found by the elemental sulphur analysis technique. As already indicated PUT1 and PUT2 showed bulk sulphur contents of 0.53 and 0.19 respectively. ESCA data indicate that PUT1 had a bulk sulphur content of 0.5%. Sulphur was not found in PUT2 by ESCA but the ESCA limit for detection of sulphur is 0.2%, and this is the order of magnitude for sulphur content found by elemental analysis.

In terms of the overall composition of the SPU's, the theoretical

N content is approximately twice that found in the ESCA data for all polymers (see Table 4.9). Theoretically the percent N assuming an ideal repeat unit is; 6.2 for PPG 1000 based SPU's (5.3 for the Tiron® extended SPU), 3.8 for PPG 2000 based SPU's (3.5 for the Tiron® extended SPU) and 4.8 for PEG 1500 based SPU's. Again it appears that the repeat unit obtained is different from that expected (this was also observed previously in the sulphur analysis of the Tiron® series).

The repeat unit of the prepolymer from the stoichiometry is expected to be a diisocyanate endcapped glycol. However, if the repeat unit of the prepolymer contains two glycol molecules and three diisocyanate molecules, the ESCA data for percent N is only slightly greater than the calculated percent N from this stoichiometry. Therefore it appears that some longer chain prepolymers are present in the polymerization. It should be noted that the ESCA analysis explores a very small region of the surface to a depth of only 50 Å. To obtain a better interpretation of the overall composition of the SPU, a bulk chemical analysis for nitrogen is needed to validate the ESCA results.

From Table 4.9, silicon is also seen to be present at the surface of several of the present SPU's. Silicon is an unwanted contaminant that may have been introduced during film preparation for ESCA analysis. Polymer samples PU02 and PUT2 show significant amounts of silicon, and an angular dependence indicating it is present at the surface. This surface contamination may complicate the interpretation of angular dependence of the other elements, and thus of hard/soft segment enrichment at the surface.

4.2 MECHANICAL PROPERTIES

It was the intention in the present investigation to synthesize a series of segmented polyurethanes that would exhibit interesting trends with respect to blood compatibility by the use of novel chain extenders. At the same time it was hoped that the introduction of these chain extenders would not have an adverse effect on the elastomeric properties of the SPU's. Therefore the stress-strain behaviour of the polymers was determined.

The results of stress-strain testing are illustrated in Figures 4.13 to 4.18 and the data for all polymers are summarized in Table 4.10. The stress-strain curves shown utilize the engineering stress and strain which does not take into account the change in cross sectional area as the specimen extends. Also the modulus shown in Table 4.10 was measured at 200% elongation (the modulus at lower elongations could not be measured due to limitations of the MTS material testing system). The modulus at lower elongations would give more information on the properties of the polymers in a region of elongations closer to that experienced in actual use as a biomaterial.

As discussed previously in Chapter 2.2.3, it is the presence of microphases or domains of hard and soft segments that give SPU's their excellent elastomeric properties and high strength. In the series of polymers prepared in this work the stoichiometry of the three components remained constant. Therefore the hard segment content of the polymer is determined largely by the molecular weight of the soft segment and to a lesser extent by the molecular weight of the chain extender (MDI was

common to all polymers). The weight percent of hard segment for the various polymers is shown in Table 4.11.

The effect of the molecular weight of the soft segment can be seen in Figures 4.13 to 4.15. SPU's based on PPG 1000 and PPG 2000 can be compared with respect to their mechanical properties. In all three series with different chain extenders the following trends are apparent. The PPG 1000 based polymers have a larger initial modulus and lower extensibilities than the PPG 2000 based polymers. The exception was PUT2 which had a lower extensibility than PUT1. However the polymer films prepared from PUT2 were very soft and gummy. The trends seen in Figures 4.13 to 4.15 are readily understood if one thinks of the decrease in soft segment molecular weight as corresponding to an increase in the hard segment content. The hard segment acts as a multifunctional crosslinker and therefore a larger content of hard segment would effectively increase the "crosslink" density, increase the strength and decrease the extensibility. These trends are consistent with those reported by other researchers (Chang and Wilkes, 1975; Sung and Smith, 1980).

It is also expected that the PPG 1000 based polymers are less phase separated that those based on PPG 2000 (Hu and Ward, 1982). However increased phase separation is believed to increase breaking strength and modulus and this trend is not observed for these polymers. Therefore the effect of the hard segment content is dominant in determining the ultimate properties of these SPU's.

A comparison between PEG based polymers and PPG based polymers with respect to ultimate mechanical properties in terms of the molecular

POLYMER	ELONGATION AT BREAK %	ULTIMATE TENSILE STRENGTH MPa (psi)	MODULUS AT 200% ELONGATION MPa (psi)
PUE1	1340	12.84 (1862)	3.19 (463)
PUE2	>3050	4.30 (624)*	0.719 (104)
PUE3	2380	0.74 (107)	0.167 (24)
PUO1	1250	9.70 (1407)	0.758 (110)
PUO2	>3180	2.21 (320)*	0.323 (47)
PUO3	2400	0.18 (26)	0.036 (52)
PUT1	1780	10.36 (1502)	0.77 (112)
PUT2	540	0.59 (86)	0.60 (87)

* Not a true tensile strength since samples did not break.

TABLE 4.10 STRESS-STRAIN PROPERTIES OF VARIOUS SPU'S

SAMPLE	HARD SEGMENT, WT. %
PUE1	35.9
PUE2	21.9
PUE3	27.2
PUO1	37.1
PUO2	22.8
PUO3	28.2
PUT1	46.9
PUT2	30.6

TABLE 4.11 HARD SEGMENT CONTENT OF THE VARIOUS SPU'S

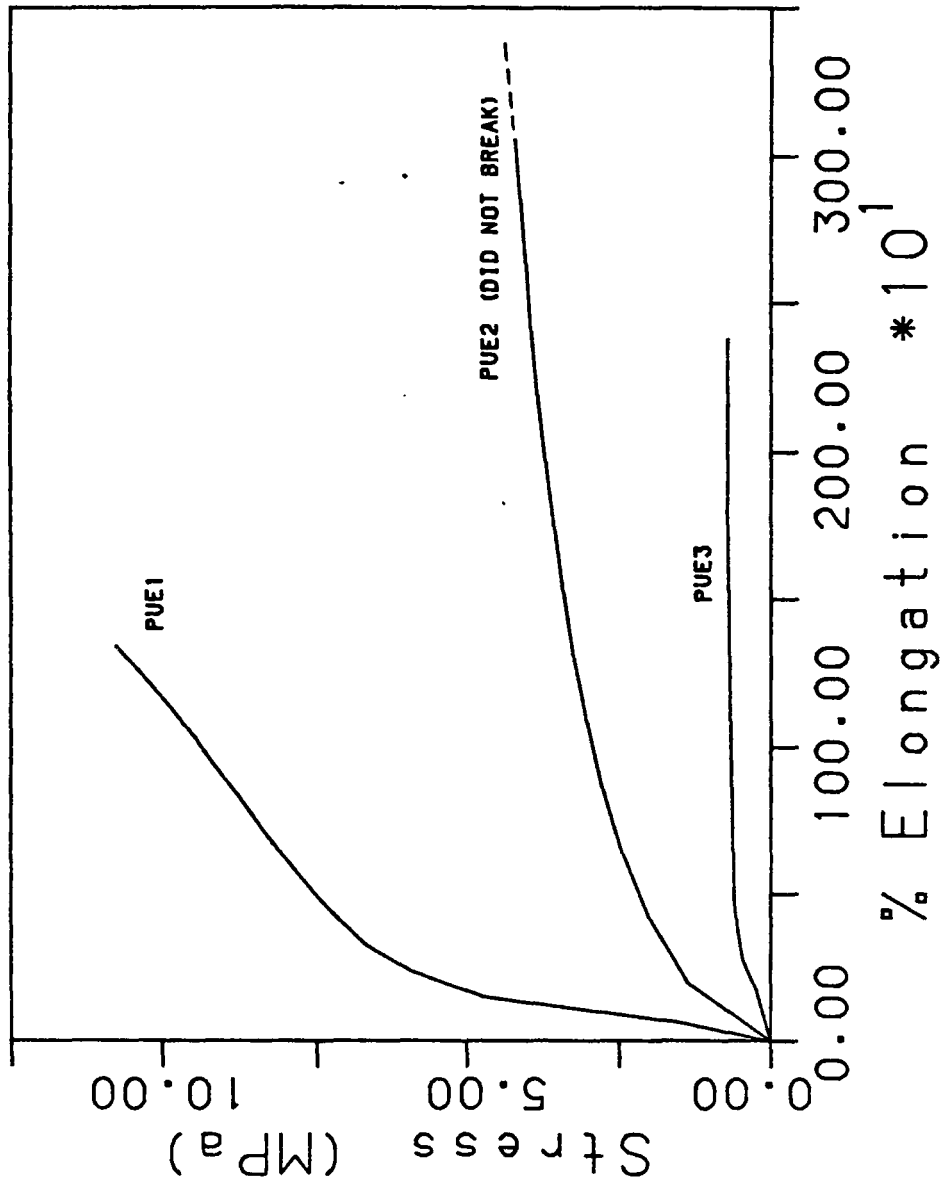


FIGURE 4.13 STRESS-STRAIN BEHAVIOUR OF POLYURETHANES; EFFECT OF SOFT SEGMENT (ETHYLENE DIAMINE EXTENDER)

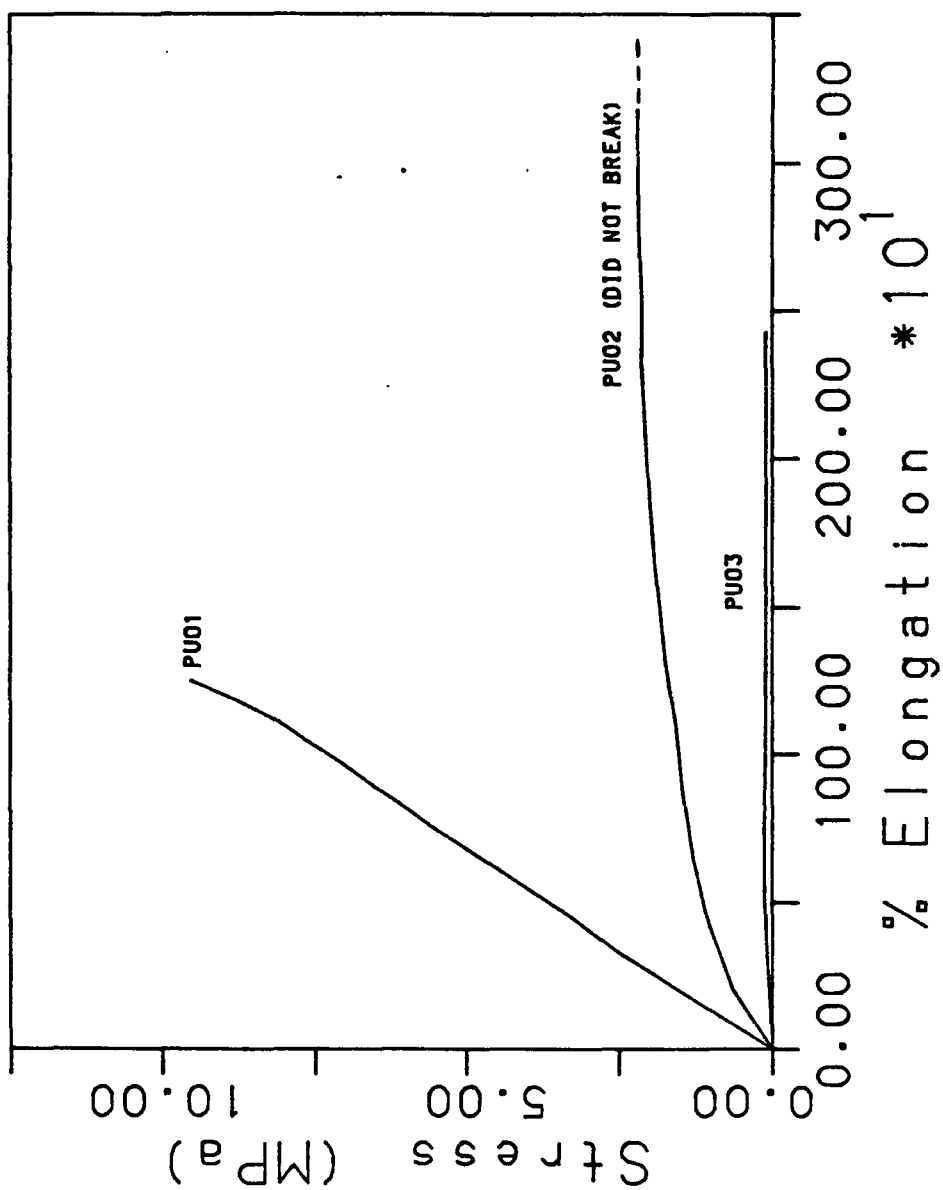


FIGURE 4.14 STRESS-STRAIN BEHAVIOUR OF POLYURETHANES; EFFECT OF SOFT SEGMENT (DHP EXTENDER)

