MEMBRANE MATERIALS FOR A NONTHROMBOGENIC BLOOD OXYGENATOR

by

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ABSTRACT

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The development of artificial lungs or blood oxygenators has stalled at the threshold of long-term (several weeks to years) devices. The lack of a suitable nonthrombogenic membrane for prolonged blood contact remains a major obstacle to this potentially lifesaving device.

Silicone rubber, the most frequently used membrane material, has desirable gas transport properties. However, all "Medical Grade" silicones have silica (SiO_2) filler and peroxide catalyst residues which probably limit its blood compatibility. The present work involved cross linking a high molecular weight poly dimethyl siloxane gum, free of filler and catalyst, by 3 MeV electrons under nitrogen containing oxygen reduced by varying degrees from atmospheric concentration. The purpose was to create a silicone surface pure in the sense of representing as closely as possible a network containing only dimethyl siloxane units.

Cross linked material produced under reduced oxygen concentrations exhibited a dramatic rise in blood compatibility, as measured by the Lee-White clotting test; far surpassing present medical grade silicone rubber. Ordinary and differential infrared spectroscopy indicated that near atmospheric oxygen concentrations in the gas surrounding the polymer during irradiation is accompanied by an appreciable concentration of carbonyl groups in the network; thus demonstrating that oxygen reactions are important. A method of prediction of sol fraction after cross linking for a Flory "most probable" molecular weight distribution resulted in severe underestimation of this number. However the method has promise as a determination of radiation cross linking efficency.

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Department of Chemical Engineering
Massachusetts Institute of Technology
December 21, 1971

Professor David B. Ralston
Secretary of the Faculty
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Dear Professor Ralston:

In accordance with the regulations of the Faculty, I herewith submit a thesis, entitled "Membrane Materials for a Nonthrombogenic Blood Oxygenator", in partial fulfillment of the requirements for the degree of Master of Science in Chemical Engineering at the Massachusetts Institute of Technology.

Respectfully submitted,

Signature redacted

Paul K. Weathersby

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My wife, Patricia, has carried more of a burden than I can express. Her patience and love throughout this endeavor have been vital to its completion.

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I. SUMMARY

Current Membranes and Materials

The day of artificial internal organs is rapidly approaching. Cardiac pacemakers, hemodialysis units, and heart-lung bypass devices are in daily use and long term artificial hearts are forseeable (35,39,56,57). However the extended use of artificial organs has many problems to overcome.

The human lung, for instance, is a relatively simple mass transfer device. Its great efficency arises from a very short (0.2μ) diffusion path for O_2 and CO_2 into and out of the blood. Engineering attempts to duplicate this function have resulted in inefficent and traumatic devices, largely because of blood's great sensitivity to changes in environment. The most popular oxygenating schemes — direct bubble and rotating disk — harm blood in three ways (7,28,40). The blood-air interface denatures plasma proteins, the foreign surface induces clotting, and both factors combined with high shear stress causes hemolysis, rupture of the red blood cell membrane.

The use of membrane and liquid-liquid contacting schemes have been considered as alternatives. The latter proposal is somewhat promising, but dangers of incomplete fluorocarbon-blood separation and protein denaturation are yet to be overcome(46,50). Membranes of silicone rubber and teflon have been constructed, with limited clinical success. Mass transfer resistance has become membrane limited (4), but so, unfortunately, has blood contact time. Experimental perfusions over 100 hours are very rare and they generally result in the patient's death (21,36, 37,39,69). Blood damage is the major drawback at this time.

Maintaining blood fluidity is sine qua non for artificial organs.

Synthetic surfaces can activate both clotting systems. The intrinsic system of surface contact followed by a reaction cascade ending in fibrinogen polymerization is thought to be influenced by surface geometry and chemistry (2, 20, 47, 64). This body defense mechanism can be inactivated by large doses of an anticoagulant such as heparin. The parallel system of platelet adhesion, secretion and agglomeration is less understood and less easily thwarted. Surfaces with adsorbed (33, 41) or bonded (48) heparin have shown passive behavior toward the intrinsic clotting system; but actively adsorb platelets, unless pretreated in a complicated procedure involving serum albumin. The blood compatibility of truly "pure" polymeric materials has never been adequately investigated.

Silicone rubber is preeminent among the non-heparinized biomaterials used today (9, 10). The rubber is a crosslinked network of linear high molecular weight polymers of dimethylsiloxane ($-O-Si(CH_3)_2-$). To achieve mechanical strengths necessary for nearly any application, submicronic fillers such as fume silica (SiO_2) are added in appreciable volume percentages. These and chemical crosslinking agents, typically aromatic peroxides, render even "Medical Grade" silicones a composite of several species. The silica is suspect since its most common use (glass) is one of the most thrombogenic materials known. Peroxides can decompose into various products, not all of them volatile enough to diffuse out of the polymer during the usual thermal cross linking.

Another method of curing silicone is the use of ionizing radiation. The various radiation sources (17, 71) are used to produce free radical sites on the linear polymer. Some radical pairs disproportionate by proton exchange, others terminate by capture of small mobile radicals (e.g. $H^{\cdot}$, $OH^{\cdot}$, $O_2^{\cdot}$), and still others form cross links by recombination. The latter produce a network without the use of chemical reagents. If the irradiation takes place in the presence of atmospheric oxygen, cross links and side groups may include "new" groups such as peroxides (-O-O-),

carbonyls (=C=O), carboxylic acids (-COOH), hydroxyls(-OH), etc. These result from the myriad combinations of polymer radicals, polymer groups, oxygen radicals, and molecular oxygen (59).

Results and Discussion

The principle purpose of this thesis was to qualitatively assess the initial clotting tendency of a pure polydimethylsiloxane cured under anoxic radiation. Infrared spectroscopy was used on the original polymer, and on rubbers cured under various concentrations of gaseous O_2 to detect structural changes. In addition a prediction of the un-cross linked sol fraction from the theory of Flory's "most probable" molecular weight distribution was compared to experimentally determined sol fractions.

Irradiation by 3 MeV electrons to a total dose of 15×10^6 rad was performed at M.I.T.'s High Voltage Research Laboratory. An unfilled polydimethylsiloxane gum from Stauffer-Wacker Silicone Co. was found to reflect a "most probable" distribution with $\bar{M}_n = 190,000$. Lee-White clotting times* on irradiated samples increased from about 20 minutes for silica - filled silicone to over 45 minutes for unfilled samples cross linked under 8 ppm O_2. Rather than an absolute figure, this time represented the limit of the clotting test before other artifacts arise, and indicated a biomaterial suitable for further investigation.

Ordinary and differential infrared absorption spectra for the un-cross linked gum showed minor bands not corresponding to methyl, siloxy, or

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*The Lee-White WholeBlood Clotting Time is a standard medical test for the ability of blood to clot, and conversely, the ability of a material to delay activation of the intrinsic clotting system. Thrombotic surfaces such as glass induce clots within 10 minutes. Other polymer surfaces may last up to 25 minutes, but times over 1 hour usually denote anti-coagulated blood. Static blood in an isolated vein will clot in only a few hours (64).

or otherexpected groups; and thus represent molecular components of an unknown nature. Spectra for the radiation cured material were similar to the gum spectra expect for small peaks in the area where carbonyl compounds absorb. These peaks were indicative of concentrations slightly above absolute instrumental sensitivity (one C=O per average chain).

When a linear polymer is cross linked, a certain number of linkages per average chain are required to produce a continuous network, or gel. At this cross link density, there is still a large amount of polymer, the sol fraction, not tied to the network and hence capable of being extracted by a solvent. For example, a "most probable" distribution of silicone polymers with $\overline{M}_n$=190,000 requires 10 cross links per number average chain for a sol fraction of 1%. The sol fraction predicted by the original molecular weight distribution and by literature crosslink yield values was lower by a factor of 20 than the experimental value measured by toluene extraction after irradiation. In retrospect, the calculation may be too sensitive to radiation dosimetry for sol fraction prediction. However this limitation may be used to advantage in the measurement of cross link yields from a sol fraction technique.

Recommendations

1. Continue study of irradiated silicone as a biomaterial by:
   A. Extending the blood compatibility study to include protein denaturation, and platelet adhesion and activation;
   B. Exploring the fabrication of flexible tubes and membranes;
   C. Examining the material with optical and electron microscopes;
   D. Improving analytical methods for trace contaminants.
2. Develop the sol fraction technique for measuring cross link network parameters, such as yield as a function of O_2 present.

II. INTRODUCTION

Scope of the Present Work

This thesis was intended to explore briefly the biomaterial potential of unfilled, chemically pure polydimethylsiloxane (PDMS). It involved the curing of a commercial unfilled gumstock by 3 MeV electrons in the presence of reduced concentrations of atmospheric oxygen.

The evaluation was intended to determine the medical usefulness of the material rather than a complete physical and chemical analysis. Thus the major experiments were the determination of the activation of blood's intrinsic clotting system (whole blood clotting time) and the fraction of material that could potentially dissolve into or become extracted by a bloodstream. The solubility of silicone polymer in water is substantially zero, but blood has formed elements and proteins with a capacity for lipid transport, thus allowing for silicone removal into the body.

Infrared absorption analyses were performed on the irradiated samples to determine the (gross) degree to which O_2 changes the chemistry of the material. It was realized that conventional IR is orders of magnitude away from the sensitivity required for molecular-level processes such as clotting activation. It was hoped that changes noticed on the level of IR would extrapolate with extension of anoxic preparations.

In defense of this cursory examination of the proposal , it should be pointed out that biomaterials research is a very low yield endeavor with almost infinite capacity for conjecture and analysis. A reasonable and rapid preliminary evaluation of the prospects of a biomaterial certainly occupies a valid place in this most subtle branch of engineering.

Presently Used Oxygenators

The human lung consists of a series of branching tubes called bronchi terminating in small sacs -- the alveoli. Atmospheric gas is transported along the bronchi and diffuses across a series of membranes and a thin aqueous fluid layer to contact blood flowing in the pulmonary capillaries. The total diffusion path is about 0.2 μ long (31). Some of the gases become dissolved in the blood, but most of the oxygen binds to the protein hemoglobin which is held within the red blood cell membrane. An adult at rest requires about 250 ml of O_2 per minute to support his basic metabolic functions. Over the same time scale, a comparable amount of CO_2 is transported countercurrently.

However the lung does not always function well. In disease states such as advanced emphysema, pulmonary edema, pulmonary embolism, or myocardial infarction, mass transfer is limited by a decrease in blood flow rate, decrease in transport area or increase of the diffusion path. Death often results from such impaired lung function. If the lungs could be supplemented or bypassed for a period of a few weeks, the natural healing processes could repair the lungs and many presently hopeless cases could be saved. In addition, the surgical procedures for cardiac repair ("open heart surgery") and heart transplant require a device to function as a gas exchanger for up to several hours while the heart and lungs are bypassed. All of these situations can greatly benefit from a suitable blood oxygenator.

Several blood-gas contacting schemes have been tried (28). The first and still most common is simply a plastic bag through which blood flows and oxygen-rich gas is bubbled. Behind the simplicity of this idea lie several serious problems. When proteins in the blood are exposed to a gas phase, the original folding of ionic groups to contact the aqueous

medium and of non-polar groups to form hydrophobic bonds in the interior is disrupted (40). The restructuring at the interface to find a new stable configuration causes denaturation — the loss of biologic activity, and the change is often irreversible (40,64). Elaborate precautions must be taken to avoid air bubbles returning to the body. Not able to dissolve, they will lodge in a small blood vessel and cut off further circulation through it. The problems of materials compatibility and shear stresses on the blood also cause damage. All these factors produce significant trauma; the use of a bubble oxygenator for more than a few hours can be fatal.

A more efficent, but no less destructive device consists of a cylindrical chamber enclosing many thin disks which are attached to a central shaft. Mounted horizontally, the chamber is partially filled with flowing blood. The rotating disks pick up a thin film of blood and present a large surface area to the gas flowing overhead. This system has the same shortcomings as the bubble oxygenator, except that the extent of hemolysis (red cell rupture) is greater (7).

Recently a group has proposed using fluorocarbon liquids as an intermediary between blood and gas (46). Some fluorocarbons can dissolve large amounts of O_2, so they propose to transfer gas across a liquid-liquid interface and avoid direct gas contact with the blood. To take advantage of the density difference between blood (1.1 g/cc) and fluorocarbons (1.7-1.9 g/cc) both falling film and bubble devices are being evaluated. Two major drawbacks seem evident. As with air bubbles, any droplets that escape into the body will form a permanent and potentially lethal blockage of part of the circulation. Although the Abcor evaluation did not mention protein damage, other investigators (50) have been troubled by a hard, discolored film on the blood after fluorocarbon contact — a reasonable description of the coat of

denatured proteins at a gas-blood interface.

Membrane oxygenators are the only construction affording moderate prospects for long term oxygenation (29). To avoid the dangers of the gas interface, various materials are employed as semi-permeable barriers. The most popular membranes are silicone rubber; but polyethylene, polytetrafluoroethylene (Teflon) and even Millipore filters have been proposed (23). The mass transfer to a moving fluid with simultaneous chemical reaction in this context has been successfully modeled (18). Since the limiting resistance to mass transfer is usually in the blood side boundary layer (4), several schemes for enhancing blood mixing have been employed. These include intermittent suction (36), hollow fibre distribution (22), embossed grooves in the membrane (61), and toroidal flow (4). The last method is reported to nearly reach a membrane limiting transfer rate.

