CONTROLLED RELEASE OF DRUGS
FROM SURGICAL SUTURE

by

AESEUN LOH

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Signature of Author ....

Department of Materials Science & Engineering

May 8, 1987

Certified by

Robert S. Langer, Jr., Elazer Edelman, and Edith Mathiowitz

Thesis Supervisor

Accepted by ....

Donald R. Sadoway

Chairman, Departmental Committee on Undergraduate Students

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ABSTRACT

Polymer based controlled release technology was adapted to use with surgical suture to supply locally directed therapy. A variety of medications were implanted within long fibers of polymer material. Release kinetic and strength of these model suture material were studied. Some of the newer polymer materials such as alginic acid, polylactic acid, and polyorthoester were used. Polymer sutures with different amounts of gentamicin sulfate and heparin were prepared and tested. From the gentamicin sulfate release kinetics, it is shown that alginic acid and polyorthoester sutures released drugs for about 3 to 5 days while polylactic acid suture released for more than 12 days. The uniaxial tensile strength of polyorthoester sutures decreased with increasing concentration of implanted drug and varied with the type of drug implanted - heparin sutures appeared to be stronger than gentamicin sutures.

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ACKNOWLEDGEMENTS

Chapter 1

Introduction

Standard drug forms are problematic. Each time a person takes medicine, the drug level in the blood rises, peaks, and then declines, eventually almost to zero. A variety of techniques have been developed to circumvent this problem. Sustained-release preparations attenuate the peaks and valleys, prolonging the duration of drug action. This is accomplished by mixing medications with substances that decrease their solubility, coating them with materials that do not dissolve in stomach acid, compressing them into dense tablets, or putting them into suspensions or emulsions. Nonetheless, the variations in drug levels are not totally eliminated and 'controlled' release formulations were developed [1]. Drugs are embedded within a piece of plastic or polymer, and must diffuse through this framework in a constant fashion over a prolonged period of time.

Controlled-release systems can provide localized delivery of the drug to a particular body compartment, with markedly diminished systemic drug levels, reduced need for follow-up care, increased preservation of medications that are rapidly destroyed by the body, increased patient comfort, and improved patient compliance.

This project involves an application of polymer based controlled drug release technology. Specifically, investigations of how some of the newer polymer materials can be used to formulate a controlled-release system from surgical sutures are

done. Post-operative care after any operation involves the ingestion or injection of a substantial amount of medication to relieve the pain and to help heal the surgical wound. Oral or parental drug administrations lead to systemic effects and requires substantial drug levels to achieve local anesthesia. In this project a variety of medications were implanted within the suture to provide locally directed therapy. Ideally the suture material should be biodegradable so that it will be absorbed when wound heals.

I have attempted to define the characteristics of a model biodegradable suture. Stable formulations of drug-implanted sutures were devised, drug release kinetics were examined, and strength-material relationship of these formulation were studied.

Chapter 2

Literature Survey

2.1 Fabrication Methods

There are several means of fabricating fibers of polymer materials into fibrous strands, including; wet-solution-spinning, dry-solution-spinning, and melt-spinning [2]. In this section, some of the advantages and disadvantages of each of these techniques are discussed and the choice of wet-solution-spinning for this thesis is supported.

In the wet-solution-spinning method, a viscous solution of the polymer stored in a hypodermic syringe are extruded through a needle into a solution in which the material will not dissolve. As the continuous filament coagulates in this non-solvent, it is wound on to a spool. In practice, the hypodermic needle diameter should be larger than the diameter of the filament needed. Moreover, the viscosity of the solution, the nature of the nonsolvent, and the temperature all affect the properties of the fibers. Very viscous solutions are needed to prevent the filament from separating into droplets at the extrution step. Although wet-solution-spun fibers account for a large percentage of synthetic fiber production (mainly viscous rayon), they have certain disadvantages. Fibers with a uniform cross section are

very difficult to produce and the process is slow. Low extrusion speeds are needed to permit precipitation in long coagulation baths.

The dry-solution-spinning process involves the extrusion of a polymer solution through a spinneret into a hot air stream which volatilizes the solvent and leaves a dry polymer fiber. The technique can be carried out on a laboratory scale, but it is difficult. Other problems encountered include the formation of droplets instead of fibers (if the solution is not viscous enough), and adhesion of the fiber to the wall of the chimney due to turbulence of the hot air stream. Moreover, inflammable or toxic solvent vapors must be removed effectively. This process, however, is carried out effectively on a large scale in industry.

In the melt-spinning process, molten polymer is extruded through spinnerets. Immediate cooling causes solidification of the fibers, which can then be stretched or collected immediately on a bobbin. The advantages of the melt-spinning technique are that the spinning process is extremely rapid, and the fibers have a uniform. circular cross section. The disadvantage of melt-spinning is that some polymers are not sufficiently stable above their melting temperature to survive the spinning process intact.