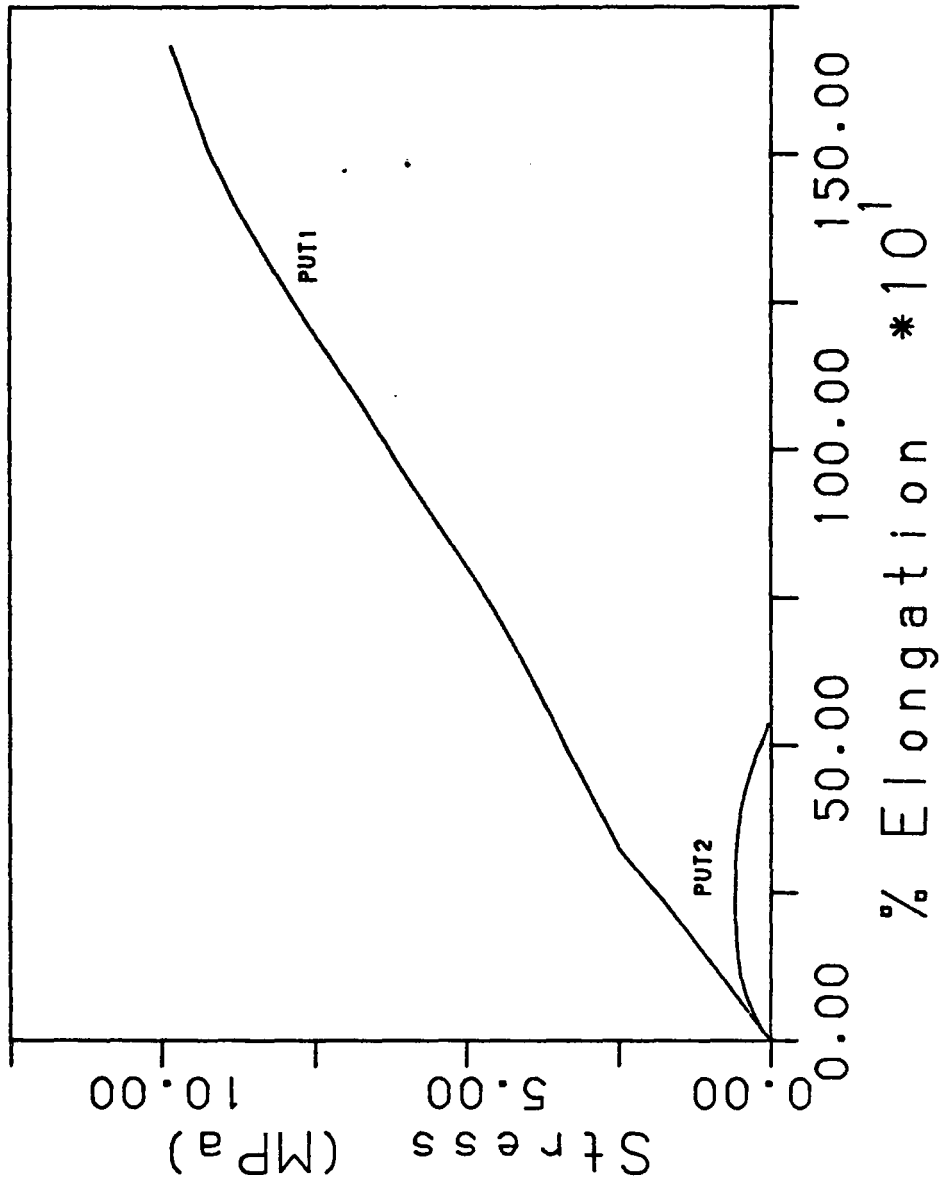


FIGURE 4.15 STRESS-STRAIN BEHAVIOUR OF POLYURETHANES; EFFECT OF SOFT SEGMENT (TIRON® EXTENDER)

weight of the soft segment is difficult since thev are chemically different. It is expected that there will be less tendency to phase separation in the PEG based polymers since the polarities of the hard and soft segments are more akin. As can be seen the PEG based polymers have a low modulus and ultimate tensile strength. This may be accounted for by the fact that PEG based polymers tend to absorb water from the environment. This hydration process makes the polymer films mechanically very weak. However from Table 4.10 it is seen that the extensibility of the polymers increases with increasing molecular weight of the soft segment. The trend with respect to extensibility is PPG 2000>PEG 1500> PPG 1000.

The effect of the different chain extenders on mechanical properties can be seen in Figures 4.16 to 4.18. Polymers based on the same soft segment all show very similar extensibilities even with the varying chain extenders (except for PUT2). The differences within these groupings of polymers occur in the initial modulus and ultimate tensile strength. The ethylene diamine extended polymers show greater initial modulus and ultimate strength than those extended with DHP or Tiron®. The DHP and Tiron® extended polymers show very similar values of these two properties.

These trends may be explained in terms of the expected phase separation of the polymers. Ethylene diamine has an even number of carbon atoms and SPU's extended with this type of extender have been found to have greater phase separation (Blackwell et al, 1982; Yoon and Ratner, 1986). DHP on the other hand has a three carbon atom chain and also a pendant hydroxyl group. Tiron® is a sulphonated aromatic chain

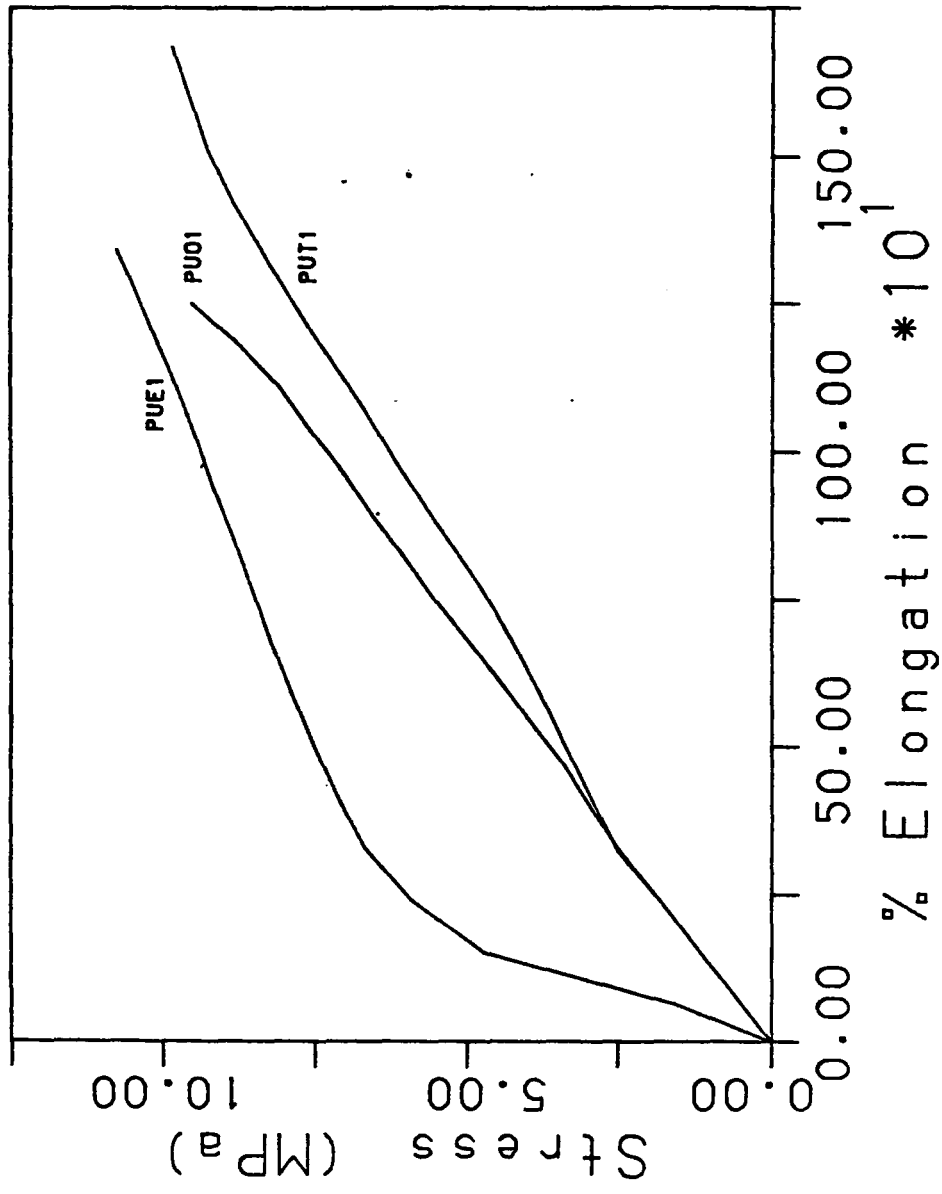


FIGURE 4.16 STRESS-STRAIN BEHAVIOUR OF POLYURETHANES; EFFECT OF CHAIN EXTENDER (PPG 1000 SOFT SEGMENT)

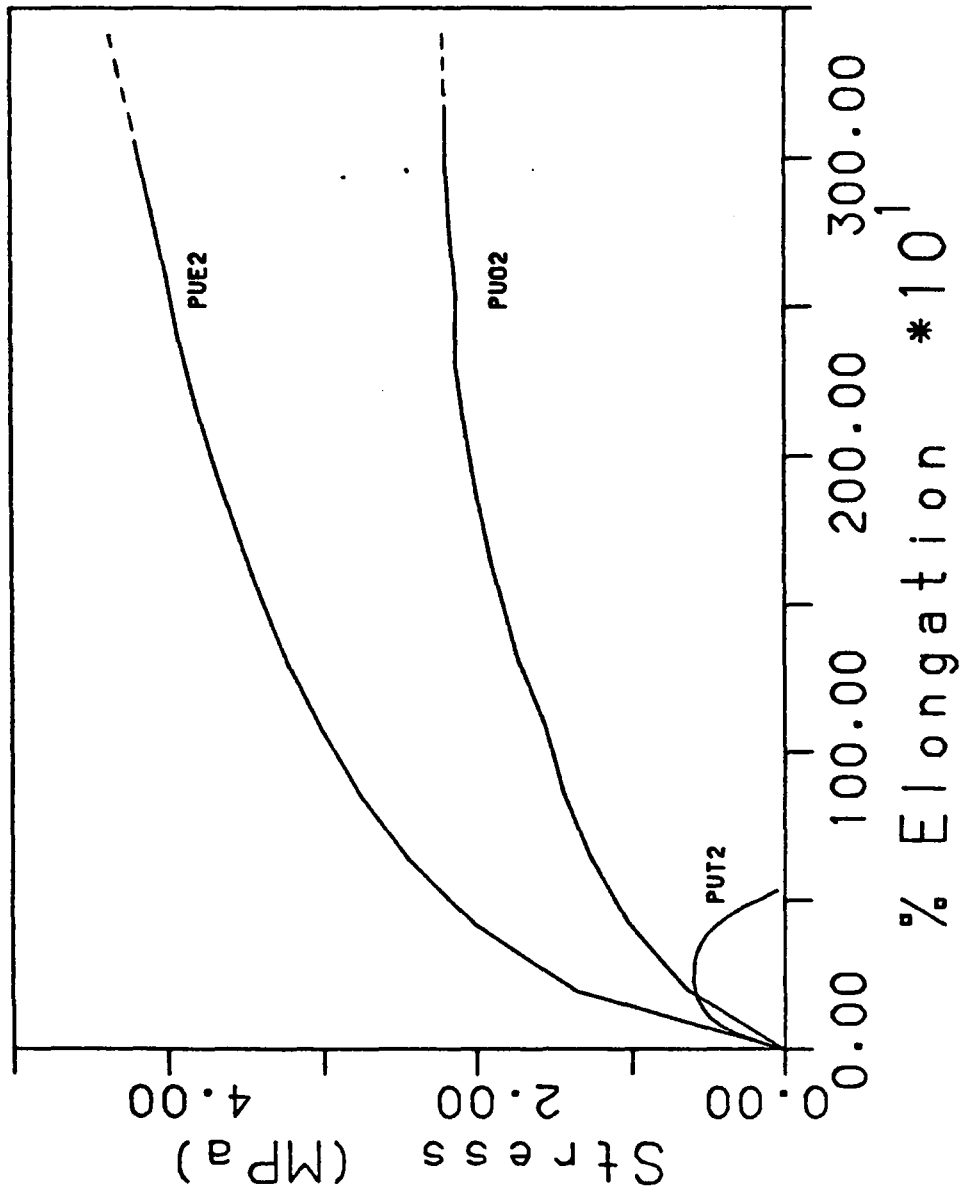


FIGURE 4.17 STRESS-STRAIN BEHAVIOUR OF POLYURETHANES; EFFECT OF CHAIN EXTENDER (PPG 2000 SOFT SEGMENT)