The clinical usefulness of all present oxygenator designs has been limited. Timmons et. al. used the Pierce-designed lung on puppies and found an intolerably high level of hemolysis after 12 hours(69). Their results were clouded by the use of an occlusive roller pump that has been implicated in red cell damage (7). Kolobow's group has used silicone membranes on lambs for up to 16 days with mixed success (37). They were forced to keep the lambs' blood anticoagulated with heparin for the entire perfusion period and still several animals died of severe clotting problems.

Dorson (21) and Landé (39) have used membrane lungs in cases with humans. In most procedures over 12 hours, the patients recovered some respiratory function but all died eventually. The deaths attributable to the oxygenator have not been consistently evaluated, but this factor was unquestionably important.

Friedman's recent study found that membrane oxygenators cause

greater thrombus formation than did bubble or disk types. However the blood cells and platelets survived better than when an air interface was present. The coagulation was not controlled even with the administration of heparin. This study also indicated that leak testing the membranes with tap water (a common procedure) aggrevated subsequent thrombosis (27). Thus it is apparent that the major obstacle to the development of a long term artificial lung is the lack of a blood compatible membrane.

Status of Biomaterials

The problem of a surface harmless to blood has been an area of intense research for many years. Until a satisfactory surface is developed, the hope of artificial internal organs will remain a hope. As yet there is no synthetic material that has the beneficial properties of normal endothelial cells. In fact, there is no substitute that will produce little enough damage for the body to repair.

Of the deleterious effects of surfaces on blood: hemolysis, protein denaturation and thrombosis; the latter is most difficult to overcome. Salzman's excellent review outlines the recent status of antithrombogenic material development and the limits of theory in this area(64).

The maintenance of a fluid blood stream seems to depend on a number of factors. Blood contacting surfaces must not activate any of the protein factors in the coagulation reaction cascade; nor may platelets adhere to the surface and become altered. The fluid dynamics must be controlled to avoid any stagnant or eddy regions where activated molecules could accumulate. The fluid flow aspects of thrombosis have been reviewed by Leonard (43), and will not be examined further here. For it is the task of the biomaterials researcher to develop a surface with the desired (and as yet undefined) chemical properties for use in a well designed system.

There are two accepted pathways for blood coagulation to occur (5). The intrinsic clotting system depends on the conversion of a specific plasma constituent, Factor XII or the Hageman Factor, to a reactive form. This activated molecule starts a series of further activations in a cascade, terminating in the polymerization of fibrinogen to fibrin and the crosslinking of these macromolecules into a network that enmeshes red blood cells, forming the familiar red clot. The initial change in Factor XII is thought to be surface induced and further research along these lines may lead to a theoretical basis for producing passive surfaces. Other coagulation factors may be surface activatable, but evidence is scanty at this point.

Another hurdle must be crossed before a material can be declared nonthrombogenic. Blood platelets are small formed elements in the blood which tend to adhere to all foreign surfaces. These platelets can become autoadhesive and form an effective plug in a bloodstream; a white thrombus. Certain proteins may accelerate or retard the initial adhesion, but once again specific function is unknown. In addition it is possible that the adherent platelets may or may not release the secretion necessary for subsequent massive platelet aggregation. With this degree of uncertainty surrounding the mechanisms of blood coagulation, it is small wonder that biomaterials research has seemed an Edisonian endeavor.

Many correlations have been advanced to explain the apparent range of thrombus resistance of various synthetic materials. Nearly all testing is done to determine the bulk chemical or surface characteristics of a candidate. This approach optimistically overlooks the possibility of minute structural variations that can, over long implantation times, lead to catastrophic clotting. Nevertheless, present techniques are suitable for obtaining rather gross indications of surface

characteristics. One is forced to prepare his samples as carefully as possible and hope that his efforts are sufficent.

The overall properties normally studied include contact angle, water wettability, surface free energy and work of adhesion. The organization of acceptable biomaterials by these standards has been only a partial success (2,20,57,64). Rules of thumb have been devised, but every hypothesis can be fitted with a counterexample. One of the more rampant theories allies blood compatibility with hydrophobicity. Yet work in this laboratory with hydrogels containing 90%$^{+}$ water has produced promising materials (48).

Several groups of researchers have fabricated polymeric systems to be more than simply passive to blood clotting. Braunwald uses a velour covering on heart valves to stimulate yet retain a small volume of red thrombosis (12). The velour anchors the clot so permanently that it becomes covered with an effective scar tissue. Adachi uses a similar approach but imbeds tissue fragments in the velour prior to implantation to accelerate the ingrowth (1). At the other extreme, Kusserow ionically adsorbs to graphite an enzyme (urokinase) that accelerates the depolymerization of fibrin (38).

One approach currently in vogue is the attachment of heparin to various polymers. Heparin is a naturally occuring polysaccharide which can effectively suspend the cascade of the intrinsic clotting system. Although there is no *a priori* reason for heparin to render many materials suitable for implantation. Leininger has attached heparin to many polymers via ionic coupling of heparin's COO^{-} and SO_3^{-} groups to quaternary amines introduced onto the base polymer (41). The artificially prolonged clotting times of these materials implies that heparin is leached off by ion exchange with plasma proteins. Covalently heparinized polymers developed in this laboratory have shown that heparin release is not

necessary for some antithrombogenic activity (48). However the performance of a "pure" passive material has never been conclusively evaluated. That this is the case for silicone will be shown in Section II-E.

Silicone as a Material

Although silicon (Si) is one of the most abundant elements in the world and although lying below carbon in the periodic table it exhibits chemistry similar to carbon, Si is not found in any living system. Si is slightly larger than C and slightly more electronegative; so it would not be expected to easily participate in normal biochemical reactions. For example, even the most inert polymers with organic backbones, such as polyethylene, are susceptible to enzymatic attack while silicones are not (44).

Silicone polymers are originally derived from minerals (10, 55). Quartz, predominantly silica (SiO_2) can be heated with graphite:

$$SiO_2 + C \xrightarrow{\Delta} Si + CO_2 \qquad (1)$$

and then oxidized by chloroform:

$$Si + 2\,CH_3Cl \longrightarrow Cl\text{-}Si(CH_3)_2\text{-}Cl \qquad (2)$$

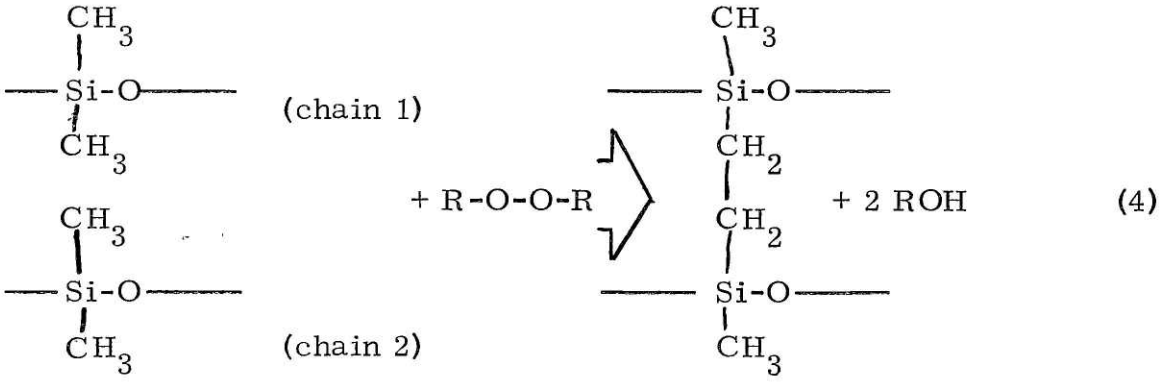
Naturally the use of other oxidants in this reaction will result in any number of silicone polymers when the reaction is continued:

$$Cl\text{-}Si(CH_3)_2\text{-}Cl + H_2O \longleftrightarrow HO\text{-}Si(CH_3)_2\text{-}OH + HCl \longleftrightarrow \left[-Si(CH_3)_2\text{-}O-\right]_n \qquad (3)$$

The reversibility of this reaction allows the molecular weight of the linear polymer to be somewhat controlled, but any equilibrium state

will involve the coexistence of many different sized molecules, from n=1 to very high n's.

Depending upon n, the degree of polymerization, the polymer can be useful as a lubricant, sealant, resin or gum. However since linear silicones cannot develop any real strength, cross linking of a high molecular weight silicone gum (n averaging several thousand) is performed to produce an elastomer. Chemical cross linking of the gum into a rubber can be done with organic peroxides, metal catalysts or acetoxy silanes. Medical Grade silicones are usually produced by the peroxide route:



(4)

where R is typically a chlorinated benzoate. With only a few of these cross links per original chain, the viscous syrup becomes a rubbery gel. One drawback to this reaction scheme is that the decomposition of peroxide into the two radicals necessary to extract the methyl protons follows zero-order kinetics. The peroxide can continue to react long after the initial cure and set period. For the production of chemically pure materials the peroxide residue is a nuisance to remove.

An alternative cure can be provided by the administration of ionizing radiation. Linear silicone polymers exposed to X-rays, electrons, deuterons or γ-radiation (24, 51) produce free radicals which then form a variety of products. A chain radical may add to a solvent molecule; thus the chain may shorten. Monomers can act in this fashion

to reduce the effective chain length (58). Effects possible in organic polymers such as double bond formation do not apply to the silicones (17, 54). Irradiation in the presence of oxygen can lead to the incorporation of "foreign" groups into the network, such as carbonyl and peroxide (59). Thus most research in the irradiation of silicones is performed under a nitrogen atmosphere.

Radiation work is quantified by using a G value — the yield of a product for a given amount of absorbed energy. For PDMS, G values have been reported from 2 to 5 crosslinks per 100 eV (9, 15, 17, 51, 54, 71), with most room temperature conditions giving close to 3.0. In radiation chemistry , the absorption of 100erg per gram is defined as a one rad dose. Thus a dose of one megarad with a G of 3 means that 3×10^{-6} moles of cross links are formed per gram of sample. Bueche found that the number average molecular weight of oligomeric PDMS increased linearly with dose of electrons from a resonant transformer, supporting the assumption that radiation efficency is not a function of the amount of radiation (15).

The ionizing radiation is believed to leave an unpaired electron on the side group. Such a mechanism would produce linkages of Si-Si, Si-CH_2-Si and Si-CH_2-CH_2-Si and liberate stoichiometric amounts of H_2, CH_4, and C_2H_6. The infrared analysis of Kantor (reported by Bueche (15)) found no evidence for ethylene linkages and a CH_2/Si-Si ratio of two. These data predict that the gas radicals would be in the proportion of 4 $CH_3^{\cdot}$ (2 per Si-Si; 2 per pair of Si-CH_2-Si) to 2 $H^{\cdot}$ for a H/C ratio of 3.5. However Charlesby's mass spectrometry on evolved gases gave H/C = 6.3 (17). Bueche's additional report of SiH yield approximately 10% of the crosslink yield further complicates the issue. This group could be formed from a silicon radical capturing a hydrogen radical after losing its methyl group. The effect would be to

lower the predicted H/C ratio to 3.4. Bueche lamely suggests that siloxane or other analytically elusive cross link might be involved, but the issue of specific cross link production remains unresolved.

It should be noted that Miller, in another reference to the elusive Kantor, explains that experimental difficulties in measuring methylene and ethylene abundances give discrepant figures from total cross link yield measured by gel fraction. The conflict is in the direction expected from the different cross link counting methods employed. Infrared sees every chemical linkage, while the gel fraction is not affected by intramolecular links (i.e. a single molecule tied into a loop).

Miller gives further evidence that simple radiation chemistry is not totally applicable to silicones (51). At low temperatures, the G values determined from gel fractions and gas yields were similar. However, over 100°C, gas liberation increased while apparent cross linking dropped off. Charlesby's gel formation data agreed well up to his limit of 150°C. The source of the unexpected trend remains unsubstantiated speculation. However the assumption of simple kinds of cross link production at room temperature appears to be acceptable. One reservation concerns the untested (and perhaps untestable) possibility that some new molecular species are produced by the radiation.

Silicone rubber is not the ideal structural material. It has lower tensile, tear, and impact strengths than organic rubbers, and is more expensive as well (55). However, their large useful temperature range, excellent chemical stability and long life make these polymers desirable in many commercial applications.

The high extensibility but poor strength can be drastically improved by the incorporation of reinforcing fillers. Silica (SiO_2), carbon black, and diatomaceous earth in particle sizes of 100 to 1000 Å are added to the unvulcanized gum (17, 55). Depending on the extent of chemical binding

of polymer and particle, substantial increase in mechanical performance results. For example; an unfilled PDMS with a tensile strength of 50 psi increased this value to over 1000 psi by the incorporation of 30% by weight silica particles (16).