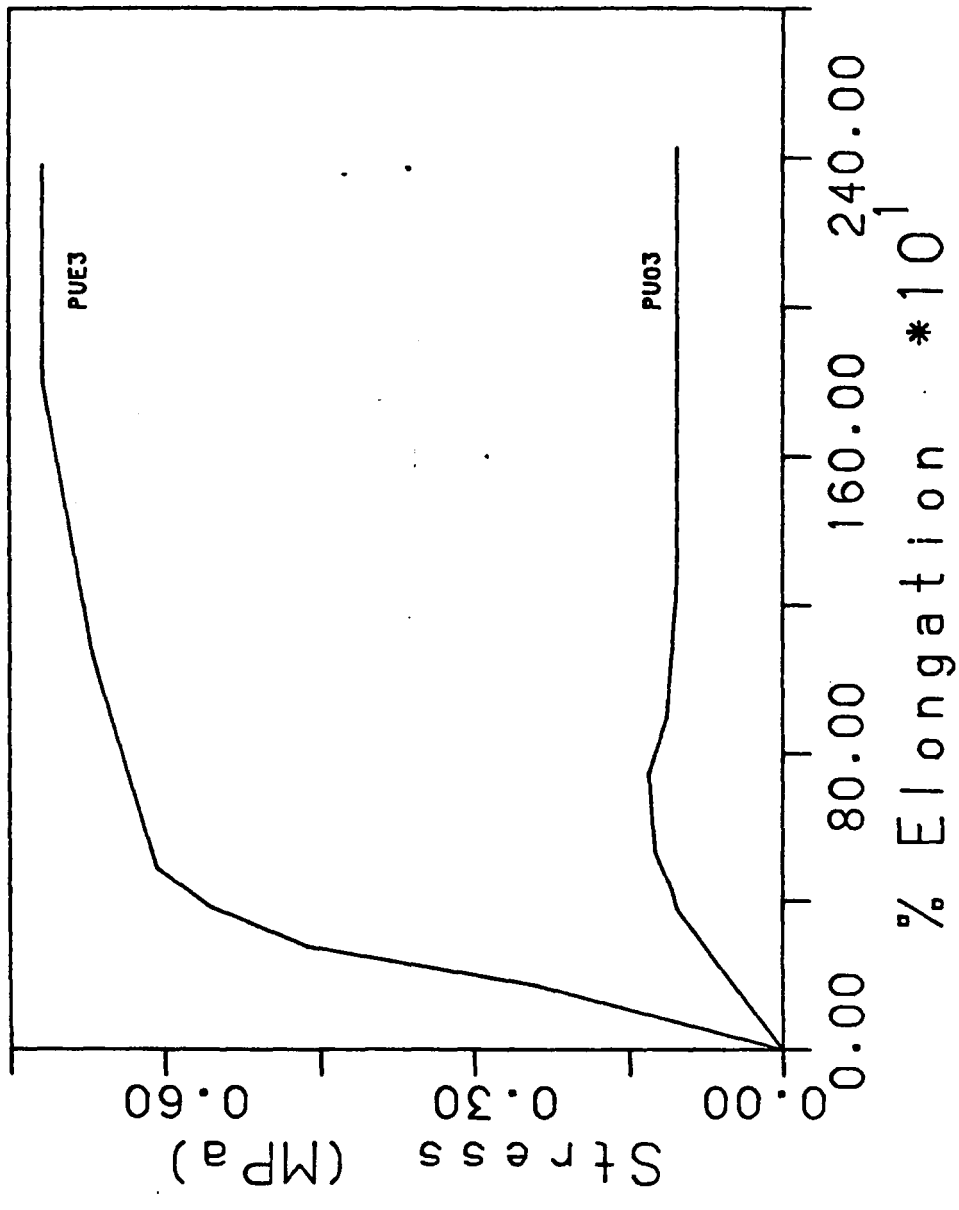


FIGURE 4 18 STRESS-STRAIN BEHAVIOUR OF POLYURETHANES; EFFECT OF CHAIN EXTENDER (PEG 1500 SOFT SEGMENT)

extender and its degree of phase separation is difficult to predict on the basis of structure. SPU's with a greater degree of phase separation have been shown to exhibit greater modulus and tensile strength (Hu and Ward, 1982).

Most of the polymers synthesized appeared to be fairly good elastomers with acceptable properties for use in biomedical devices. In relation to materials currently used for blood contacting devices (e.g. Biomer, Avcothane, Pellethane, etc.), the SPU's of this study have ultimate strengths four to ten times smaller and elongations two to five times greater. Polymers based on PPG 1000 had the highest tensile strength with good elongation properties (over 1000% elongation) and probably represent the most useful of the polymers synthesized from a mechanical standpoint. PPG 2000 based polymers even though possessing high extensibilities did not have particularly high tensile strength. Again it should be noted that the lack of modulus data at lower elongations (5-100%) prevented assessment of mechanical behaviour of the polymers in a more relevant range of strain values. Also other mechanical properties (e.g. creep, stress relaxation and fatigue) which are very important from a biomaterial standpoint were not evaluated in this study.

4.3 FIBRINOGEN ADSORPTION STUDIES

Experiments to determine adsorption of the plasma protein fibrinogen were performed on the SPU's synthesized as a means of assessing their interaction with blood. Previous work from our group has shown that the adsorption of fibrinogen from plasma to a variety of materials is transient (Brash and ten Hove, 1984; Wojciechowski et al, 1986). The objective of the fibrinogen adsorption studies in the present work was to determine whether fibrinogen adsorbs to segmented polyurethanes in the same or a different manner as it does to these other, less blood-compatible materials. Also it was hoped that some trends in fibrinogen adsorption could be seen as a function of structural features of the segmented polyurethanes.

4.3.1 Adsorption of Fibrinogen as a Single Protein from Buffer

Initially the adsorption of fibrinogen was examined as a single protein from buffer solution. In order to validate the radiolabeling technique, three solutions having the same total fibrinogen concentration but different ratios of labeled and unlabeled protein were used. This test also provided information on the reproducibility of the adsorption measurement. These measurements are shown in Table 4.12.

It can been seen from Table 4.12 that the adsorption measurements did give reproducible results (three replicate runs at 10% labeled fibrinogen). Also the radiolabeling of the fibrinogen does not appear to affect the adsorption to a large extent.

Water contact angles were determined to provide a measure of the

FIBRINOGEN ADSORBED

($\mu g/cm^2$)

POLYMER	LABELED FIBRINOGEN CONTENT 90%	50%	10%
PIIF1	0.821	0.871	0.933
PUO1	1.093	1.136	1.304, 1.276, 1.292
PUT1	0.874	0.863	0.916, 0.906, 0.909
PUE2	0.644	0.747	0.723, 0.778, 0.781
PUO2	0.688	0.697	0.755. 0.747, 0.740
PUT2	0 745	0.653	0.724, 0.709, 0.700
PUE3	0.014	0.014	0.047, 0.044, 0.036
PUO3	0.019	0.024	0.029, 0.041, 0.037

TABLE 4.12 FIBRINOGEN CAPACITIES OF SPU SURFACES: ADSORPTION FROM SINGLE PROTEIN FIBRINOGEN SOLUTIONS IN TRIS BUFFER, pH 7.4, AT LABELED FIBRINOGEN CONCENTRATIONS OF 90%, 50% AND 10% (TOTAL FIBRINOGEN CONCENTRATION = 1 mg/mL, ADSORPTION TIME = 2 HOURS).

hydrophilicity of the surfaces. Table 4.13 lists the water contact angles and the fibrinogen capacities (average of the five adsorption measurements for each polymer in Table 4.12) for the various polymers.

The water contact angles did not vary greatly from surface to surface showing that all surfaces have similar wettability. From the contact angle values it may be concluded that all the surfaces are moderately hydrophobic. The PEG based polymers appear to be slightly more hydrophilic than the PPG based polymers but the difference is not as great as might be expected based on the high water absorption of PEG based SPU's (Whicher and Brash, 1978). It is possible that contact angles measured when the polymers are fully hydrated, for example "underwater" contact angles (Andrade et al, 1982), would give more realistic wettability information. Such contact angles would also be more suitable for correlations with data obtained under fully hydrated conditions (e.g. adsorption from an aqueous media).

The fibrinogen capacities of the PPG 1000 and PPG 2000 based polymers indicate monolayer adsorption of fibrinogen. The values of fibrinogen surface concentration lie between that for end-on adsorption (1.6 μ g/cm^2) and side-on adsorption (0.2 μ g/cm^2) of fibrinogen (Wojciechowski, 1986). It is therefore believed that the monolayer contains a distribution of molecular orientations relative to the surface.

The fibrinogen capacties of the various SPU's divide into three categories. The PPG 1000 based polymers show the highest average adsorption followed by the PPG 2000 based polymers. PEG based polymers had the lowest average adsorption.

POLYMER	WATER CONTACT ANGLE (degrees)	FIBRINOGEN ADSORBED ($\mu g/cm^2$)
PUE1	64	0.895
PUO1	64	1.220
PUT1	65	0.894
PUE2	69	0.735
PUO2	66	0.725
PUT2	67	0.706
PUE3	60	0.031
PUO3	62	0.030

TABLE 4.13 WATER CONTACT ANGLES AND FIBRINOGEN CAPACITIES OF SPU SURFACES: ADSORPTION FROM SINGLE PROTEIN FIBRINOGEN SOLUTIONS IN TRIS BUFFER, pH 7.4 (CONC. OF FIBRINOGEN = 1 mg/mL)

The PEG based polymers showed basically no adsorption of fibrinogen. There are two possible explanations for this observation. First, the PEG based polymers may be truly hydrophilic contrary to the water contact angle data. In this case the surface would quickly become hydrated in contact with the buffer solution. The fibrinogen that is adsorbed is then easily washed from the surface during the rinse to remove the bulk fibrinogen (see Experimental section). The behaviour of the PEG based polymers both mechanically in air (low modulus and tensile strength) and in a wet environment (PEG based polymers under water tended to soften and peel from a glass substrate) support the explanation that the surface is hydrophilic, and that adsorbed protein may be "lost" on rinsing. The other possible explanation is simply that fibrinogen is not adsorbed to the PEG based surface. In support of this explanation several groups have observed minimal protein adsorption onto polyethylene oxide surfaces in which the polymer chains are the same as the PEG chains in the soft segment of the present SPU's (Suzuki et al, 1983; Gregonis et al, 1984; Golander et al, 1986).

Fibrinogen adsorption capacities of polymers with different chain extenders but the same soft segment are not significantly different. The data indicate that it is the soft segment or polyether that most strongly affects the adsorption and that the hard segment (chain extender) has no noticeable influence on adsorption. This finding correlates with ESCA results reported earlier. These results showed that there was an enrichment of the soft segment in the surface of the polymer. Therefore the interaction between fibrinogen and the surface would be expected to be determined by the soft segment.

As stated previously, fibrinogen adsorption for PPG 1000 based SPU's is greater than that for PPG 2000 based SPU's, and this also correlates with the fact that the hard segment content in the surface is greater for PPG 1000 based SPU's. Therefore the adsorption of fibrinogen may be related to the concentration of each segment type in the surface.

PEG based SPU's have been found to be less platelet retentive than PPG based SPU's (Merrill et al, 1980). This is consistent with findings of this study since adsorbed fibrinogen is believed to be platelet reactive and fibrinogen was not adsorbed on the PEG based SPU's.

4.3.2 Fibrinogen Adsorption from Plasma

The transient adsorption of fibrinogen from plasma has been termed the "Vroman effect" (Brash and ten Hove, 1984). It is believed that fibrinogen dominates the protein layer in the first 1 to 2 seconds and then is replaced by high molecular weight kininogen (HMWK) and other proteins. The rate at which fibrinogen is adsorbed and replaced is dependent on the surface type (Brash and ten Hove, 1984).

In the present experiments, adsorption times of a few seconds are not accessible so the Vroman effect cannot be observed using normal plasma. However it has been found (Brash and ten Hove, 1984; Wojciechowski et al, 1986) that by diluting the plasma, the concentration of HMWK and other fibrinogen-replacing proteins is decreased to the point where they cannot replace the fibrinogen. It is for this reason, that fibrinogen adsorption experiments from plasma are carried out using plasmas diluted to varying extents.

The "Vroman effect" is illustrated in Figures 4.19 and 4.20 for adsorption of fibrinogen onto glass. In Figure 4.19, fibrinogen adsorbed is plotted against bulk concentration as a percent of normal plasma where 100% plasma corresponds to 2.5 mg/mL fibrinogen for the single protein curve. It can be observed that both the single protein and plasma curves are linear and increasing up to 0.5%. The surface is assumed to be filling with protein with little interaction between molecules. At concentrations greater than 0.5%, competitive effects can be seen in plasma curves. The "Vroman effect" is illustrated as fibrinogen is rapidly displaced from the surface and essentially removed at 5% normal plasma.

In Figure 4.20, the "Vroman effect" is seen by plotting fibrinogen adsorbed versus time for various plasma concentrations. The 0.5% plasma curve shows fibrinogen being adsorbed and then replaced after about 10 minutes. Fibrinogen adsorption cannot be seen at 2.5% plasma because the displacement is too rapid. Concentrations less than 0.5% plasma show no displacement of fibrinogen since the fibrinogen - replacing proteins are not present in sufficient quantities to displace the fibrinogen. The plateaux for these curves are determined by the fibrinogen concentration.

Fibrinogen adsorption on the SPU's synthesized for the present study was determined at plasma concentrations from 0.25 to 10% of normal. The curves obtained are shown in Figures 4.21 to 4.26. Adsorption times of 5 minutes were used in all experiments. These curves of adsorption versus plasma concentration show the maxima which are characteristic of the "Vroman effect". Adsorption peaks at approximately 0.5% plasma and then decreases at higher plasma concentrations.

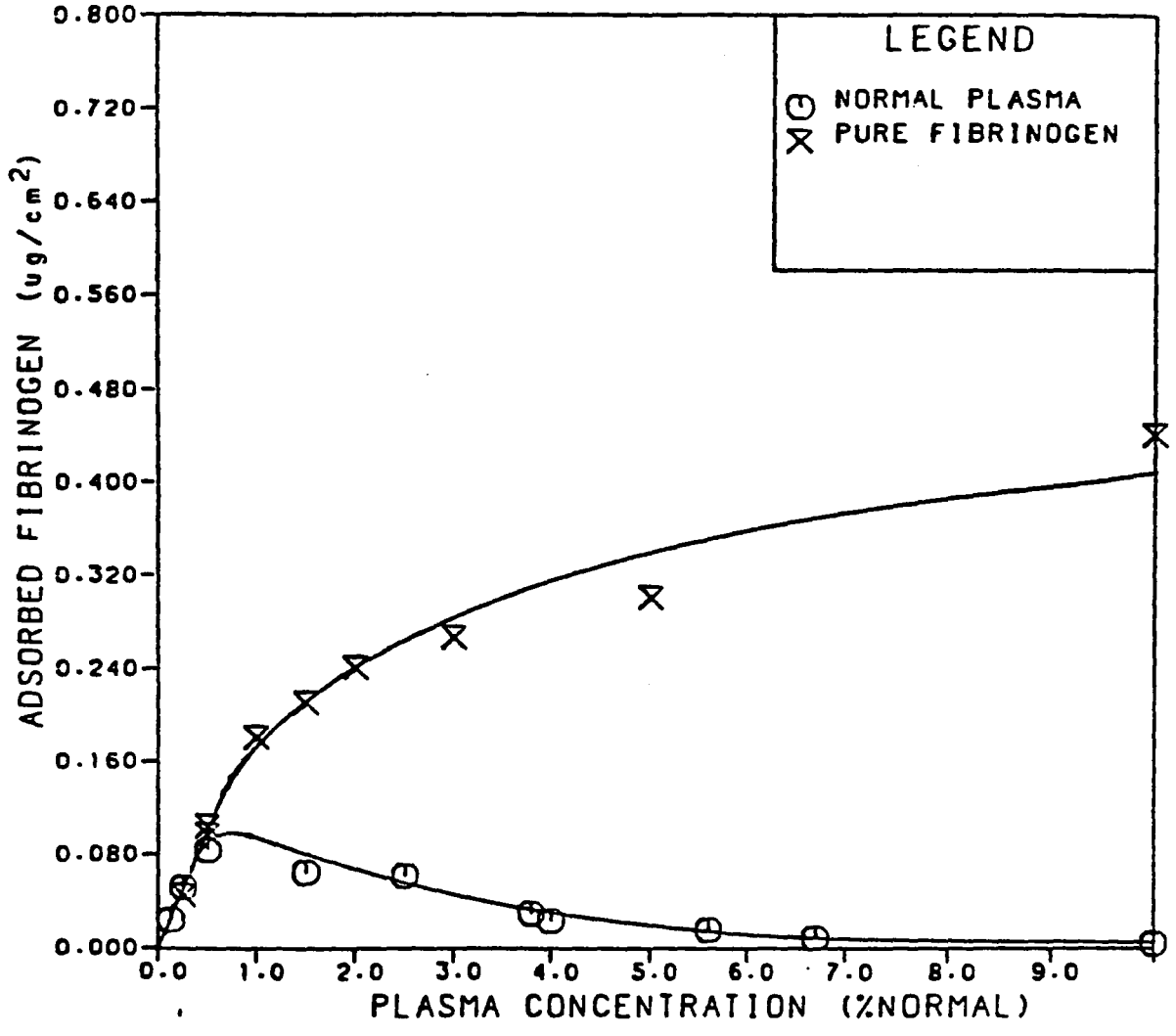


FIGURE 4.19 FIBRINOGEN SURFACE CONCENTRATION VERSUS BULK CONCENTRATION FROM TRIS AND FROM PLASMA AT 5 MINUTES (Wojciechowski, 1986)

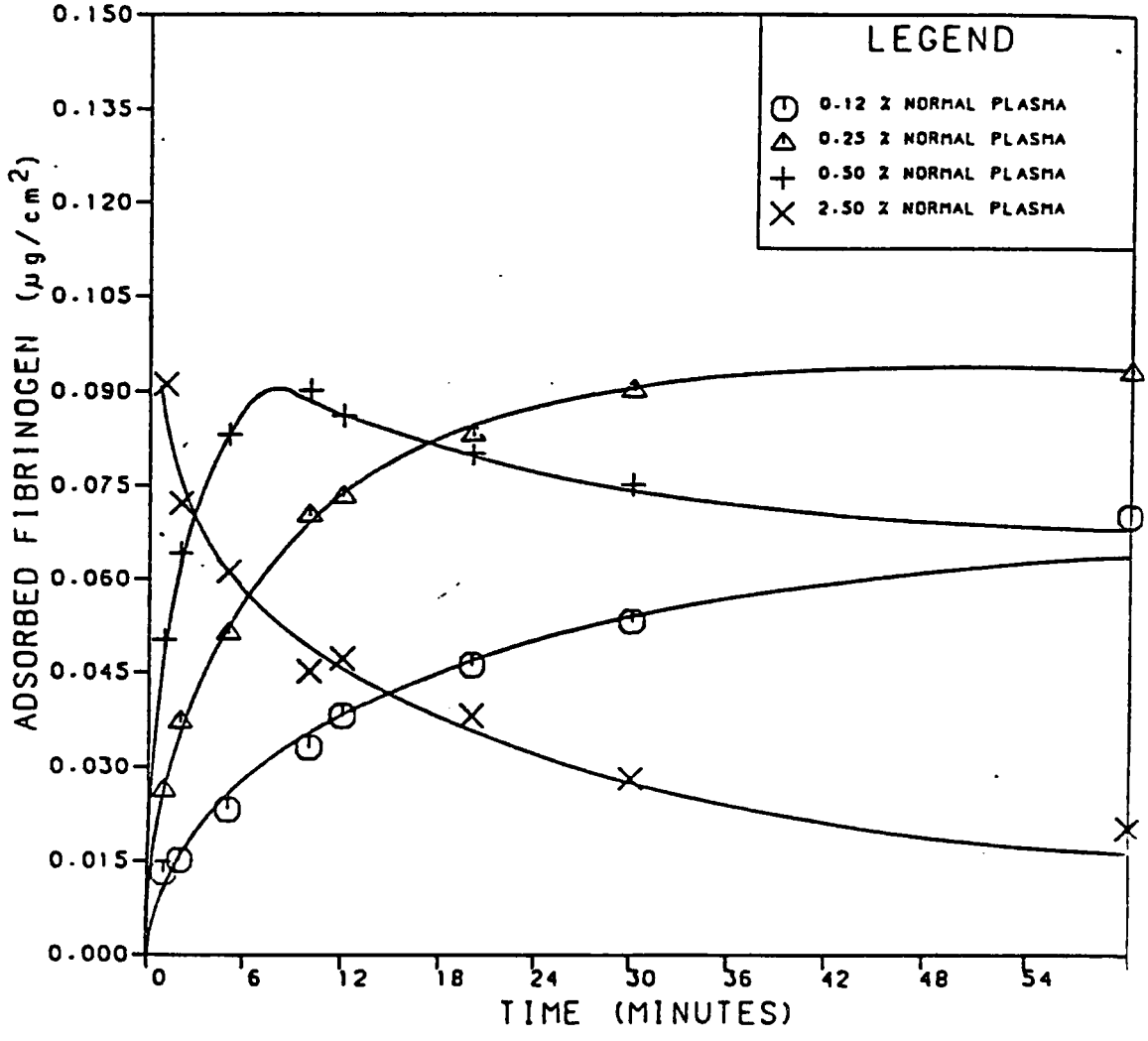


FIGURE 4.20 FIBRINOGEN SURFACE CONCENTRATION ON GLASS VERSUS TIME FOR DIFFERENT PLASMA CONCENTRATIONS (Wojciechowski, 1986)