It is interesting to note some comparisons between peroxide and radiation cured silicones (71). Beside the usual disadvantages of residual catalyst and long reaction times (conventional post curing requires 24 hours at 250°C), peroxide cured rubbers have inferior long term properties. After periods of order one year, peroxide samples degrade and lose tensile strength and hardness. Osthoff found silicone stress relaxation to be aggrevated by water and carbon dioxide. However the rubber cured with high energy electrons exhibited no stress relaxation even at high temperatures with CO_2 and H_2O present. He concluded that the chain scission causing the relaxation was due to hydrolysis by the acidic and basic peroxide residues.

In the steady state solution of a mass transfer (without chemical reaction) differential equation, the continuous phase properties of solubility and diffusibility appear together as a product. This product is defined as the permeability of the material.

Gas permeability is of utmost importance for a membrane oxygenator. Silicones have the highest O_2 and CO_2 permeabilities of any polymer family, thus they are the natural choice for oxygenator membranes. Gas solubility is roughly the same for all polymers since atomic packing does not vary much. The higher permeability of silicones is due to significantly enhanced flexibility of the Si-O bond as compared to C-C or C=C. Robb's study of the self-diffusivity of various silicones indicated that the progress of diatomic gases was due to the motion of groups of 3 dimethylsiloxy units (63).

Another result of Robb showed that O_2 and CO_2 permeability in PDMS decreased about 50% with the addition of up to 60% filler and only

10 to 20% over a wide range or radiation cross link density. Buckles work with medical grade silicones showed a similar level of filler influence (14). Thus for membrane development, the removal of filler could improve gas transfer slightly, but varying the radiation dose would not be justified by mass transfer considerations.

Silicone as a Biomaterial

Since the advent of biomaterials, silicones have been prevalent among medically useful polymers. Dow-Corning has been producing "Medical Grade" PDMS (peroxide cure, silica filler) since 1943 (9, 10). Silicone's chemical inertness, reasonable ease of fabrication and good elastic properties make it a desirable material for conducting body fluids, reinforcing and replacing joints, coating implants (e.g. cardiac pacemakers) and filling numerous cavities. It is relatively slow in activating the intrinsic clotting system and exhibits low permanent adhesion of platelets and proteins. Thus silicone is the most popular material for membrane oxygenators, artificial hearts, and cannulae for extracorporeal circulation.

In the drive to heparinize all possible plastics, silicone was not overlooked. Leininger bonded a quaternary amine to side groups and successfully adsorbed heparin (41, 42). Hufnagel dissolved heparin in the rubber and let it release into the bloodstream when implanted (33). However, as with other ionically bonded systems; heparin release was sporadic and unpredictable, except to the extent that it thwarted the intrinsic clotting system. Efforts in this laboratory to covalently bond heparin to silicone, including the author's previous attempt at a thesis, were slightly encouraging but rather unsucessful (25, 49).

Various pieces of evidence in the literature indicate that simple

PDMS has not been given a fair chance to demonstrate its blood compatibility. Nearly every report has concerned silicones which were peroxide cured and filled — usually with SiO_2. As pointed out earlier, peroxides are rather unspecific in their reactions and continue to decompose after implantation. They and their residues can also diffuse to the blood surface and (plausibly) activate clotting factors, attach platelets, or leach out and cause damage elsewhere in the circulation. They form cross links that are unstable over long periods when contacted with CO_2 in an aqueous environment, e.g. blood. Silica is suspect since the most common occurence of it — in glass — causes one of the most thrombogenic reactions known (5). Evidence exists that silica particles can migrate to the surface during fabrication (57).

Thus it is small wonder that ordinary silicones present problems in medical situations. Musolf's study on various silicones (peroxide cured, silica filled) implanted in canine vena cavae showed differences(53) in thrombogenesis with different side groups; carbonyl being one of the worst. Even medical grade PDMS containsmore than just polymer and filler. Kolobow was plagued by an alkaline extractable substance from commercially available membranes (37). Nose's group was forced to exceed manufacturer's cleaning and sterilizing specifications because of thrombosis problems (56). Nyilas did an exhaustive study on a popular medical grade PDMS to explain erratic blood compatibility (57). He found traces of acetoxy groups, aromatic diacyl peroxide and various radical fragments. It is quite evident that blood has probably never been exposed to the model methyl surface of a pure polydimethylsiloxane.

III. PROCEDURES AND MEASUREMENTS

Molecular Weight Distribution

The gum stock of linear polydimethylsiloxane* was examined by standard methods of physical chemistry to determine the average molecular weights. Two separate experiments were performed to gain an inference of the molecular weight distribution.#

The method of osmotic pressure effectively counts the number of non-solvent molecules in a solution. The average molecular weight determined in this method, the number average, is defined by:

$$\bar{M}_n = \frac{\text{weight of sample}}{\text{moles of polymer in sample}} \qquad (1)$$

Flory used thermodynamic arguments to show that the number average molecular weight can be obtained from the solution osmotic pressure at various concentrations:

$$\pi/c\Big|_{c=0} = RT/\bar{M}_n \qquad (2)$$

where $\pi/c\Big|_{c=0}$ is the limiting ratio of osmotic pressure to polymer solution concentration; R is the gas constant; and T is the temperature at which the measurement is made. Taking this limit is necessary because macromolecules interact with one another even at concentrations below 1% ;van't Hoff's law applies only at infinite dilution.

With broad range molecular weight distributions, caution must be exercised in interpreting the $\bar{M}_n$ obtained from osmometry (6).

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* Stauffer-Wacker Silicone Corporation, Compound SWS-06804

Unless otherwise noted, all references in this section from Flory (26)

Since the thermodynamic arguments require that the membrane used allows free movement of solvent but not of solute (i.e. polymer) molecules, the smaller polymeric molecules may diffuse across the membrane over long time scales. This effect will produce erroneously high molecular weights.

The method of intrinsic viscosity gives a higher weighting to larger molecules. Since this experiment measures the increase in solvent viscosity, larger macromolecular coils cause a disproportionately large disturbance in fluid streamlines. The viscosity average molecular weight is defined by:

$$\overline{M}_v = \left(\frac{\sum_i m_i^{1+a} n_i}{\sum_i m_i n_i} \right)^{\frac{1}{a}} \qquad (3)$$

where n_i is the number of molecules having a molecular weight w_i and a is an experimentally determined constant for a given polymer-solvent-temperature system.

The intrinsic viscosity, $[\eta]$, is defined as the fractional increase in solvent viscosity per unit of polymer concentration, extrapolated to zero concentration. The relation between intrinsic viscosity and molecular weight has been found experimentally and with some theoretical justification to be:

$$[\eta] = K' \overline{M}_v^{\,a} \qquad (4)$$

The system parameters K' and a (known as Mark-Houwink constants) are tabulated in references such as the "Polymer Handbook" (11).

Flory has found that polymers synthesized by condensation of end groups of bifunctional monomers form a distinctive distribution of molecular weights. Knowing a given distribution enables one to predict ratios of various average molecular weights, percentage of

any weight fraction, and the fraction of original material remaining soluble after a given number of randomly located cross links have been introduced.

Since silicone polymers are generally made by condensation of terminal hydroxyls on linear siloxanes, or by scission and condensation of cyclic molecules, one might expect the polymer to have a Flory most probable molecular weight distribution. The statistical origin of this distribution is based only on the well established principle of equal reactivity of end groups of all sizes of polymers. For a "most probable distribution", the following relation will hold:

$$\frac{\overline{M}_v}{\overline{M}_n} = \left[(1+a)\,\Gamma(1+a) \right]^{\frac{1}{a}} \qquad (5)$$

Radiation Dosimetry

The M.I.T. 3 MeV Van de Graaff generator was chosen as the radiation source because of its high power output, convenience, and characterizable nature of its energy. This generator produces high fluxes of monoenergetic electrons in a nearly parallel beam of convenient diameter. Mr. K. A. Wright operated the machine during all experiments.

The operating characteristics and energy dissipation distribution of this accelerator have been previously established (30, 70). Detailed calculations on the dose distribution in the experimental materials are given in Appendix A. It is shown that despite various absorber geometry and composition, the reported dose of 15 megarads is accurate to within 5% or better.

Samples were placed on a belt which moved them at constant

velocity under the window of the acceleration tube. The dose rate was determined by the beam current and the speed of the belt. Dose rates of either 5 or 10 megarads per minute were administered. All the samples were irradiated at room temperature. The samples that were subject to high dose rates, and those heavily encapsulated in glass, were air cooled with a fan. After each dose of 5 megarads the samples were checked to insure that their surfaces were not hot to the touch (i.e. more than about 30°C above room temperature).

A dose of 15 megarads was chosen for all samples to crosslink the silicone into a rubbery network yet allow a measurable fraction to remain soluble. This sol fraction was compared to that predicted by literature G values and the theory of random cross linking of a Flory "most probable distribution" of molecular weights.

Anoxic Methods

Consistent with the theme of this investigation, the samples were prepared under various concentrations of gaseous O_2. Those done under 21% oxygen required no special techniques but were prepared in air.

A glove box (Fisher Scientific Co., Isolator/Lab) was fitted with a line to a cylinder of compressed nitrogen (Airco "Prepurified"). When samples were in the box, N_2 was continually bled in at the rate of 2 or 10 cfh. A vent was always left open to avoid ex- and implosions. The materials necessary to seal the samples were kept in the box so that it remained closed except during the introduction or removal of samples through an air lock.

Partway through the experimental program, a fan was installed in the box to obtain more efficent mixing of the gas inside. (Calculations assuming the box acted as a well-stirred tank indicated that only about

100 cu ft of N_2 would be necessary to lower the residual O_2 to about 100 ppm.) This figure was never reached in the box, so an attempt was made to scavenge the oxygen with an alkaline pyrogallol solution. This effort also failed.

During a period the glove box was being repaired, a glove bag was tried. The samples and sealing materials were placed in the deflated bag which was liberally purged and filled with nitrogen. After allowing 10 hours for the gases in the silicone samples to come to equilibrium absorption, the samples were sealed and taken to the Van de Graaf generator.

One final method was used to prepare very low oxygen content samples. 16 mm glass tubes were closed at one end and fitted with 24/40 ground glass fittings and glass stopcocks at the other end. Tubes and irregular masses of gum in aluminum foil were inserted and the fittings were set in place. Vacuum was slowly applied and a low pressure maintained for one hour. Then bottled Argon was slowly bled in until the system was again at atmospheric pressure. The cycle was repeated and the entire tube was then irradiated.

Gas in the glove box and glove bag was sampled in a gas sampling bottle and analyzed on a Beckman GC-5 gas chromatograph. Air was used to calibrate the instrument, and peak areas (height x width at half height) were taken from the thermal conductivity cell output. The low column temperature used to separate O_2 and N_2 fluctuated somewhat, resulting in some nonreproducibility. Use of several alternating samples brought the experimental error within acceptable limits. Calculations from the GC data are in Appendix C.

This analysis was not used in the Argon filled tubes experiments. Argon was used to overcome any diffusion limitation on the lighter nitrogen molecules displacing oxygen. The gas chromatograph column

packing used was not expected to effectively separate Ar and O_2. Instead a calculation was made assuming that the tube was "well mixed" and the vacuum pump removed constant ratios of the gases present. If on the other hand, the gas removal was a diffusion-limited process, the easier removal of nitrogen during the first evacuation would be opposed by the easier removal of oxygen during the second. Hence the calculation should give at least order of magnitude indication of residual oxygen.

The samples were sealed in bags of either 0.00025" Mylar (polyethylene terephthalate -PET) or 0.010" low density polyethylene (LDPE) film. Most samples were thin silicone films at the bottom of aluminum weighing pans (diameter-5.2 cm; height-1.0 cm). A conservative estimate of the amount of O_2 diffusing through the bag material during the time — about 20 minutes — was made using the steady state permeability equation:

$$V = P \times \theta \times \Delta P \times (A/t) \qquad (6)$$

where V is the volume of gas through; P the permeability; θ the time interval; ΔP the driving partial pressure differential; and A and t the area and thickness of the film. Using $P = 4.0 \times 10^{-10}$ for LDPE, and $P = 0.045 \times 10^{-10}$ cc(STP)-cm/cm^2-sec-cm Hg for PET (11), and assuming 21% of 1 atmosphere driving force across the film stretched tightly over the aluminum pan; one gets 0.0024 cc O_2 across 3 Mylar sheets and 0.00064 across one LDPE sheet. These figures correspond to increases of 11 ppm and 4 ppm respectively. These steady state calculations give higher transport than the actual case of gradual film saturation. Also, several layers of Saran wrap were added as a safety margin during transport. It seems reasonable to conclude that the introduction of oxygen after sample preparation is of minor consideration.

Gel Fraction

In considering the medical consequences of biomaterials, small polymer molecules should not be ignored. A cross linked polymer sample will always have a small portion that is not covalently bonded to the network structure, owing to the statistics of polymerization and cross linking. These molecules are free to work their way to the surface and contact the bloodstream. Silicones are extremely insoluble in aqueous mediums (e.g. blood plasma), but blood contains proteins which bind to hydrophobic and lipid material to transport it through the circulation. Thus even though the exact amount of silicone that the body could transport, and the amount necessary before harm results, is unknown; it is advisable to keep the sol fraction at a minimum.