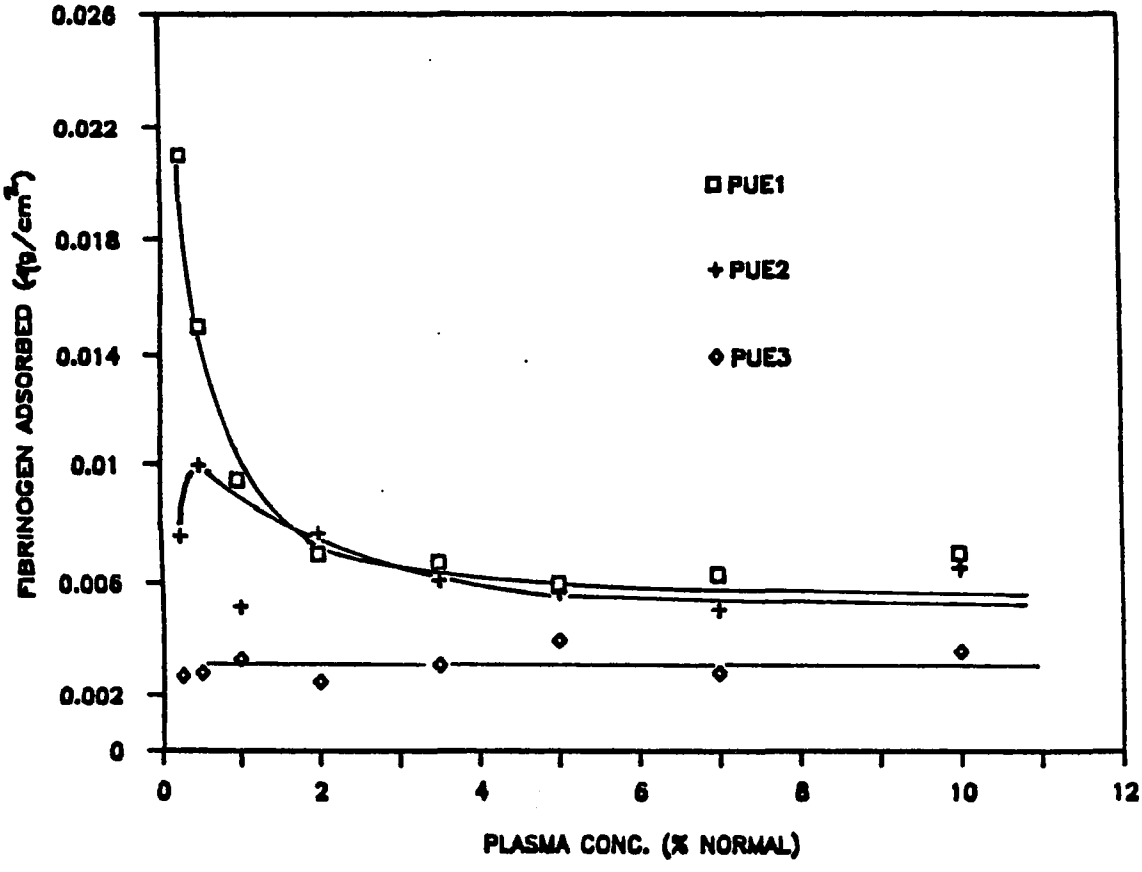


FIGURE 4.21 5 MINUTE FIBRINOGEN ADSORPTION FROM PLASMA TO POLYURETHANES; EFFECT OF SOFT SEGMENT (ETHYLENE DIAMINE EXTENDER)

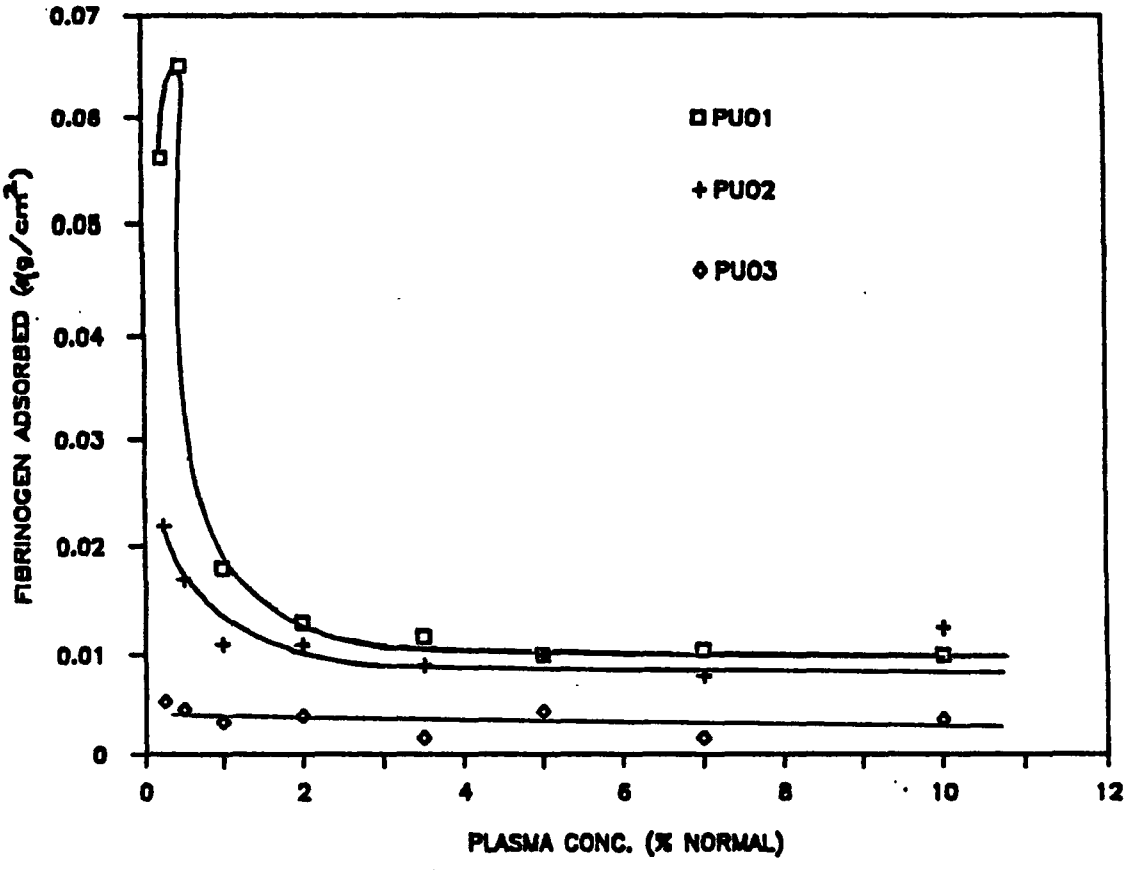


FIGURE 4.22 5 MINUTE FIBRINOGEN ADSORPTION FROM PLASMA TO POLYURETHANES; EFFECT OF SOFT SEGMENT (DHP EXTENDER)

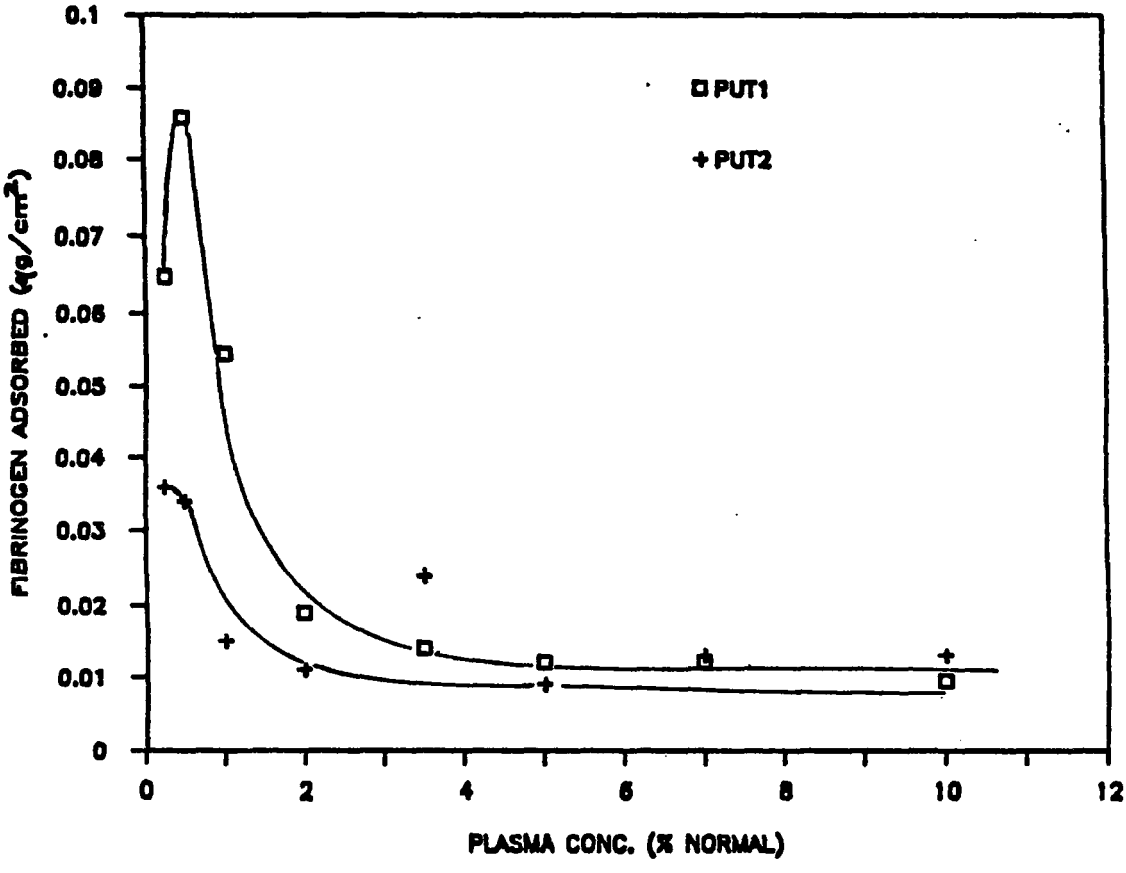


FIGURE 4.23 5 MINUTE FIBRINOGEN ADSORPTION FROM PLASMA TO POLYURETHANES; EFFECT OF SOFT SEGMENT (TIRON® EXTENDER)

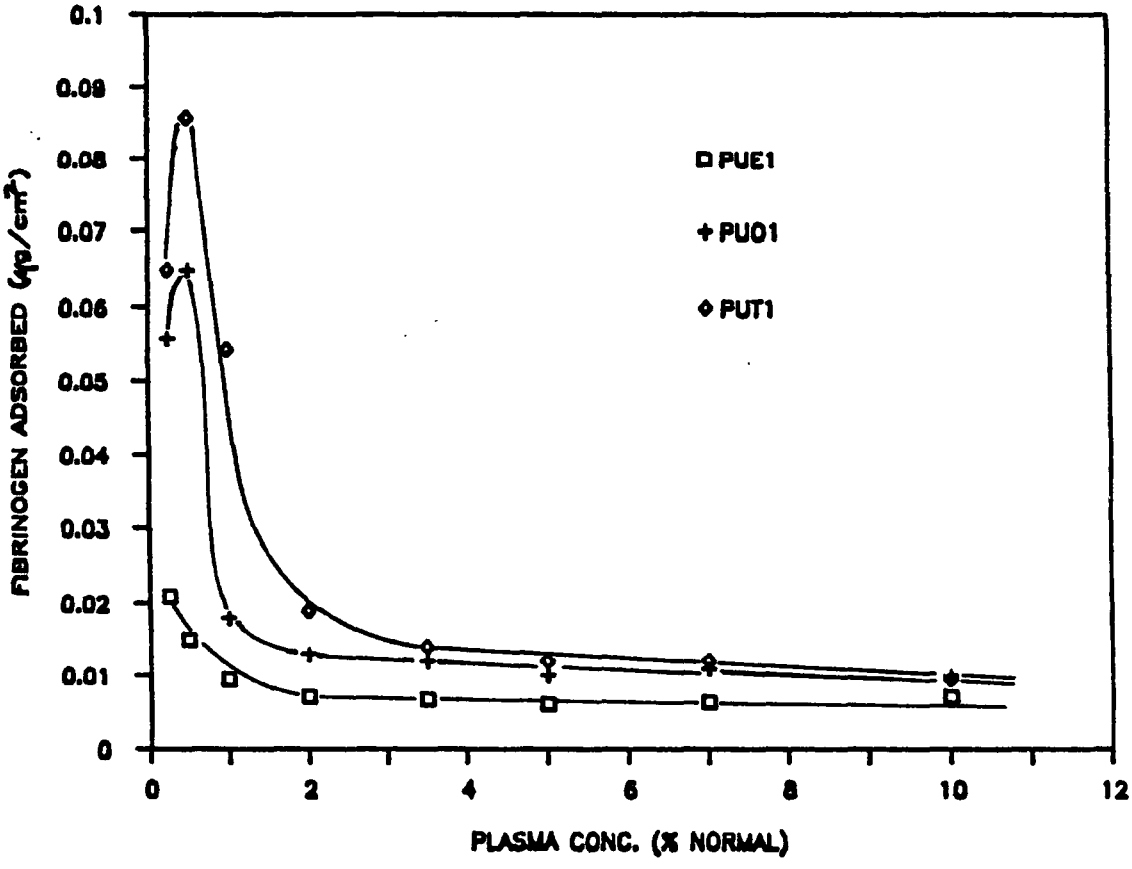


FIGURE 4.24 5 MINUTE FIBRINOGEN ADSORPTION FROM PLASMA TO POLYURETHANES; EFFECT OF CHAIN EXTENDER (PPG 1000 SOFT SEGMENT)

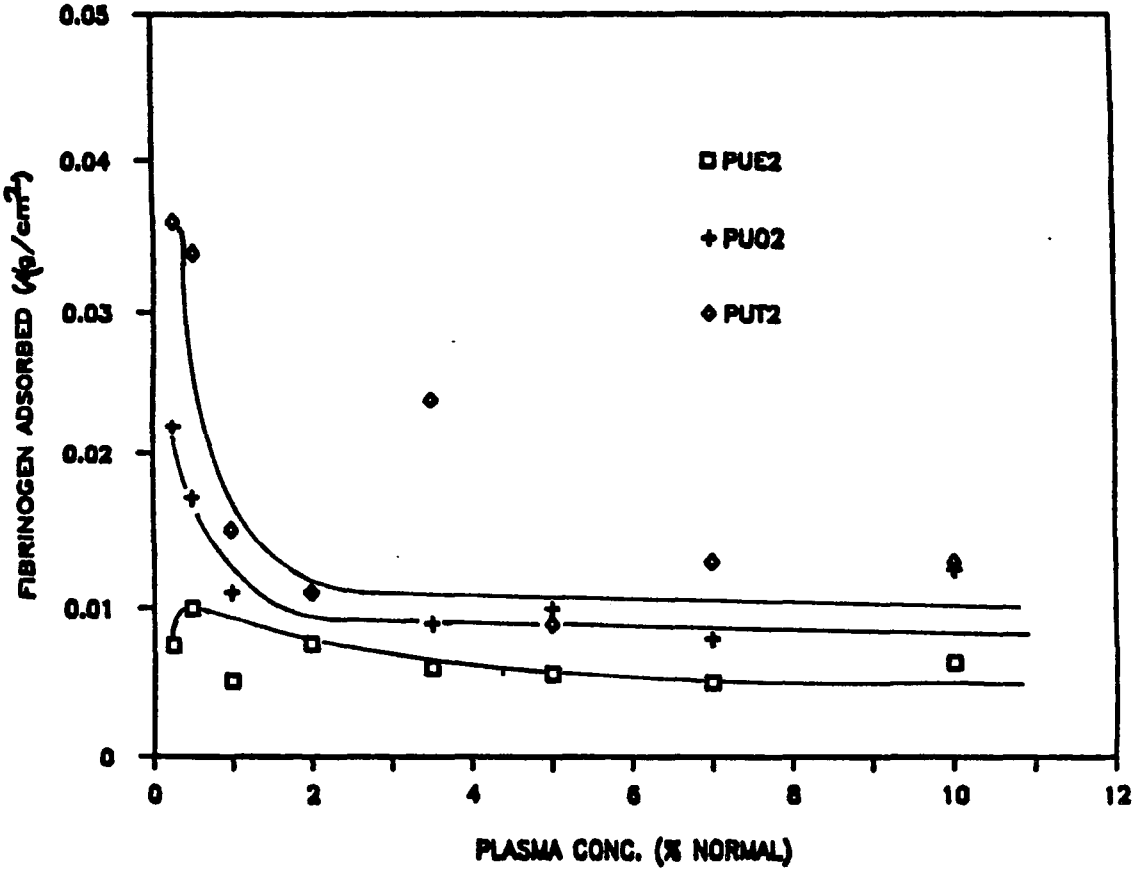


FIGURE 4.25 5 MINUTE FIBRINOGEN ADSORPTION FROM PLASMA TO POLYURETHANES; EFFECT OF CHAIN EXTENDER (PPG 2000 SOFT SEGMENT)

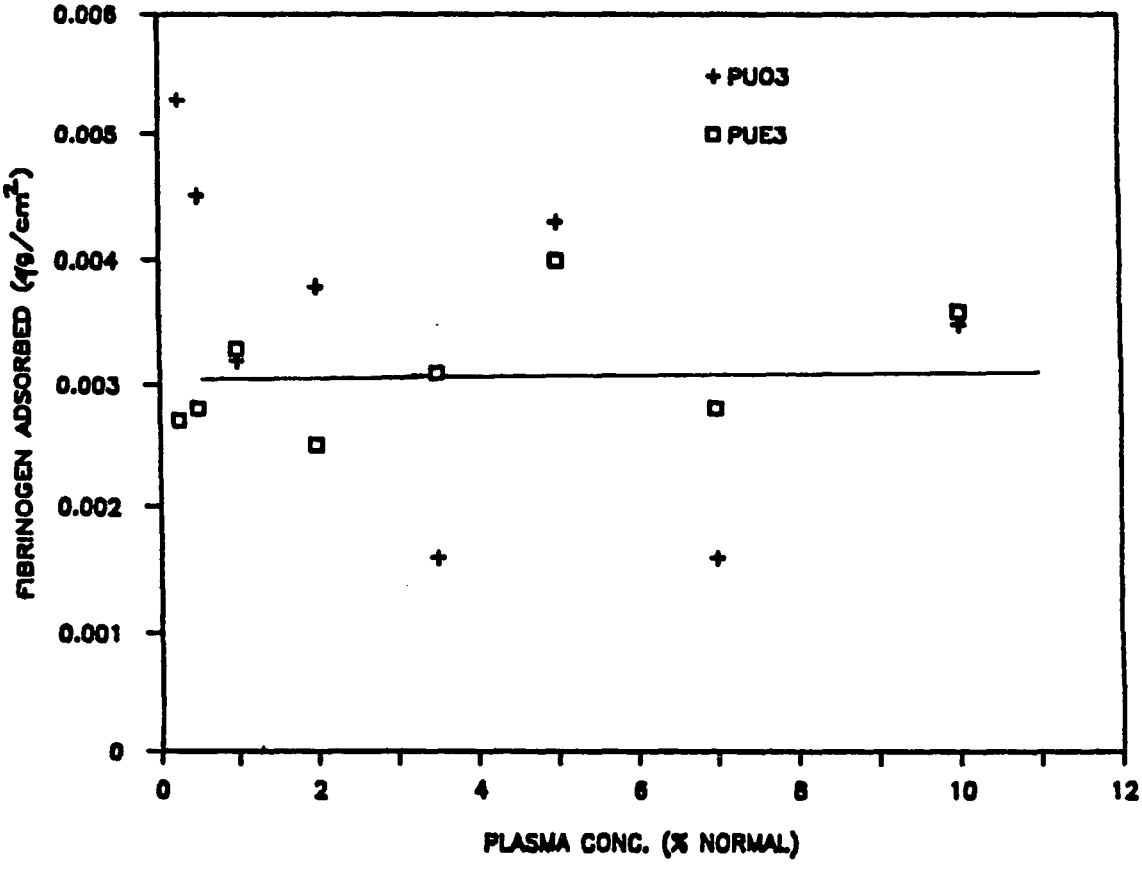


FIGURE 4.26 5 MINUTE FIBRINOGEN ADSORPTION FROM PLASMA TO POLYURETHANES; EFFECT OF CHAIN EXTENDER (PEG 1500 SOFT SEGMENT)

Figures 4.21 to 4.23 illustrate the effect of the soft segment on fibrinogen adsorption from plasma. The same general trends can be observed in each case. The peak adsorption for all PPG based SPU's occurs at between 0.25 and 0.50% plasma. The PPG 1000 based SPU's show peak adsorption values greater than PPG 2000 based SPU's. Both types show approximately equal "residual" adsorption at higher plasma concentration. The PEG based SPU's show very low fibrinogen adsorption with no peak (i.e. the Vroman effect is not observed for these materials).

Figures 4.24 to 4.26 show the effect of the chain extender on adsorption of fibrinogen from plasma. Again some very definite trends can be observed from these Figures. The peak adsorption is greatest for SPU's extended by Tiron® followed by those extended with DHP. SPU's extended with ethylene diamine showed the lowest peak adsorption. Figure 4.26 shows data for polymers based on PEG. Again, as for the single protein fibrinogen, the adsorption of fibrinogen is so low that a comparison of chain extenders cannot be made.

The peak adsorption values from Figures 4.21 to 4.26 are summarized in Table 4.14. As for the single protein adsorption results (Table 4.13) the data seem to be divided into three groups based on the soft segment. The highest peak adsorptions occur for PPG 1000 based SPU's followed by those SPU's based on PPG 2000. The PEG based SPU's showed no peak adsorption and again it is possible that the fibrinogen is lost from the surface of this hydrophilic polymer in the rinse step to remove bulk radioactive solution.

The peak adsorption on polymers having the same soft segment

POLYMER	PEAK ADS. ($\mu g/cm^2$)	PEAK POSITION (% PLASMA)
PUE1	0.021	0.25
PUO1	0.065	0.5
PUT1	0.086	0.5
PUE2	0.010	0.5
PUO2	0.022	0.25
PUT2	0.036	0.25
PUE3	No Peak	---
PUO3	No Peak	---

TABLE 4.14 FIBRINOGEN ADSORPTION FROM PLASMA FOR SPU SURFACES

appears to show a trend with respect to the chain extender. For both PPG 1000 and PPG 2000 based polymers the order of adsorption is Tiron® extended>DHP extender>ethylene diamine extended. The highest peak height (0.086 μ g/cm^2) occurred for the polymer PUT1. This value is close to that for glass (0.090 μ g/cm^2 at 1% plasma) which is considered thrombogenic (Brash and ten Hove, 1984). All the other SPU's had significantly lower peak adsorptions.

It might be tempting at this point to associate thrombogenicity with higher peak adsorption of fibrinogen from plasma based on the above observation. This is based on the fact that SPU's are considered to be fairly thromboresistant and with the exception of PUT1 all SPU's in this study showed low peak adsorptions.

This notion was developed further by Wojciechowski (1986). PUO2 was selected as typical of the polyurethanes synthesized in this study. It had a characteristically low peak fibrinogen adsorption and was compared to other types of materials. Figures 4.27 and 4.28 show fibrinogen adsorption data from plasma on various surfaces for 5 minute and 24 hour adsorption times respectively.

Figure 4.27 for 5 minute adsorptions shows that PUO2 has the lowest peak adsorption of fibrinogen and that adsorption was reduced to zero at much lower plasma concentrations than for the other surfaces (Wojciechowski, 1986). The curve for glass, a thrombogenic surface, lies between two silicone coated surfaces that are considered to be less thrombogenic. The relation between these curves and thrombogenicity is thus not clear-cut.