The amount of soluble material in a cross linked polymer depends on the molecular weight distribution of the linear ploymer, as well as on the method of crosslinking. Ionizing radiation is reported to produce crosslinks at random throughout the sample, dependent only on the absorbed dose (8, 17). Thus the crosslinking process can be modeled as one wherein all polymer segments have equal probability of forming a cross link.

Bovey has reported an equation for the gel fraction of a randomly crosslinked polymer having a "most probable" distribution (8). This equation is identical to the one reported by Charlesby for a Poisson distribution (a Poisson distribution is considerably less polydisperse than a Flory "most probable distribution" and generally results from a much different polymerization mechanism) (17). Morgan has rederived the sol-gel relation from Flory's original equations and his expressions are used here (52). The final equation he obtained was :

$$w_s = \frac{(1 - P)^2}{P} \frac{1}{(\rho w_g - \ln P)^2} \quad (7)$$

or alternatively:

$$\rho = \frac{1 - P}{w_g \sqrt{w_s P}} \quad (8)$$

where w_s = weight fraction sol in final sample = $1 - w_g$

P = fraction of original monomers reacted to linear polymers

ρ = fraction of polymer units involved in cross links

Equation (7) is third order in w_s but can be quickly solved by iteration with a desk calculator if P and ρ are known. Equation (8) provides a count of cross links explicitly from gel fraction data.

These equations, and their derivation are both sensitive to P and ρ. For a condensation polymer, Flory has shown that:

$$P = 1 - (1/\bar{x}_n) \quad (9)$$

where $\bar{x}_n$, the number average degree of polymerization, is the number average of original units which condensed to form a polymer molecule. For silicones where the original units may have had one, four or more DMS units, the value of P and of $\bar{x}_n$ is not immediately apparent. Both the dimethyl-dihydroxy-siloxane and the cyclic tetramer thereof are probable starting units, so each was considered in the prediction of gel fraction.

Infrared Spectroscopy

Infrared spectroscopy (IR) was chosen as an analytical tool in this work because of its versatility in the determination of a wide range of functional chemical groups. This technique is not an extremely sensitive

one for trace analysis — normal IR can detect concentrations of 1 % and certain differential IR techniques can lower the detection limit by 1 or 2 orders of magnitude. However below this concentration most instrumental analyses are inadequate and specific chemical tests must be devised or adapted for each chemical group which is suspected. These tests are generally difficult to prepare and usually involve aqueous reagents. Their application to a solid hydrophobic system would be a laborious process. From these considerations, infrared was chosen as a suitable first step in the analysis of a pure silicone biomaterial.

The IR spectrum of silicone is prominent in two regards. First the absorption intensities above 7.5 μ are five to ten times more intense than normal organic compounds (66). Second is the fidelity with which functional groups absorb at their characteristic frequencies. The silicon atom apparently insulates the side groups from vibrational interferences of nearby atoms (66). This increases the prospects for identifying groups present even when the spectrum of a close model compound is not available.

All silicone polymers exhibit a strong band between 9 and 10 μ due to Si-O stretching. In addition the major substituents exhibit absorption peaks at their normal vibrational and rotational frequencies. A summary of the locations of common and probable uncommon groups is given in Table I. Uncommon groups were chosen for their liklihood of becoming "contaminants" during PDMS irradiation with O_2 present.

The detection of cross links is a definite strain on the limits of IR. In a lightly crosslinked rubber, only one in several thousand substituents is changed, and the linkage may be chemically similar to groups already present. Kantor's work (reported by Miller (51)) required using low molecular weight silicone such that high radiation doses did not produce

TABLE I

Infrared Absorption Bands of Silicone Polymers

Group	Wavelength (s), Microns	References
Si-O	8.8-9.9	65, 66
$Si-CH_3$	3.3-3.7, 7.25, 7.8-8.0, 11.6-13.1	19, 32, 34, 65, 66
$Si-(CH_3)_2$	7.95, 11.7, 12.5, 14.3 and above bands	32, 34, 66
$Si-C_2H_5$	8.0, 9.9, 10.3	32, 65, 66
$Si-C_6H_5$	7.0, 8.9, 10.0, 13.7-14.5	19, 32, 65, 66
$Si-CH=CH_2$	6.2-6.3, 7.1-7.2, 9.8-10.0, 10.2-10.6	19, 32, 66
Si-H	4.4-4.8, 10.5-12.5	32, 51, 65, 66
Si-OH	2.7-3.1, 10.5-12.0	32, 51, 65, 66
$Si-O-CH_3$	3.55, 8.4	13, 66
Si-OOCR	5.7-5.9, and R bands	66
Si-O-O-Si	10.0-12.0	19
$Si-CH_2-Si$	7.38	51, 66
$Si-CH_2-CH_2-Si$	8.80	51
$Si-NH_2$	2.8-2.95, 6.5	66
Si-NH-Si	2.95, 8.5, 10.7	66

a gel network. By measuring the differences in absorption of solutions of irradiated and nonirradiated polymer (to a precision 50 times greater than possible with the instruments available in this study) he obtained G values for specific cross link groups. The present work is intended to detect groups in greater abundance than are cross links.

Several sample preparations were used for the IR work. Thin (order of 0.005") sheets of gum were solvent cast on aluminum dishes and irradiated to produce films suitable for direct use in the spectrometer. The uncross linked gum was pressed between two NaCl crystals (NaCl is transparent to infrared light) to hold it in the beam. Pellets of ground samples were prepared in a KBr matrix according to standard techniques (19). The direct film technique gives best resolution in the functional group region — 3 to 8 μ. The inability to use the un cross linked material in this form precluded the direct differential measurement of irradiation produced groups. However differential spectra of gum in NaCl plates against naked films were attempted.

The spectra were obtained from two machines : a Perkin-Elmer Infracord Model, and a Perkin-Elmer Model 237-B (with grating).

Blood Compatibility

The final value of this project rests in its ability to produce a blood compatible material. However, a realistic evaluation of this aspect is the most difficult of all the tests to complete. Salzman has outlined the biochemical assays he considers a necessary prerequisite for *in vivo* testing of a biomaterial. The simplest of these procedures is the Lee-White clotting time.

This easily performed determination has been a standard in clinical laboratories for nearly sixty years. A few cc's of fresh human blood

are drawn into a small test tube. The tube is placed in a 37°C water bath and tilted every 30 seconds until clot formation is evident. The elapsed time from first blood-tube contact until clot formation occurs is known as the whole blood clotting time (WBCT). The test is used extensively as an indication of a patient's clotting mechanism (5). Clotting times for a number of materials with normal blood has been well established, even though the standard deviation of these determinations can be 20% of the reported standard time. Table II is a compilation of clotting times from Leininger (39). Notice that no polymer has a clotting time over twenty minutes. Glass, which is not included in the table, clots in 5-7 minutes.

The Lee-White test is not the ideal analytic tool. The end point is sometimes obscured because of the tough layer of denatured protein which forms at the air interface. This layer adheres to hydrophobic tubes such as silicone. Imai has proposed an alternate method of weighing the clot (essentially a gel fraction) after measured periods of time (35). The weight levels off after a time comparable to the WBCT.

Any of these air contact methods have certain shortcomings. Many materials containing ionically bonded heparin will interfere with the clotting reaction cascade and prolong the test almost indefinitely. This case is suspect because the blood will clot at an air interface in about an hour and clots form in isolated blood vessels in not much longer times (64). Therefore any suspiciously long clotting times are checked to see whether the blood has been anticoagulated.

A series of Lee-White clotting tests were performed in the Surgical Research Laboratory of the Beth Israel Hospital, Boston; under the direction of Doctors E. W. Salzman and P. Damus.

TABLE II

Whole Blood Clotting Times of Various Materials (39)

Polymer	Clotting Time	
	Unheparinized (minutes)	Ionically Heparinized (hours)
Polystyrene	9	24+
Polyethylene	11	24+
Polyvinylchloride	12	0.75
Cellophane	6	1
Natural Rubber	10	1
EPR Rubber	5	1
Fluorinated Silicone Rubber	18	1
Silicone Rubber*	15	1

* i.e. "Medical Grade", with peroxide cure, silica filler

Sample Preparation

Three types of silicone samples were prepared and irradiated. In all cases the silicone was PDMS of Stauffer-Wacker Silicone Corp. Brand SWS-06804, used as received.

1. Thin, flat samples suitable for IR films and gel fraction measurements were solvent cast in 2" diameter aluminum weighing dishes. Solvents were either toluene or hexane (ACS Reagent Grade without further purification) and were evaporated for one day at 2 mm Hg pressure and room temperature. At this point no visible solvent remained. Further evaporation was either two days under the same conditions or one day at 10 mm Hg and 100°C.

2. Test tubes for WBCT were solvent cast in the same manner. 10 x 75 mm pyrex test tubes were doubly cleaned, rinsed with distilled water, and oven dried. They were covered with aluminum foil to prevent contamination. The first batch were soaked in sterile isotonic saline (and some in sterile albumin solution) for one day before testing. Subsequent batches were tested without any post-irradiation soak, except a rinse with distilled water.

3. Flat sheets of silicone gum were molded by heating in a hydraulic press between sheets of aluminum and teflon covered paper. The teflon was peeled away before irradiation.

In the final anoxic preparation (within a 16 mm tube) neither form 1. or 3. could be used. To allow preparation of KBr pellets, a few grams of gum were rolled in aluminum foil. The dose uncertainty in this sample precluded a meaningful gel fraction measurement.

IV RESULTS

Initial Weight Distribution

NUMBER AVERAGE: Solutions were prepared in A.C.S. Reagent Grade Toluene. A Mechrolab #502 Membrane Osmometer was equipped with Schlicher and Schell #08 Membranes which were conditioned in successive nonpolar solvents. All runs were made at 37°C and readings made at the first indication of equilibrium — about 5 minutes after introduction of the sample. Five duplicate samples at each of six concentrations were run. Concentrations were determined by evaporating (to constant weight) known volumes of each concentration in aluminum pans and weighing the residue on a Sartorius Model 2662 balance. A plot of π / c, including standard deviations of all measurements gave $\overline{M_n}$ = 190,000 $\pm$ 15 %. Details are in Appendix B.

VISCOSITY AVERAGE: These solutions were prepared in the same solvent and the concentrations were determined in the same manner as described above. The viscometer used was a glass, spiral-capillary Ubbelohde. All runs were made in a water bath thermostated to 25.0°C. Five to seven runs of each solution were performed; each run was of order 100 seconds so the correction for capillary entrance and kinetic energy effects was neglected. Plots of η_{sp} / c and $\ln \eta_{rel} / c$ in the recommended range of η_{rel} of 1.1 to 2.0 (26) gave $[\eta]$ = 0.845 (Appendix B). Using the Mark-Houwink constants of $K' = 21.5 \times 10^{-5}$ and a = 0.65 (11), $\overline{M}_v$ = 340,000. No error limits were obtained since M-H error is unknown.

DISTRIBUTION: Without fractionation, the molecular weight distribution is uncertain. However this gum gave $\overline{M}_v / \overline{M}_n = 1.8$, and for a Flory "most probable distribution", this ratio is 1.84 when a = 0.65.

Gel Fraction

The molecular weight determinations indicate that the gum has a "most probable distribution" of molecular weights. If the linear polymer was made from a dimethyl siloxane the number average molecular weight means that $\overline{x}_n = 2570$, and if the cyclic tetramer were used; $\overline{x}_n = 640$. The corresponding values of P are 0.99961 and 0.9984. A yield of 3.0 cross links / 100 eV gives $\rho = 0.006914$ for use in equation III-7. Solving by iteration, the prediction is $w_s = 0.29\%$ if the larger P is used; $w_s = 3.60\%$ if using the smaller P.

Data on Samples Irradiated at 15.0 megarads:

O_2 Level	Total Weight (g)	Gel Weight (g)	w_s
21%	0.7169 ± 0.0003	0.6863 ± 0.0003	$0.0440 \pm 2.5\%$
12%	0.9407 "	0.8822 "	0.0622 "
3%	0.5714 "	0.5392 "	0.0564 "

Using equation III-8, the same set of P values and the experimental sol fraction for the 21 % O_2 sample, G = 0.84 and G = 3.5 for the cases of dihydroxy-dimethyl siloxane and the tetramer, respectively. An experimental error of 15 % in the molecular weight and 2.5 % in the sol fraction can combine to give a maximum error of 14 % in the calculation of ρ.