The curves for the 24 hour fibrinogen adsorption isotherms, shown

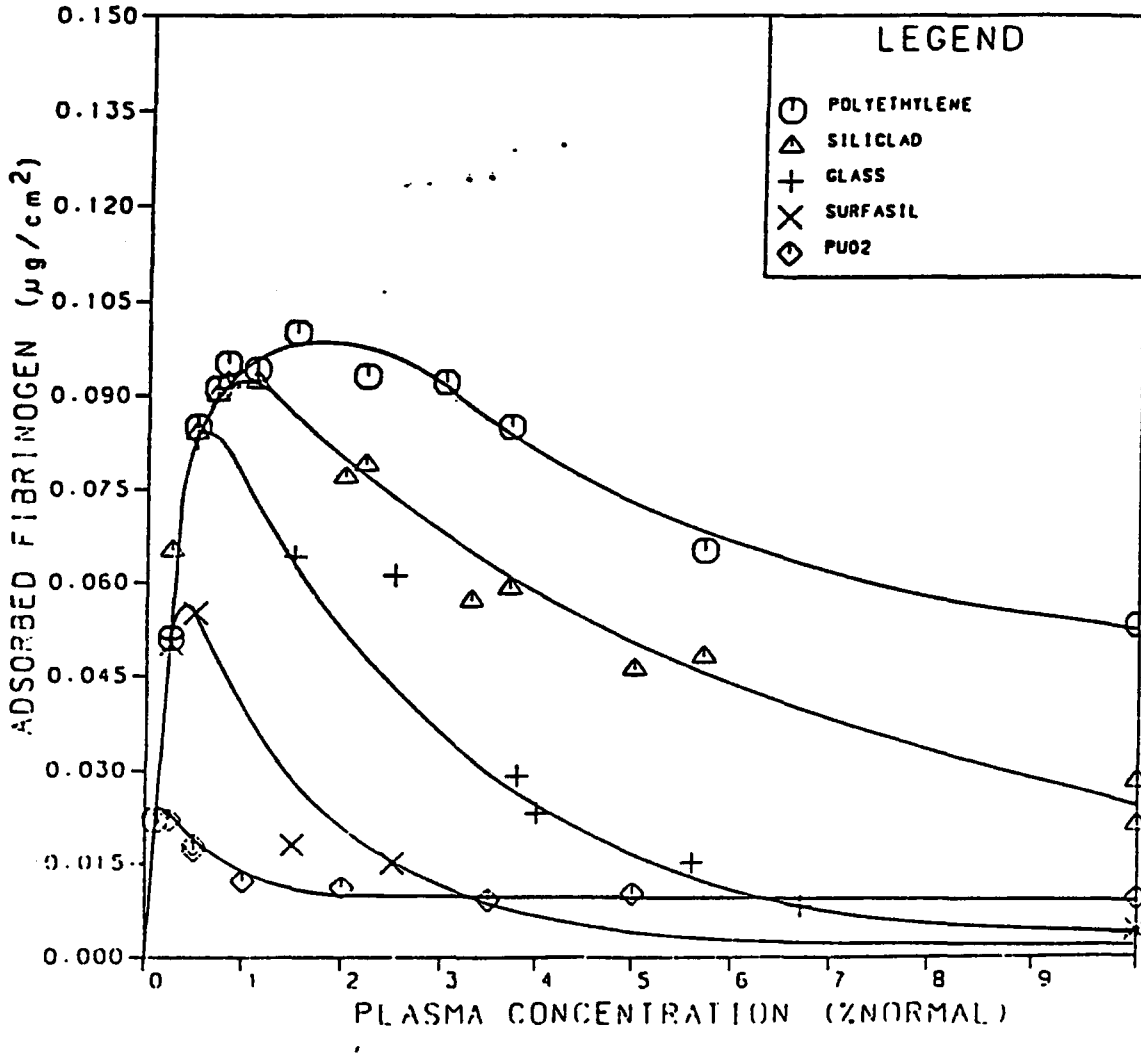


FIGURE 4.27 5 MINUTE FIBRINOGEN SURFACE CONCENTRATION VERSUS PLASMA CONCENTRATION ON DIFFERENT SURFACES (Wojciechowski, 1986)

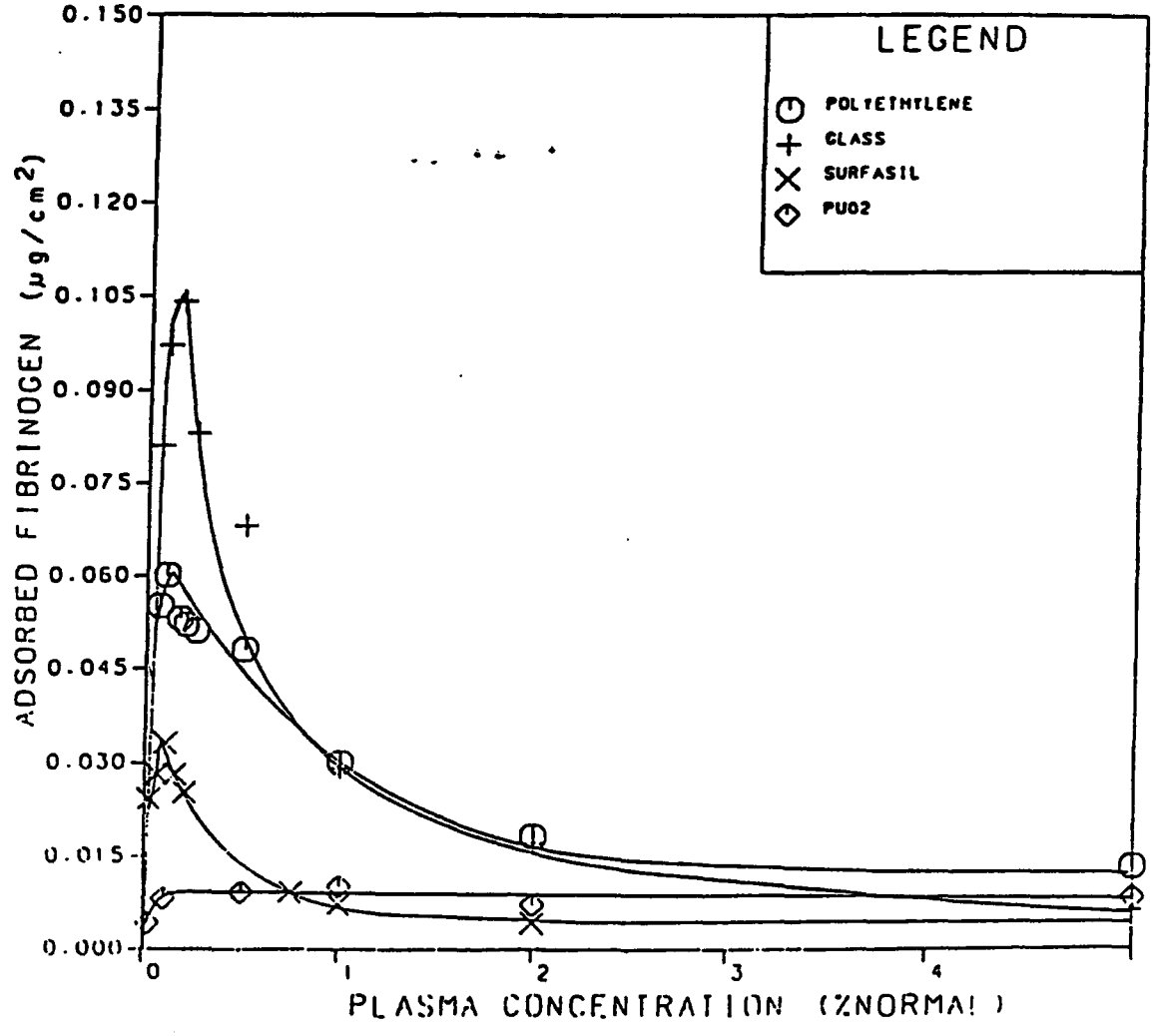


FIGURE 4.28 24 HOUR FIBRINOGEN SURFACE CONCENTRATION VERSUS PLASMA CONCENTRATION ON DIFFERENT SURFACES (Wojciechowski, 1986)

in Figure 4.28, are markedly different than those for the 5 minute isotherms. From Figure 4.28, adsorption on PU02 shows no evidence of a peak and is constant at about 0.008 $\mu g/cm^2$, a very low value. This indicates that the displacing components are present in sufficient amounts to remove fibrinogen at all dilutions studied (Wojciechowski, 1986). It also appears from these curves that the peak height at 24 hours might be at least qualitatively related to thrombogenicity. If the order of thrombogenicity is accepted as glass>polyethylene>Surfasil>PU02 then Figure 4.28 shows that the highest peak adsorption is associated with the most thrombogenic surface. There is also a suggestion in Figure 4.28 that plasma concentration at peak adsorption may increase with increasing thrombogenicity.

It is still unknown exactly how this phenomenon of transient fibrinogen adsorption can be related to ultimate thrombogenicity of a surface. Two possibilities suggest themselves. One is related to the activity of the clotting factors and the other is related to the reactivity of platelets with respect to adsorbed fibrinogen. If the activity promoting thrombosis is the activation of coagulation, then fibrinogen retention is probably desired. This is due to the fact that fibrinogen when removed from the surface is being displaced by HMWK and other clotting factors (Vroman et al, 1980; 1982). If the property promoting thrombosis is the adhesion and activation of platelets, then fibrinogen adsorption is undesirable. This is because adsorbed fibrinogen is thought to be platelet reactive (Salzman et al, 1969; Vroman, 1972).

The results of the present study on fibrinogen adsorption to SPU's show interesting differences compared to other materials, which are considered more thrombogenic. It was found that the surfaces of the various SPU's while showing a range of fibrinogen adsorption levels, nonetheless adsorbed less than the other materials.

With the development of a larger data base involving a wider range of material types it may be possible to use this test as a simple and rapid indication of blood response to biomaterials. Once it is exactly known what type of behaviour with respect to fibrinogen adsorption is needed for a thromboresistant material, the SPU can likely be appropriately tailored to match this response.

CHAPTER 5

SUGGESTIONS FOR FUTURE WORK

As a result of this study it is hoped that the development of segmented polyurethanes for blood contacting applications will continue. The present work has produced some interesting results that warrant further investigation and has also stimulated ideas for new areas of study for SPU's. The following is a list of some of the potential areas for future work in this field;

1. The characterization of segmented polyurethanes using LALLS. Although results of this analysis were poor, characterization using LALLS would give an absolute $\bar{M}w$, instead of using GPC or intrinsic viscosity which rely on non-polyurethane parameters. The use of LALLS in analyzing SPU's remains relatively unexplored.
2. Contact angle measurements made under water could provide more relevant wettability information on hydrophilic materials such as PEG based SPU's that absorb water. These data may be more suitable for correlations with other types of behaviour in the hydrated state (e.g. adsorption of fibrinogen from an aqueous medium).
3. Other mechanical properties should be investigated. Creep,

stress relaxation and fatigue testing would provide important information from a biomaterial standpoint.

4. The adsorption of other plasma proteins should be examined to determine their behaviour at the SPU/plasma interface.

5. PEG based SPU's provided interesting results that should be explored further. The minimal protein adsorption found by other researchers as well as in the present work may be associated with some degree of thromboresistance and should be studied in greater detail.

6. The possibility of layering PEG based SPU's onto a PPG based SPU may improve two properties in relation to biomaterials. First it may provide a more thromboresistant surface and secondly it should improve the poor mechanical properties of PEG based SPU's.

7. Other PPG monomers should be examined in order to complete the series (eg. PPG 500, PPG 3000, PPG 4000, etc.). This would allow confirmation of the trends found with PPG 1000 and PPG 2000 based SPU's with respect to mechanical properties and fibrinogen adsorption.

8. The use of novel chain extenders is an area worthy of continued research. Although the soft segment was found to dominant most properties examined, the chain extender did illustrate some influence on the trends observed. Also the odd/even carbon number effect of the chain extender on phase separation should be investigated further.

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APPENDIX A

SAFETY AND HANDLING PROCEDURES FOR SPU SYNTHESIS

As the result of several major chemical accidents in the last few years, safety and awareness of the potential hazards of toxic chemicals and how they can be controlled has been heightened at both the academic and industrial levels. Certainly the most tragic example of toxic chemical leak occurred in Bhopal, India in December, 1984. The chemical was methyl isocyanate (MIC) used in pesticide production. The impact of the Bhopal incident made the public aware of the toxic danger of isocyanates.