Infrared Analyses

Figure I is a low resolution spectrum of the un-crosslinked gum in the form of a KBr pellet. The bands at 3.45, 7.25, 8.00 and 12.5-12.8 μ are due to CH_3 and Si-CH_3 motions. The broad, offscale band at 9-10 μ reflects a very large contribution of Si-O pairs. The $(CH_3)_2$-Si

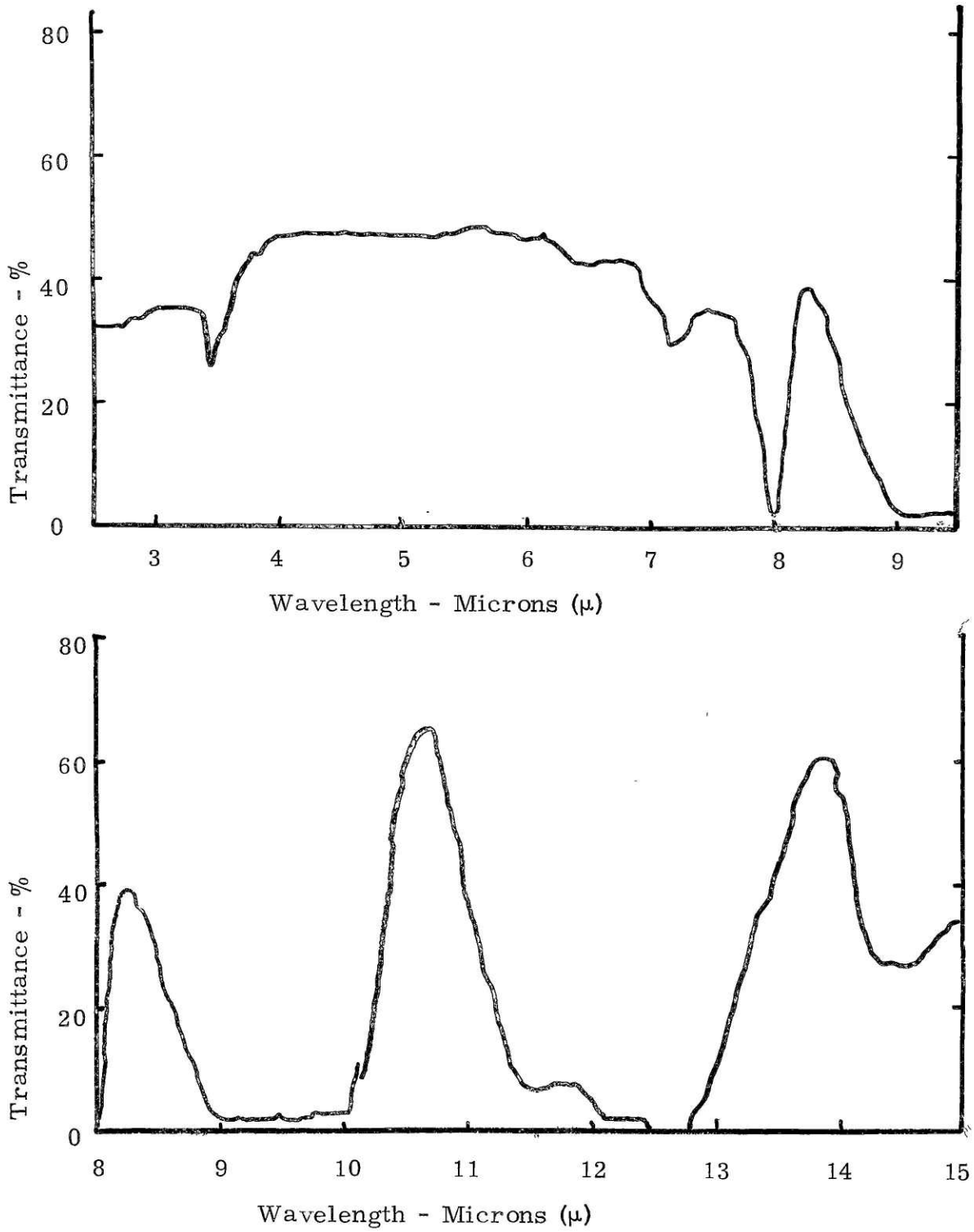


Figure I - Infrared Absorption of PDMS Gum - KBr Pellet

units also show up between 14.2 and 14.5 μ.

Figure II is a spectrum of the same material pressed between two NaCl plates. The much higher crystal quality of the plates compared to the pellet allows higher resolution in the functional group region — below 8 μ. Most of the higher wavelength absorptions are lost, and the methyl bands at 3.5 and 7.2 μ are slightly off scale. The peak at 2.8 μ is characteristic of -OH and presumably refers to hydroxyl end blocks of the basic polymer. The presence of vinyl groups is indicated at 6.3μ and 5.2μ (which could be the first overtone of a strong vinyl peak lost in the strong Si-O region just above 10μ). The smaller peaks at 3.85, 4.1 and 4.95 μ are not found in any literature spectrum of PDMS, but published spectra do not amplify absorbances in this region. The groups which normally absorb at these wavelengths — ammonium ions, acetylenes, sulfur compounds, and metallic carbonyls — do not seem very likely contaminants (19).

Thin films of the samples irradiated at 15 megarads show hardly any differences from these figures. The only new peak present in most of the samples irradiated in O_2 atmospheres of 3 - 21 % is one between 5.8 and 5.9μ. A small absorbance in this region was found in nearly every one of the films cured in an appreciably oxygen-rich atmosphere. One example is Figure III.

Differential spectra were attempted with irradiated films run against the pressed gum sample in the reference beam. The slight difference in film thicknesses and the attenuation from the NaCl plates produced exaggerated gum-type peaks or their mirror images with all but one of the irradiated films. This match of gum and 3 % O_2 film gave a plot of high noise level and a few large peaks and troughs at wavelengths where the gum alone absorbed. However, it did exhibit a peak at 5.73μ which is characteristic of esters, anhydrides, amides,

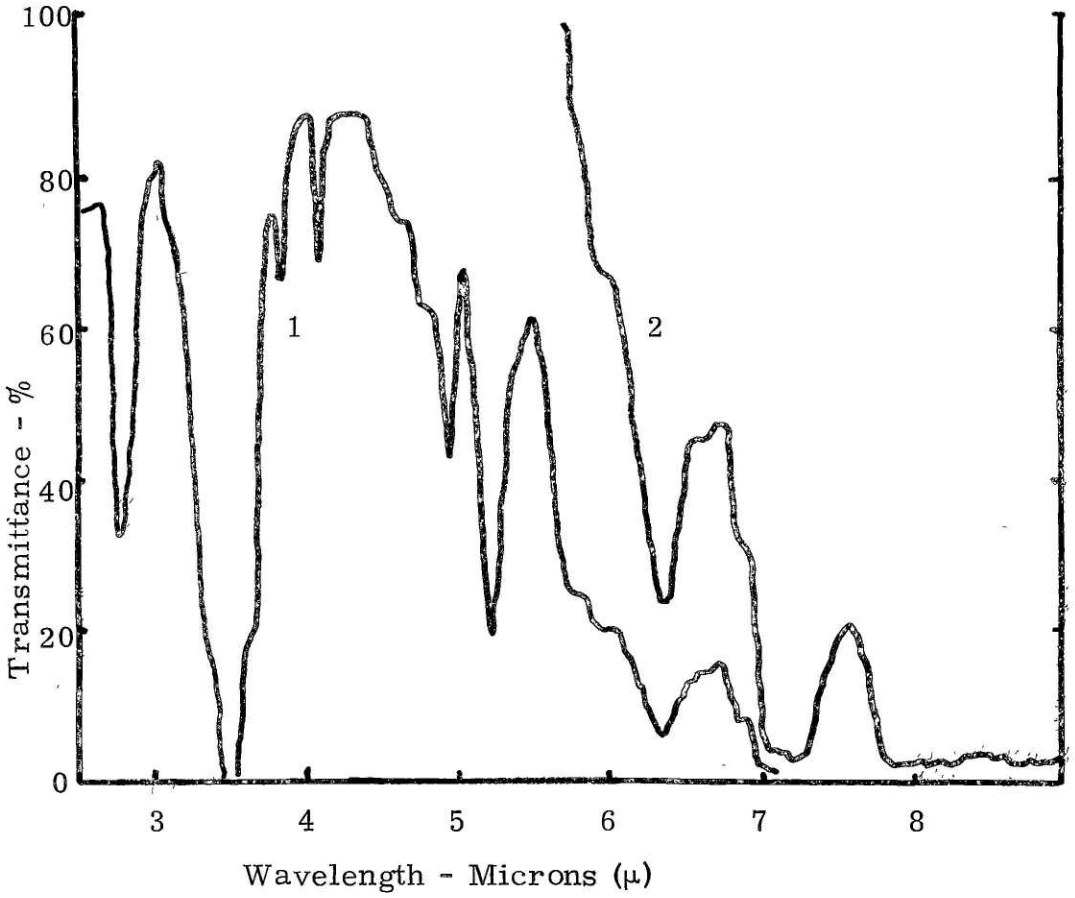


Figure II - Infrared Absorption of PDMS Gum - 0.125 mm Film Between NaCl Crystal Plates

Curve 1 : Reference Beam Unblocked
Curve 2 : 50 Mesh Copper Screen over Reference Beam

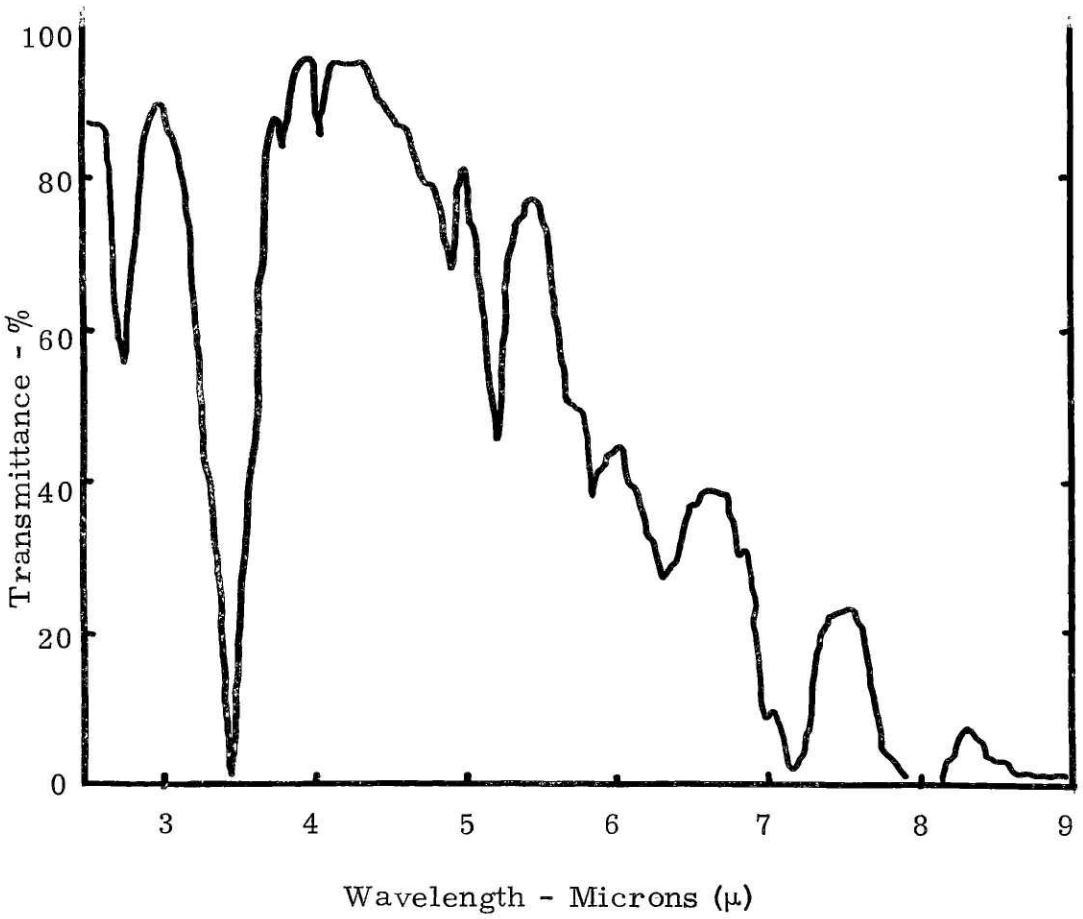


Figure III - Infrared Absorption of PDMS Rubber
Cross Linked Under 21 % O_2
0.016 cm Film

and carboxylic acids. The other bands of each of these carbonyl compounds fall in a wavelength region that could not be satisfactorily examined, either by the normal or differential method.

Whole Blood Clotting Time

Experiment I

Material	Times (min)	Average (min)
Plain Glass	8.5, 8.5	8.5
Siliclad[1] Glass	16, 21	18.5
Silicone[2], 21% O_2[3], saline[4]	18, 20	19
" " albumin[4]	16, 32	24
" 3% O_2, saline	17, 27.5	22
" " albumin	30.5, 31.5	31

Notes: 1. SiO_2 filled silicone solution poured into test tubes, then poured out and allowed to evaporate.

2. Unfilled silicone (PDMS), radiation cured.

3. Gaseous oxygen level at time of irradiation.

4. Soaked in sterile saline (or sterile saline-albumin) solution for 24 hours prior to test.

Observations: Tubes were autopsied after all had been declared clotted. Glass tubes had massive adherent thrombi. The SiO_2 filled Siliclad tubes werenot completely clotted, and were adherent only at the air-interface film. The unfilled silicone tubes were clotted even less and had similar adhesion. To resolve the ambiguities, a second set of determinations were made such that more information than just the Lee-White time could be obtained.

Experiment II

Material (Number of Samples)	Clotting Time Range (min)
Plain Glass (3)	7 - 8
Siliclad Glass (3)	21.5 - 24
Unfilled Silicone, 2-3% O_2, unsoaked (10)	24 - 44
" " 8 ppm O_2 " (11)	34 - 45+

Observations: Glass and filled silicone tubes clotted before a hard film formed at the air-interface. By 30 minutes the unfilled silicone tubes all had this tough layer and subsequent clotting time determination became doubtful. Several apparently clotted tubes were broken open and no clot was found except for the area immediately next to the air-interface. At 35 minutes the blood in one of the remaining tubes was poured into a clean glass tube where it clotted fully in about 5 minutes. Between 40 and 45 minutes, the air-interface film on all the remaining tubes was removed with a stainless steel spatula. These tubes proceeded to clot in about 5 minutes.

V. DISCUSSION OF RESULTS

Qualitative Summary

The most significant results are also the least tangible — the Lee-White clotting times. The very important observation is that the silicone surfaces do not induce clotting up to the limit of this test. With strong indications that the test only concludes because of gas interface reactions, the silicones have passed the first biomaterials hurdle. They appear to be less activating to the intrinsic clotting system than any other synthetic polymer used without anticoagulating additives. Nyilas (57) has pointed out that WBCT for commercial and other peroxide-cure silicones range from 15 to 28 minutes. Radiation curing significantly exceeds that range.

The explanation for this fact is not at all clear. The infrared work can give only a slight indication of the molecular character of the material. The undefined peaks found in the gum as well as the cured sample remains a puzzle and a potential hazard. The types of compounds found in the wavelength region of question are all very reactive substances. Implantation of these silicones could be dangerous unless these peaks were identified as being inert, or preferrably, were removed entirely.

The probable identification of a carbonyl compound involves large uncertainties. The peak had a signal-to-noise ratio of only 2 to 5 in the spectra where it was found. The optics and mounting systems can only locate peaks well to about $\pm$ 0.05 μ. This range can conceivably encompass nearly every type of carbonyl group, since under the right conditions, ketone, aldehyde, anhydride and carboxylic acid can absorb at 5.75 $\pm$ 0.05 μ. Their exact locations when bonded to silicon are unknown and have not been reported in the literature. Bellamy indicates

that organic carbonyl groups have molecular extinction coefficents of 150 to 500 absorbance units - g/mole / (cm of path - mg/ml) (3). The limit of detection with the spectrometers used in this work is thus about 4×10^{-4} g/cc of an arbitrary carbonyl compound (MW - 100, ϵ - 250) in a 6 mil film. This corresponds to about 1 C = O group per number average chain. The data indicates that this very small occurrence can adversely affect the blood compatibility of a material.

The gel fraction analysis remains somewhat ambiguous in regard to its originally intended use. The original unit used in the polymer synthesis has a strong effect on the predicted gel fraction, even though the final polymer seems to follow a Flory "most probable distribution" of molecular weights. Since the synthesis route of the gum used is unknown, no great confidence could be placed in the prediction; but the assumption of polymerization from the cyclic tetramer agrees much better with the literature G values.

The lack of a trend in the measured gel fractions presumably reflects an error in the extraction procedure — such as losing a small piece of the sample — rather than a sporadic cross link yield with decreasing oxygen content. The calculation of G values from sol fraction data seems to be a promising technique. Taking pains with sample handling, the error analysis indicates that ρ and other cross link counting parameters can be measured to better than 15% error. This method relies only upon the assumption of a specific molecular weight distribution and circumvents the problems of the Flory χ factor. Thus the problems of gel fraction sensitivity to network parameters can become a useful analytic tool, at least in the PDMS system.

Prospects

The outlook for further fruitful investigation into anoxic irradiated

silicones is excellent. Two parallel courses can be outlined.

Application of the technique to vastly improve membrane oxygenator biocompatibility is quite promising. Films of 5 mil thickness were routinely prepared for IR work so the fabrication of membrane dimension samples should present no great problem. Medical grade membranes of about this thickness frequently contain microscopic pinholes which are a threat to oxygenator integrity. Buckles believes that these holes are largely caused by gas production and other reactions of peroxide curing agents (14). If his reasoning is correct, membranes produced by the new method (at low dose rate) will be substantially free of this problem. Mechanical properties, particularly tear strength, will always be a problem in unfilled silicones. It will be necessary to support the membranes on a grid or mesh to reduce stress. Grafting onto other polymers will lead to eventual diffusion of contaminants across the silicone to the blood surface unless extraction procedures are followed beforehand.

The blood compatibility of these silicones is far from conclusively proven. A full battery of further in-vitro, ex-vivo, and in-vivo tests must ascertain such factors as platelet adhesion and release of aggregation factors, protein denaturation and adsorption, and alteration of gas transport and mechanical properties by prolonged blood contact.

At the same time further research into the factors associated with the observed antithrombogenicity should be conducted. The presence or absence of the carbonyl groups can be elucidated by use of higher resolution spectrometers (e.g. multiple internal reflectance models which amplify absorbances from the surface of the sample). The differential method can be better exploited by close matching of samples. If necessary, model samples of Si-C=O compounds could be synthesized or obtained to locate their exact absorption peaks. The presence of

peroxides from irradiation in O_2 as discussed by Okamura (59) should be determined by halogenation, since IR absorption of this group is so weak that there is not even an extinction coefficent published for it. The use of Nuclear Magnetic Resonance Spectroscopy could be investigated since carbonyl protons are in a different magnetic environment from the methyl protons.

Summary

CONCLUSIONS

1. Silicone rubber cured by irradiation is influenced by the presence of ambient gaseous oxygen.

2. A decrease in ambient O_2 is accompanied by a rise in Lee-White whole blood clotting time, up to the ultimate limit of this test.

3. The presence of carbonyl groups in silicones irradiated in atmospheric O_2 can barely be detected by normal infrared spectroscopy. A lower limit of detection is about 1 carbonyl per 5000 methyl groups.

4. Prediction of gel fraction after irradiation is too sensitive for use in design. The method shows promise in analyzing networks.

RECOMMENDATIONS

1. Continue the study of blood compatibility of these materials.

2. Explore the bonding of silicone to suitable membrane supports.

3. Examine samples at various oxygen contents and dose rates for the presence of surface irregularities or pinholes.

4. Continue searching for contaminants with IR, NMR and wet chemistry.

5. Explore the sol fraction method as a means of quantifying variations in G values from the presence of O_2.

APPENDIX A

DOSIMETRY CALCULATIONS

The following figure is the dose versus penetration curve for 3 MeV electrons from the M.I.T. Van de Graaff (30):

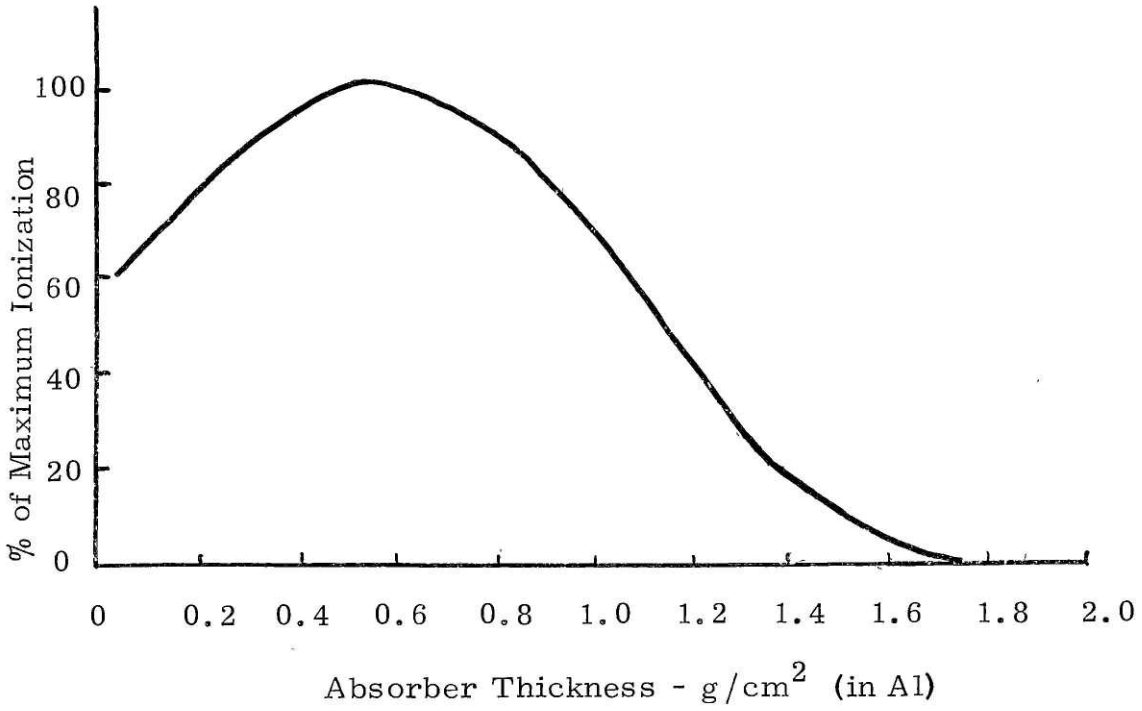


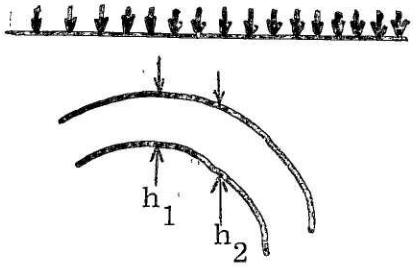
Figure IV - Dose vs. Penetration of 3 MeV Electrons

This shape is typical for MeV range electrons in dielectric materials. For lower atomic weight materials , the curve broadens out but retains this characteristic shape (from electron capture cross section considerations) . Data has been published for behavior of aluminum and plexiglas (polymethylmethacrylate) and since silicon is next to aluminum in the periodic table, its dose curve -- Figure IV — will be used.

Dose received by planar samples is directly determinate from the figure. Absorbers have been placed in the "horn" of the accelerating tube of the Van de Graaff such that material moving underneath at a constant

speed are not exposed to transverse dose gradients from the radial decay of beam current (72). The only gradient is vertical and can be obtained from the sample thickness and density.

The irradiation of test tubes proved to be a much more difficult problem. The tubes were placed on the belt so that the incident radiation was presented with the side of a cylinder; the silicone gum forming an inner annulus. The vertical projection of glass absorber thickness varies around the tube so calculation of the effective dose is complicated.

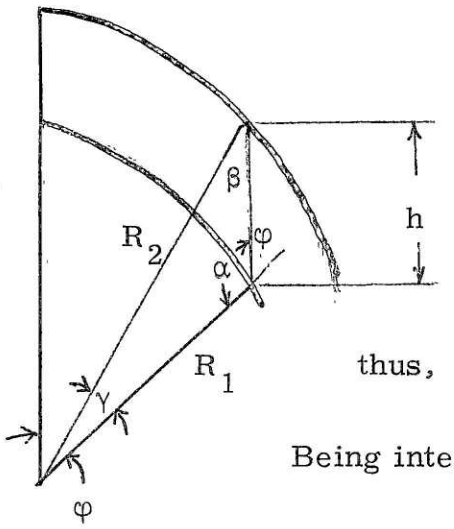


Uniform Radiation Flux

Non uniform mass distribution of absorbing mass along the beam, i.e. $h_2 > h_1$

Now examine a small section of the test tube wall :

R_2 = outer tube radius
R_1 = inner tube radius
h = effective wall thickness
φ = azimuth angle



$$\alpha = 180° - \varphi \qquad (1)$$

$$\sin \alpha = \sin (180° - \varphi) = \sin \varphi \qquad (2)$$

$$\frac{\sin \alpha}{R_2} = \frac{\sin \beta}{R_1} = \frac{\sin \gamma}{h} \qquad (3)$$

thus, $$\sin \beta = (R_1/R_2) \sin \varphi \qquad (4)$$

Being interior angles of a triangle, $\alpha + \beta + \gamma = 180°$

$$\gamma = 180° - (180° - \varphi) - \beta = \varphi - \beta \qquad (5)$$

Combining equation (3)' — the law of sines — and equations (2) and (5) ;

$$h = R_2 \frac{\sin (\varphi - \beta)}{\sin \varphi} \qquad (6)$$

which can be expanded to :

$$h = R_2 / \sin\varphi \ (\sin\varphi \cos\beta - \cos\varphi \sin\beta) \qquad (7)$$

substituting equation (4) and clearing the $\sin\varphi$ term :

$$h = R_2 \left(\cos\beta - \frac{R_1}{R_2} \cos\varphi \right) \qquad (8)$$

Now since $\sin\beta = (R_1 / R_2) \sin\varphi$, and $\sin^2\beta + \cos^2\beta = 1$,

$$\cos\beta = (1 - \sin^2\beta)^{1/2} = \left[1 - \{(R_1/R_2)(\sin\varphi)\}^2 \right]^{1/2} \qquad (9)$$

Substituting eqn. (9) into (8) and defining a fatness ratio t :

$$t = R_2 / R_1 \qquad (10)$$

the final expression for effective thickness in terms of azimuth angle and tube geometry is :

$$h = R_2 \left[\left(1 - \frac{\sin^2\varphi}{t^2}\right)^{1/2} - \frac{\cos\varphi}{t} \right] \qquad (11)$$

This expression is evaluated for the experimental parameters used :

$2 R_2 = 0.4105'' = 1.0427$ cm ; $R_2 = 0.521$ cm

from a Starrett No. 436 Micrometer

R_1 from an indirect measurement of the rise of water in the tube when a known volume is added : 3.00 cc of H_2O raised the level 5.34 cm.

$$R_1 = 2 \left(\frac{\text{vol. of water}}{\pi \cdot \Delta \text{level}} \right)^{1/2} = 2 \left(\frac{3.00}{\pi \cdot 5.34} \right)^{.5} = 0.423 \text{ cm}$$

The thickness of the silicone lining the glass tube is estimated at 10 mil. The inner diameter is thus reduced to

$$R_1' = 0.423 - (0.0010 \times 2.54) = 0.398 \text{ cm}$$

Therefore : $t = 1.23$ $t' = 1.31$

The calculation of h and therefore the actual radiation dose at any position in the top half of the tube (i.e. φ between -90° and +90°) is obtained from equation (11). Since the interior of the tube is gas with very small density and absorption, the dose at the inner surface on the bottom of the tube is identical to the dose at the corresponding point vertically above on the inner surface. Only the absorption of the silicone itself need be considered.