Isocyanates as already discussed are used extensively in the manufacturing of polyurethanes, with toluene diisocyanate (TDI) and 4, 4' diphenylmethane diisocyanate (MDI) being the two isocyanates of major commercial importance. All three isocyanates (MIC, TDI, and MDI) are considered to be very reactive, flammable and highly toxic. The exposure limits set by the U.S. Occupational Safety and Health Administration for eight hour periods are 0.02 ppm for MIC and MDI and only 0.005 ppm for TDI.

The reason why MIC represents an even more potentially hazardous material is because it is highly volatile whereas TDI and MDI are essentially nonvolatile. MIC boils at 39.1°C and has a vapour pressure of 348 mm Hg at 20°C. A second reason for the potential of MIC to be more hazardous is that its vapour is about twice as heavy as air and therefore stays close to the ground (Worthy, 1985). The combination of these two properties along with its toxic characteristics resulted in the

devasting tragedy in Bhopal.

The use of MDI and TDI nonetheless require special care to ensure minimal exposures. In the synthesis of SPU for this thesis, MDI, was used exclusively and therefore safety data are given only for MDI. MDI was from the Mobay Chemical Corporation and a material safety data sheet (MSDS) was provided giving material specifications, physiological considerations and handling precautions. The MSDS is presented in the following pages.

MATERIAL SAFETY DATA SHEET

DIVISION ADDRESS

Mobay Chemical Corporation
Polyurethane Division
Penn Lincoln Parkway West
Pittsburgh, Pennsylvania 15205

ISSUE DATE 9-28-83
SUPERSEDES 6-21-82

TRANSPORTATION EMERGENCY: CALL CHEMTREC
TELEPHONE NO 800-424-9300. DISTRICT OF COLUMBIA 202-483-7616

MOBAY NON-TRANSPORTATION EMERGENCY NO.:
412-923-1800

I. PRODUCT IDENTIFICATION

PRODUCT NAME.....: Mondur M (Flaked)
PRODUCT CODE NUMBER.....: C-004
CHEMICAL FAMILY.....: Aromatic Isocyanate
CHEMICAL NAME.....: 1,1'-methylenebis (isocyanatobenzene)
SYNONYMS.....: Diphenylmethane diisocyanate, MDI
Methylene diphenylisocyanate
CAS NUMBER.....: 26447-40-5
T.S.C.A. STATUS.....: On Inventory
CHEMICAL FORMULA.....: $C_{15}H_{10}N_2O_2$

II. HAZARDOUS INGREDIENTS

COMPONENTS:	%:	CURRENT TLV:
4,4' Diphenylmethane Diisocyanate (MDI) CAS #101-68-8	98	0.02 ppm (0.2 mg/m^3) ceiling value
Other - MDI isomers	2	---

III. PHYSICAL DATA

APPEARANCE.....: Solid Flakes
COLOR.....: White to light yellow
ODOR.....: Slightly musty odor
MOLECULAR WEIGHT.....: 250
MELT POINT/FREEZE POINT..: 99°F(37°C)
BOILING POINT.....: 381°F (194°C) to 390°F (199°C) at 5 mmHg
VAPOR PRESSURE.....: Less than 10^{-5} mmHg at 77°F (25°C)
VAPOR DENSITY (AIR=1)....: 8.5
SPECIFIC GRAVITY.....: 1.19 at 77°F (25°C)
BULK DENSITY.....: 9.93 lbs/gal
SOLUBILITY IN WATER.....: Reacts slowly with water to liberate CO_2 gas
% VOLATILE BY VOLUME.....: Negligible

IV. FIRE & EXPLOSION DATA

FLASH POINT °F(°C).....: 395°F (202°C) Pensky-Martin Closed Cup
EXTINGUISHING MEDIA.....: Dry chemical (e.g. monoammonium phosphate, potassium sulfate, and potassium chloride), carbon dioxide, high expansion (proteinic) chemical foam, water spray for large fires.
SPECIAL FIRE FIGHTING PROCEDURES/UNUSUAL FIRE OR EXPLOSION HAZARDS:
Full emergency equipment with self-contained breathing apparatus should be worn by fire fighters. During a fire, MDI vapors and other irritating, highly toxic gases may be generated by thermal decomposition or combustion. (See Section VIII.) At temperatures greater than 400°F (204°C), MDI can polymerize and decompose which can cause pressure build-up in closed containers. Explosive rupture is possible. Therefore, use cold water to cool fire-exposed containers.

V. HEALTH EFFECTS DATA

ANIMAL TOXICITY -

ORAL, LD50
(INGESTION).....: Greater than 31,600 mg/kg (Rat)
DERMAL, LD50
(SKIN CONTACT).....: Greater than 10,000 mg/kg (Rat)
INHALATION, LC50.(4 hr): Approximately 400 mg/m^3 (Rat)
AQUATIC LC50.(24 hr)...: Greater than 500 mg/l (Daphnea, Limnea Invertebrates and Zebra Fish).
EYE EFFECTS.....: Not irritating (Rabbits) OECD Guidelines.
SKIN EFFECTS.....: Slight irritation (Rabbits) OECD Guidelines. Skin sensitizer in guinea pigs.

OTHER.....: No conclusive evidence has been developed to indicate that MDI is carcinogenic, teratogenic or that it causes reproductive effects in animals or humans. However, MDI has been reported by NIOSH to be mutagenic to Salmonella typhimurium bacteria in the presence of a mammalian liver activating system (commonly called the Ames test). There is not full agreement in the scientific community on the significance of these Ames test results and their relationship to human safety in assessing the risk of cancer in man. Preliminary steps for an animal lifetime inhalation study on MDI have been performed.

HUMAN EFFECTS

OF OVEREXPOSURE.....: Inhalation. Inhalation of dust, vapors or aerosols in concentrations above 0.02 ppm can produce irritation of the mucous membranes in the respiratory tract, running nose, sore throat, productive cough and a reduction in lung function. Extensive exposures to concentrations well above the TLV could lead to bronchitis, bronchial spasm and pulmonary edema. These effects are usually reversible. However, due to low volatility, high exposures are not anticipated except if the material is overheated or sprayed as an aerosol into the air. Hypersensitivity pneumonitis has also been reported. Another type of response is hyperreactivity or hypersensitization. Persons with a preexisting unspecific bronchial hyperreactivity or persons with a specific isocyanate hypersensitivity (as a result of previous repeated overexposure or a single large dosage) will respond to small isocyanate concentrations at levels well below the TLV of 0.02 ppm. Symptoms could be immediate or delayed and include chest tightness, respiratory distress or asthmatic attack. Skin. MDI reacts with skin protein and tissue moisture and can cause localized irritation as well as discoloration. Prolonged contact could produce reddening, swelling, or blistering and, in some individuals, skin sensitization resulting in dermatitis. Eyes. Dust, vapors, or aerosols are irritating to the eyes and can cause lachrymation (tearing effect). Corneal damage can occur; however, indications are that the damage is reversible and does not result in permanent injury. Ingestion. Ingestion could result in irritation and some corrosive action in the mouth, stomach tissue and digestive tract. However, it is not considered a common occupational route of exposure.

THRESHOLD LIMIT VALUE (ACGIH): 0.02 ppm (0.2 mg/m^3) ceiling.
PERMISSIBLE EXPOSURE LIMIT (OSHA).....: Same as TLV

VI. EMERGENCY & FIRST AID PROCEDURES

EYE CONTACT.....: Flush with clean, luke warm water (low pressure) for at least 15 minutes, occasionally lifting eyelids, and obtain medical attention.

SKIN CONTACT.....: Remove contaminated clothing. Wash affected areas thoroughly with soap and water. Wash contaminated clothing thoroughly before reuse.

INHALATION.....: Move to an area free from risk of further exposure. Administer oxygen or artificial respiration as needed. Obtain medical attention. Asthmatic-type symptoms may develop and may be immediate or delayed up to several hours. Treatment is essentially symptomatic.

INGESTION.....: Do not induce vomiting. Give 250 ml of milk or water to drink. Do not give anything by mouth to an unconscious person. Consult physician.

NOTE TO PHYSICIAN..... Medical supervision of all employees who handle or come in contact with MDI is recommended. These should include preemployment and periodic medical examinations with respiratory function tests (FEV,FVC as a minimum). Persons with asthmatic-type conditions, chronic bronchitis, other chronic respiratory diseases or recurrent skin eczema or sensitization should be excluded from working with MDI. Once a person is diagnosed as sensitized to MDI, no further exposure can be permitted.

VII. EMPLOYEE PROTECTION RECOMMENDATIONS

EYE PROTECTION.....: Safety glasses with side shields or goggles. Contact lenses should not be worn.

SKIN PROTECTION.....: Chemical resistant gloves. Cover as much of the exposed skin area as possible with appropriate clothing. If skin creams are used, keep the area covered by the cream to a minimum.

RESPIRATORY PROTECTION...: An air-supplied respirator must be worn during spray applications, during long-term (over 1 hour) exposures when the product is heated or in environments of high concentrations well above the TLV of 0.02 ppm. For short-term (less than 1 hour) emergency situations at concentrations near the TLV, an air-purifying respirator equipped with organic cartridges or cannisters and dust filters can be used. However, due to the poor warning properties of MDI, proper fit and timely replacement of filter elements must be ensured. Observe OSHA regulations for respirator use (29 CFR 1910.134).

VENTILATION.....: Local exhaust should be used to maintain levels below the TLV whenever MDI is processed, heated, or spray-applied. For spray-applications, an air-supplied respirator must also be worn.

OTHER.....: Safety showers and eyewash stations should be available. Educate and train employees in safe use of product. Follow all label instructions.

VIII. REACTIVITY DATA

STABILITY.....: Stable under normal conditions
POLYMERIZATION.....: May occur if in contact with moisture or other materials which react with isocyanates. Also temperatures over 400°F (204°C).
INCOMPATIBILITY (MATERIALS TO AVOID)...: Water, amines, strong bases, alcohols, metal compounds, or surface active compounds.
HAZARDOUS DECOMPOSITION PRODUCTIONS.....: By fire: carbon monoxide, oxides of nitrogen ..traces of HCN, MDI.

IX. SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED:
If material is molten, allow to solidify then shovel into open containers. Flakes can be swept and placed into open container. Spill area should be decontaminated by pouring liquid decontamination solution over area and allowing to react for 10 minutes. Collect in open containers, remove to safe area and cover loosely. Decontamination solutions: non-ionic surfactant TMN-10 (20%) and water (80%); concentrated ammonia (3-8%), detergent (2%) and water (90-95%). Respiratory protection is recommended during spill clean-up. (See Respiratory Protection, Section VII.)

WASTE DISPOSAL METHOD: Waste must be disposed of in accordance with federal, state, and local environmental control regulations. Incineration is the preferred method. Empty containers must be handled with care due to product residue. Decontaminate containers prior to disposal. DO NOT HEAT OR CUT EMPTY CONTAINER WITH ELECTRIC OR GAS TORCH. (See Sections IV. and VIII.)

X. SPECIAL PRECAUTIONS & STORAGE DATA

STORAGE TEMPERATURE (MIN./MAX.).....: No minimum restrictions/41°F (5°C) Maximum temperature for freshly distilled MDI.
AVERAGE SHELF LIFE.....: 3 months
SPECIAL SENSITIVITY (HEAT, LIGHT, MOISTURE): If container is exposed to high heat, 400°F (204°C) it can be pressurized and possibly rupture. MDI reacts with water to form CO_2 gas. This gas can cause sealed containers to expand and possibly rupture.
PRECAUTIONS TO BE TAKEN IN HANDLING AND STORING: Store in tightly closed containers to prevent moisture contamination. Do not reseal if contamination is suspected. Material must be refrigerated for optimal shelf life.

XI. SHIPPING DATA

TECHNICAL SHIPPING NAME..: Diphenylmethane Diisocyanate
D.O.T. HAZARD CLASSIFICATION.....: Non-regulated
FRT. CLASS FKG.....: Chemical NOI (Isocyanate) NMFC 60000
PRODUCT LABEL.....: Mondur M Label
REASON FOR ISSUE.....: Revision
APPROVED BY.....: J.H. Chapman/K.S. Booth
TITLE.....: Polyurethane Div. Industrial Hygiene
DATE APPROVED.....: 9/26/83