Using a density of Pyrex glass of 2.8 g/cc and equation (11) along with the values of R_2, t , and t', the absorption curve of the inner top surface of the glass, the inner top surface of the silicone (which is the same as the inner bottom surface of the silicone), can be calculated and plotted. The absorption at the outer bottom surface of the silicone is obtained by graphically adding the difference between these two curves to the curve for the inner top surface of the silicone.

Figure V shows effective absorber thickness as a function of azimuth angle. The middle curve (2) refers to the inner surface of the silicone, with the top and bottom curves (3) and (1) showing the absorber thicknesses at the bottom outer and top outer surfaces, respectively.

These sharp absorber gradients are misleading unless used in conjunction with Figure IV (Dose vs. Absorber Thickness). One must take absorber thickness points from Figure V and obtain the corresponding percentage of maximum ionization (i.e. relative dose) from Figure IV. Using this procedure on the curve for inner silicone surfaces, the maximum and minimum absorber thicknesses give relative doses of 79 and 92 % at these points. Since they represent entry and exit points on Figure IV, the average dose along the surface is actually 94 % ; with the dose range being 79 - 100 %. Rotating the tube 1/4 turn along its center line midway through the irradiation

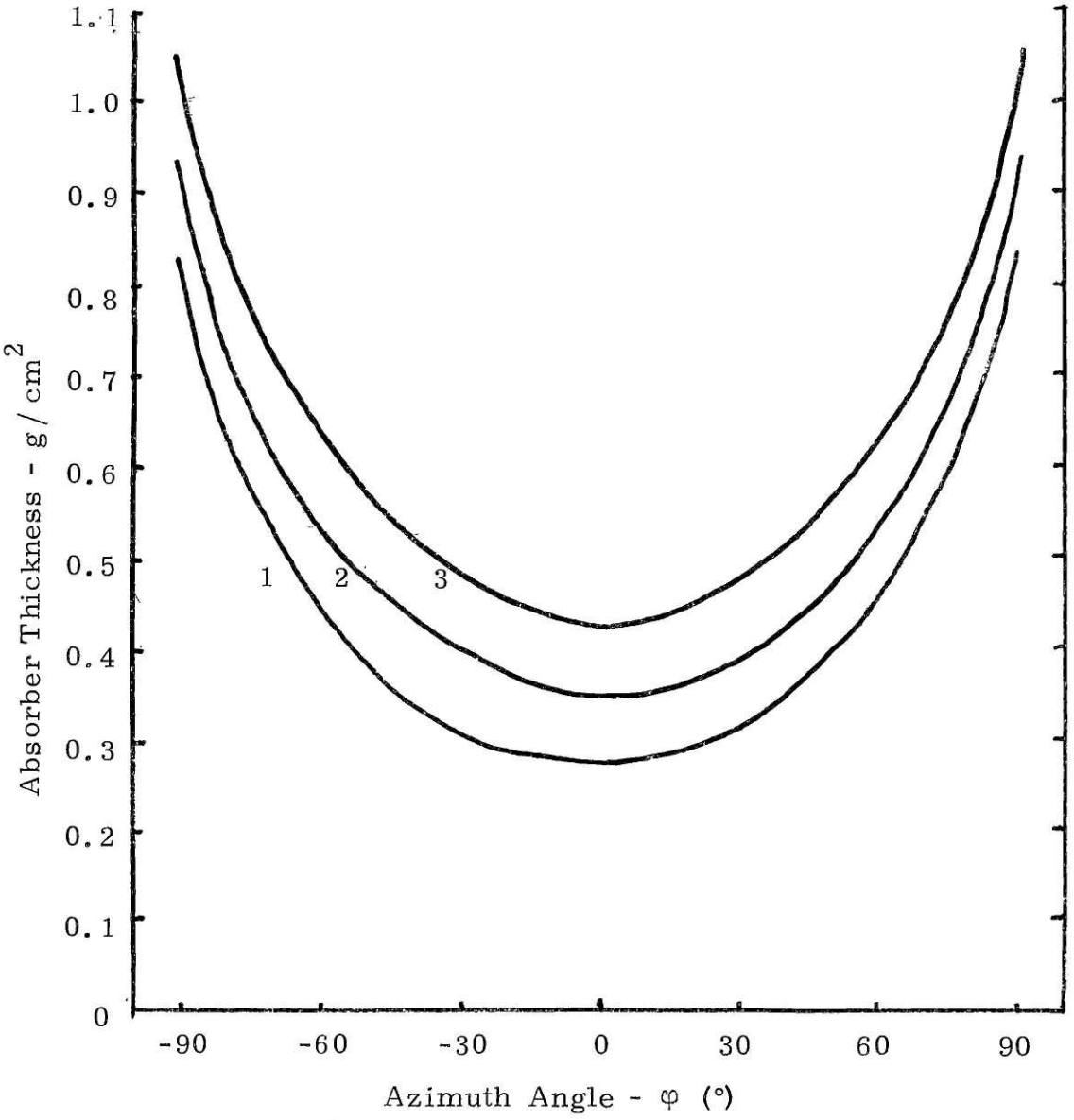


Figure V - Absorber Thickness Around Tube Interior

Curve 1 : Outer Top Silicone Surface ; t = 1.23

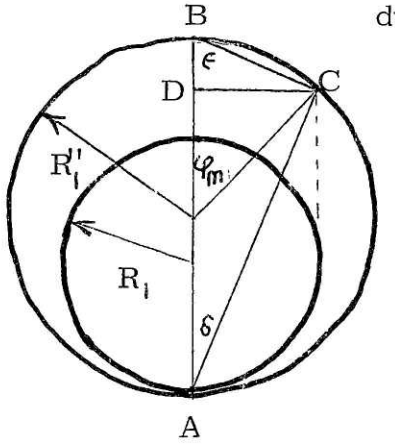
2 : Inner Silicone Surfaces ; $t' = 1.31$

3 : Outer Bottom Silicone Surface ; Curve 2 + (Curve 2 - Curve 1)

brings the extremes of dose level closer together. The average dose at this surface remains 94 % but the high and low values become 87 and 97 % of the maximum ionization. Rotating the tube at moderately high speeds during irradiation would eliminate the angular variation in dose, but the average effective thickness would have to be determined from suitable integrations of Figure V.

All of the calculations performed in this section have assumed that absorber shape does not affect the dose-penetration curve (Figure IV). In actuality, geometry can introduce back and side scattering of the radiation. These effects are second order, however, and need not be considered in dose calculations at this accuracy (72).

The final irradiations performed were done with the test tubes enclosed in a larger tube. The added absorber material must be considered. The tubes do not fit snugly and thus are not concentric during the irradiation. Consider the sketch of this geometry. Angle BCA is 90° since triangle ABC is enscribed and side AB is a diameter. Thus $\varphi_m = 2\,\delta$.



$$\text{and} \qquad \overline{CD} = \overline{AB}\ \frac{\sin\delta \sin\epsilon}{\sin(\delta+\epsilon)} \qquad (12)$$

$$\text{becomes:} \quad \overline{CD} = (\overline{AB}/2)(\sin 2\delta) \qquad (13)$$

and since $\overline{CD} = R_1$ and $\overline{AB} = R_1''$

$$\delta/2 = \sin^{-1}(R_1/R_1'') = \varphi_m \qquad (14)$$

where φ_m is the azimuth angle of the "thickest" point on the outer tube which has absorbing material above the inner tube.

Measurements of R_1'' and R_1'' were made on the outer tube using a set of calipers .

$$R_1'' = 0.2664'' = 0.667 \text{ cm} \qquad t'' = 1.23$$
$$R_1'' = 0.3222'' = 0.818 \text{ cm}$$

From equation (14), $\varphi_m = 38°40'$; and from equation (11), $h_{max} = 0.179$ cm.

$$h_{min} = R_1'' - R_1'' = 0.141 \text{ cm}$$

Combining these with the maximum and minimum effective thicknesses of the test tube, the entry and exit absorbance thicknesses are 0.74 and 1.44 g/cm^2. Using the same procedures as before and rotating the outer tube 1/4 turn midway during irradiation gives the average dose along the inner silicone surface as 71 % of the peak ionization, with a range of 16 to 90 %.

Summary

Sample Form	Dose - Megarads			
	Peak Ionization	Average	Maximum	Minimum
# Flat sheets, 3mm	15.0	14.0	15.0	13.2
" " , 5 mil	15.0	13.3	13.4	13.2
* Test Tubes	20.0	18.8	19.4	17.4
Test Tubes in Large Tube	28.0	19.9	25.2	4.5

0.25" sheet of LDPE over samples during irradiation

* Rotated 1/4 turn midway during irradiation

APPENDIX B

Molecular Weight Calculations

Osmometry

Data from Mechrolab Model 502 Rapid Membrane Osmometer, 37.0°C, Schleicher & Schuell No. 08 Membranes conditioned one day each in 50%water-50%isopropanol, 100%isoproparol, 50% isopropanol-50%toluene, 100%toluene. Measurements at 5 - 11 minute intervals. Volumes with measuring pipettes $\pm$ 0.02 ml. Weights from Sartorious Model 2662 Balance $\pm$ 0.0002 g. Concentration determined by evaporation.

Nominal conc.	solvent	.1g/dl	.15g/dl	.2g/dl	.25g/dl	.3g/dl	g/dl
solvent heights (cm of solvent)	17.39	17.56	17.62	17.72	17.83	17.91	18.03
	17.36	17.53	17.62	17.72	17.82	17.91	18.03
	17.39	17.56	17.64	17.73	17.82	17.92	18.02
	17.38	17.55	17.62	17.71	17.83	17.92	18.02
	17.37	17.55	17.65	17.72	17.82	17.91	18.02
		17.53					
avg. height	17.378	17.547	17.630	17.720	17.824	17.916	18.024
σ	.013	.014	.020	.003	.005	.005	.005
Δ height	0.0	.169	.252	.342	.446	.538	.646
σ	---	.027	.023	.016	.018	.018	.018
σ in %	---	16%	9%	4.7%	4.0%	3.3%	2.8%
final weight of pan		1.4346	1.4269	1.4402	1.4407	1.4400	1.4415
empty wt. of pan		1.4286	1.4202	1.4286	1.4261	1.4222	1.4209
wt.(g)		0.0060	0.0067	0.0116	0.0146	0.0178	0.0206
error%		6.7%	6.0%	3.4%	2.7%	2.2%	1.9%
volume, cc		6.00	5.00	6.00	6.00	6.00	6.00
conc g/dl		0.100	0.134	0.193	0.243	0.297	0.343
error, final %		7.0%	6.4%	3.7%	3.0%	2.5%	2.2%
Δh/c		1.69	1.88	1.77	1.83	1.81	1.88
error %		23%	15.4%	8.4%	7.0%	5.8%	5.0%

Plotting the data and error limits in the traditional manner :

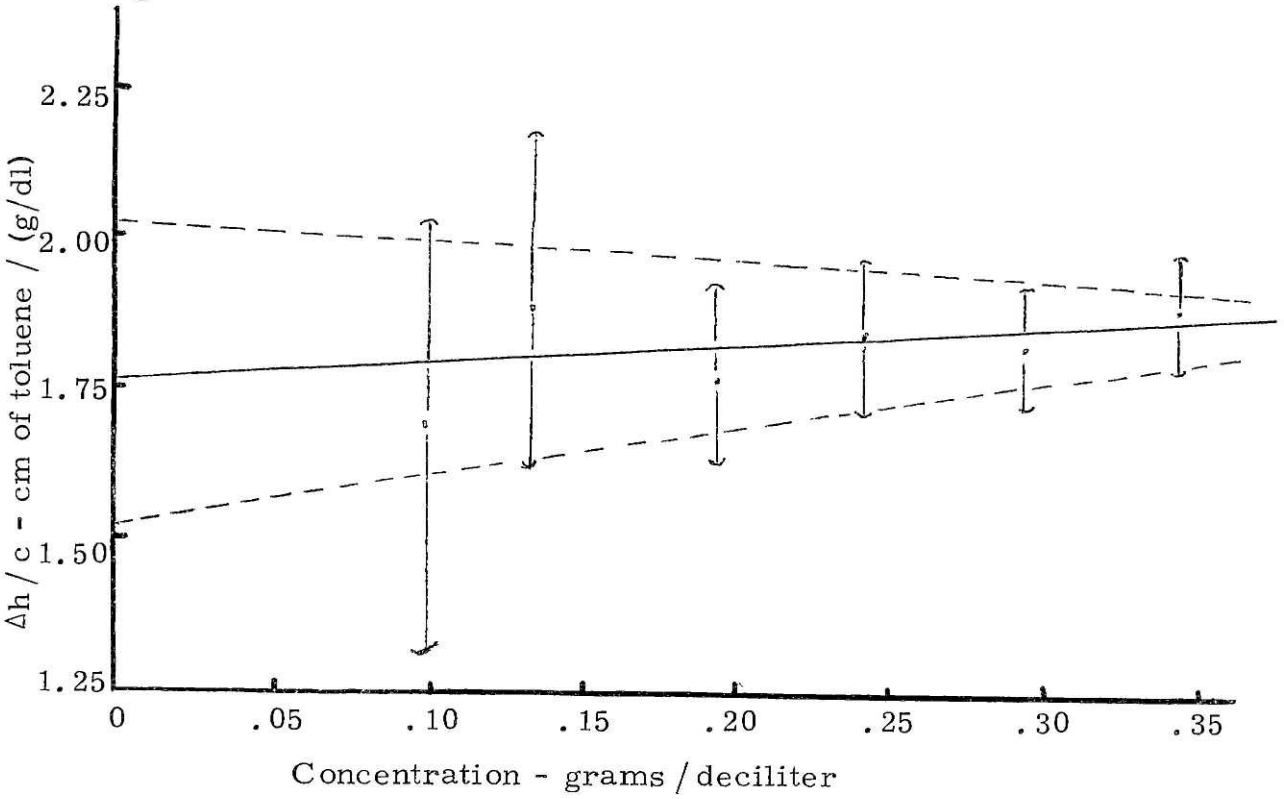


Figure VI - Plot of Osmometry Data

The intercept is taken as 1.77 ± 0.25 cm of toluene / (g/dl). From equation (III-2) ;

$$\bar{M}_n = R\,T \,/\, \text{intercept}$$

$$= \frac{8.314 \times 10^{7}\ \text{g-cm}^2 \times 335\ ^\circ\text{K} \times 10^{-2}\ \text{dl/cc}}{\text{sec}^2 - ^\circ\text{K} - \text{mole} \times 0.850\ \text{g/cc} \times 980\ \text{cm/sec}^2} \times \frac{\text{g}}{1.77\ \text{cm-dl}}$$

$$= 190{,}000 \pm 15\,\%$$

Viscometry

Data from a spiral capillary, glass, Ubbelohde viscometer and a Cletimer Model 254 stopwatch. Temperature of water bath : $25.0 \pm 0.1^\circ$C. Solutions made with toluene (A.C.S. Reagent Grade). Concentrations determined by evaporation of solutions to constant weight. Weights and volumes measured as in osmometry.

Since the flow times were of order 100 sec, the flow time was assumed directly proportional to viscosity. Thus $\eta_{rel} = \theta_{soln} / \theta_{solvent}$, and $\eta_{sp} = \eta_{rel} - 1$.

Nominal conc.	solvent	1g/dl	solvent	.5g/dl	.25g/dl	.125g/dl
flow times (sec)	86.2	184.6	86.2	130.7	106.1	95.7
	85.9	186.7	86.5	130.1	105.5	95.6
	85.8	186.7	85.6	129.7	106.1	95.4
	85.8	187.0	85.6	130.5	104.6	95.3
	86.0	185.5	85.5		105.4	
	85.9		85.9			
avg.time	85.93	186.15	85.88	130.25	105.54	95.50
η_{rel}	1.00	2.1663	1.00	1.5167	1.2289	1.1120
η_{sp}	--	1.1663	--	0.5167	0.2289	0.1120
final weight of pan		1.3767	--	1.3663	1.3558	1.3554
empty pan weight		1.3409	--	1.3390	1.3375	1.3406
wt. (g)		0.0358	--	0.0274	0.0184	0.0148
volume (cc)		4.00	--	6.00	8.00	12.00
conc. (g/dl)		0.895	--	0.457	0.230	0.123
η_{sp} / c		1.303	--	1.131	0.9950	0.9105
$\ln \eta_{rel} / c$		0.864	--	0.911	0.896	0.863

Since η_{rel} is higher than recommended for good data (6, 26) at the 0.895 concentration, this point will not be plotted. The Mark-Houwink constants for PDMS in toluene at 25°C are (11):

$K' = 21.5 \times 10^{-5}$ and $a = 0.65$ in the range of molecular weights from 200,000 to 13,000,000. Error limits on the viscosity average molecular weights, since the accuracy of the Mark-Houwink constants are not given and are expected to be appreciable compared to the experimental error, were not calculated.

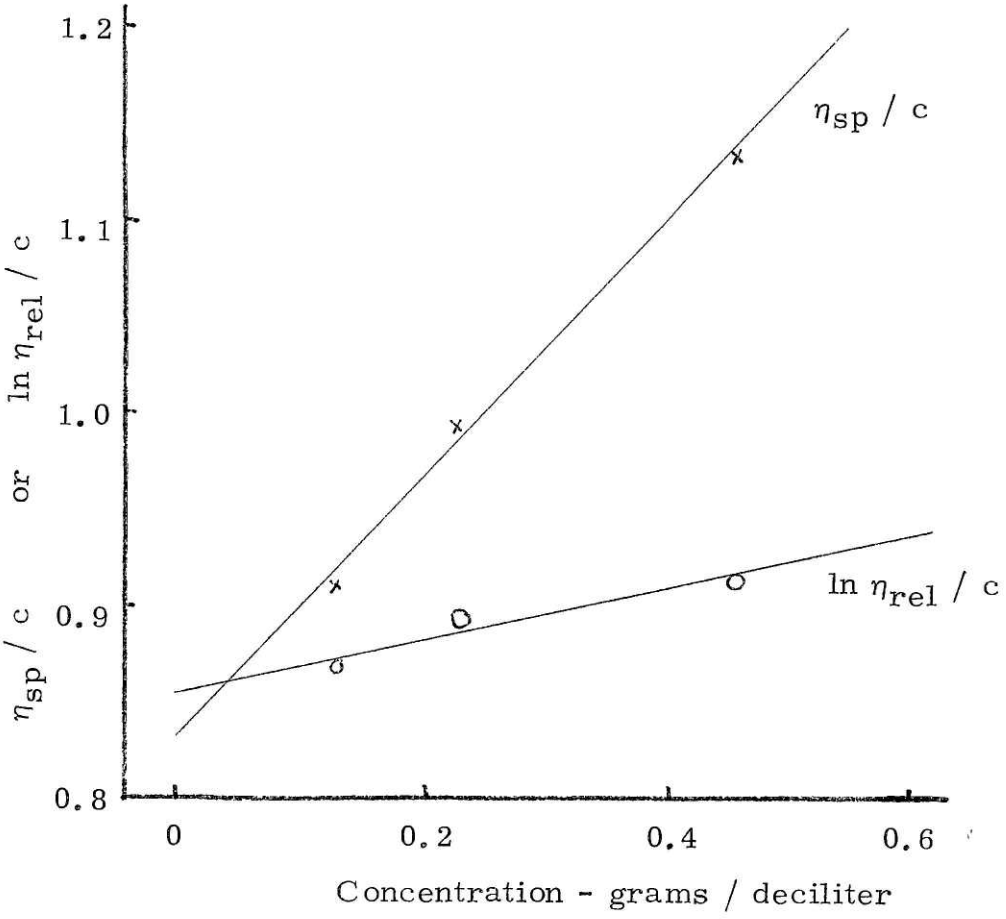


Figure VII - Plot of Viscometry Data

$$[\eta] = \text{intercept} = \frac{0.859 + 0.831}{2} = 0.845$$

$$0.845 = 21.5 \times 10^{-5} \overline{M}_v^{.65}$$

$$\overline{M}_v = 339,000$$

APPENDIX C

Oxygen Content Calculations

Example : Set of samples from October 17, reported as 3 % O_2

Beckman GC-5 Gas Chromatograph with thermal conductivity detector

Carrier gas : Helium (Airco "Pre-purified") ; 2 cylinders, set at 80 psig

Flow rates : 18 , 19 cc/min (Rotameters)

Column Temp : 46-48°C Detector Temp. : 29-31°C

Filament Current : 250 ma Sample Size : 0.500 cc (Teflon sealed hypo)

Chart : 1 mV full scale ; Slow Speed

Peak areas by Peak Height x Width at Half Height

AIR:

Run Number	O_2 Area	(Attenuation)	N_2 Area	(Attenuation)	N_2/O_2
1	148.5	(128)	585.9	(128)	3.95
3	105.6	(128)	539.0	(128)	5.10
5	179.5	(128)	636.2	(128)	3.54
Air average	144.5 ± 37	(26%)	587.0 ± 49	(8.3%)	4.20
SAMPLE:					
2	348.0	(8)	657.7	(128)	1.89x16
4	401.2	(8)	778.2	(128)	1.94x16
6	290.5	(8)	670.2	(128)	2.31x16
Sample avg.	346.6 ± 56	(16%)	702.2 ± 54	(7.7%)	$2.05 \pm .22$ x16 ($\pm$11%)

Average O_2 in sample by O_2 peak ratios :

$$\% O_2 = 21\% \left(\frac{346.6 \times 8}{144.5 \times 128}\right) = 3.15 \% O_2 \pm 42\% \text{ (i.e. } \pm 1.3 \% O_2)$$

Average O_2 in sample by N_2/O_2 ratio. (Both have same thermal conductivity to within 10% so direct comparison of peak areas is valid)

$N_2/O_2 = 2.05 \times 16 = 32.7 \pm 11\%$

$\% O_2 (1 + 32.7) = 100.0 \%$

$\% O_2 = 2.97 \pm 0.3 \%$ by volume

Calculation of % O_2 in final set of samples :

Outer Tube connected to vacuum pump, pressure gages, and Argon cylinder. System pressure slowly lowered from ambient (P_a) to a constant lower pressure (P_v) and then, after one hour, slowly returned to P_a. Procedure repeated twice.

Assuming that the vacuum pump removes a constant ratio of gases, and that the Argon (Airco "Prepurified") contains no oxygen, the final percentage of oxygen in the system is given by :

$$\% O_2 = (O_{2,\text{init.}}) \left(\frac{P_{v1}}{P_a}\right) \left(\frac{P_{v2}}{P_a}\right) = 21\% \, P_{v1} P_{v2} / P_a^2$$

P_a = 760 mm Hg Tube #1: P_{v1} = 10 mm Hg ; P_{v2} = 9 mm Hg

Tube #2: P_{v1} = 5.0 mm Hg ; P_{v2} = 4.2 mm Hg

Tube #1 : % O_2 = 21% $\left(\frac{9 \times 10}{760^2}\right)$ = 33 ppm O_2

Tube #2 : % O_2 = 21% $\left(\frac{5.0 \times 4.2}{760}\right)$ = 8 ppm O_2

The test tubes in Tube #2 were used for the Whole Blood Clotting Times reported as Experiment II in Section IV.

APPENDIX D

Nomenclature

Note : When more than one meaning exists for a symbol, the proper application should be apparent from the context.

A	Area
c	concentration, generally grams per deciliter
h	effective wall thickness for radiation absorption
IR	infrared
K'	Mark-Houwink viscosity coefficent
ln	natural logarithm
MeV	million electron volts
$\overline{M}$	average polymer molecular weight
MW	molecular weight
P	pressure, or permeability of a polymer film, or the fraction of original units that have reacted during a polymerization reaction
PDMS	polydimethylsiloxane
R	gas constant, or radius
t	thickness of a polymer film, or tube fatness ratio = R_2/R_1
V	volume
w	weight fraction
WBCT	whole blood clotting time (Lee-White test)
$\overline{x}$	average number of units in a linear polymer chain
$\alpha, \beta, \gamma, \delta, \epsilon$	interior angles of a triangle
Γ	gamma function (mathematical operator)
Δ	heating required during a reaction, or change in a quantity
ϵ	molecular extinction coefficent (in IR)

η	viscosity of a liquid
$[\eta]$	intrinsic viscosity of a polymer solution
θ	time
μ	micron = 10^{-6} meter
π	3.14159, or osmotic pressure of a solution
ρ	fraction of polymer units forming cross links
$\sum$	indicator for "sum of the following"
σ	statistical standard deviation about the mean
φ	azimuth angle
χ	Flory Chi-factor

Subscripts

a	ambient conditions
g	referring to the infinite network (gel)
i	referring to one species in a sequence thereof
m	maximum azimuth angle for effective absorption of the outer tube
n	number average
s	referring to the material still soluble (vs. in gel)
v	viscosity average, or vacuum conditions
1	inner radius
2	outer radius

Superscripts

a	Mark-Houwink viscosity exponent
'	different quantity, as different inner tube radius
"	inches, or referring to the large outer tube for irradiation

APPENDIX E

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APPENDIX F

Location of Original Data

All original data is located in Room 12-171 of the Massachusetts Institute of Technology. Professor E. W. Merrill is the custodian of this material.