Wet-solution-spinning method was chosen to fabricate polymer sutures for this thesis work because the technique was relatively simple and the tools were readily accessible. Moreover, the high temperature usage in the dry-solution-spinning method and the melt-spinning method was avoided since it had possibilities of destroying the drugs implanted in the suture. Figure 2.1 shows the experimental set-up for the wet-solution-spinning method. A viscous polymer solution is prepared and sucked into a hypodermic syringe. With the tip of the needle placed inside the coagulation bath, the syringe-pistol is pushed slowly to extrude the polymer fibers. The fibers are left in the bath until they are hardened. When the hardening process is done,

Wind-up spool

Hypodermic
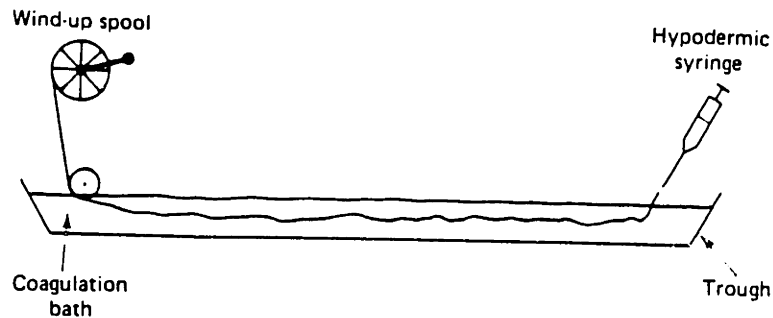syringe

Coagulation
bath

Trough

Figure 2.1: Apparatus for the laboratory wet-solution-spinning of fibers [2].

fibers are taken out of the bath either by a wind-up spool or just by picking up with a forcep.

2.2 Suture Material Selection

Before describing various materials that have been considered for the suture material, some discussion of the general manner by which most polymers degrade in the tissue environment would be useful [3]. With few exceptions, polymers rarely erode by means of slow dissolution while maintaining their initial strength and integrity in the residual mass. Polymers are considered to undergo four stages when first inserted in the aqueous environment of the body. The first stage, hydration, is variable in rate, degree and effect, and is dependent upon the nature of the polymer. This stage of absorption may be completed within minutes or hours after implantation unless the implant volume is so large that the diffusion of water into the mass takes longer. The primary effects result from disruption of secondary and tertiary structures stabilized by van der Waal's forces and hydrogen bonds.

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The second stage is manifested by the loss of implant strength, usually as a result of covalent bond cleavage involving the polymer backbone. In the case of absorbable polyesters, the strength loss rate is controlled entirely by the rate of hydrolytic cleavage of the polymer backcone and is independent of any known enzyme systems. In this cl; 's of polymers, the strength loss rate is dependent upon temperature, pH, and especially upon the degree of crystallinity of the polymer.

The third stage of degradation involves the beginning of the mass loss process. While the covalent bond cleavage continues to occur from stage 2, the polymer is degradated to a molecular weight level below that required for coherence. The actual molecular weight reduction necessary to reach this stage depends upon many factors such as, conformation and crystallinity. It is noted that at the end of stage 2, most or all of the original mass is still present and that it is only during and after stage 3 that actual mass loss or absorption occurs.

The fourth stage involves the complete removal of polymer from the tissue. The polymer may lose mass simply by the solubilization of low molecular weight species into the intercellular fluid. Alternatively, small fragments may be removed from the implant site by phagocytes and eventually carried to the lymphatic system for completion of the solubilization process.

The degradation of polymer materials inside a tissue environment generally occurs following these four stages. It is also possible that polymeric masses may be removed from implant sites without actual reduction in the chain length through solubilization processes involving side chain modification rather than backbone scission.

Only biodegradable polymers were considered for this project since the suture material should erode within the incision after the surgical procedure has taken place. Materials, including some of already known biodegradable suture materials,

such as, alginic acid with polylysine coating, polylactic acid, polyanhydride, and polyorthoester were considered as candidates. Polyanhydride did not fare well because the suture was too brittle when it emerged from the coagulation bath. Alginic acid with polylysine coating formulation was considered since this is used for the controlled release in microspheres. However, alginic acid without the polylysine coating appeared to be a better suture material since polylysine made the suture weaker. Therefore, the biodegradable polymer materials actually used for suture preparation were alginic acid, polylactic acid, and polyorthoester.

2.3   Drug Selection

Drugs considered for implantation in the sutures were acetylsalicylic acid, gentamicin sulfate, cortisone acetate, and heparin. Of these, gentamicin sulfate and heparin were actually used since gentamicin sulfate had a distinct spherical shape which was easily recognizable under the SEM and also because of its easy assayability and heparin since it had a clinical application in an animal heart-transfer experiments. The Scanning Electron Micrographs in figures 2.2 to 2.4 show why gentamicin sulfate was chosen over acetylsalicylic acid and cortisone acetate.

Sutures are expected to be weaker when drugs are implanted since the polymer chain gets disrupted. Therefore, it is better to use a smallest possible size drug particles when making suture. Thus, drugs were sieved with 53um openings - the smallest sieve available in the lab - before they were combined with the polymer solution.
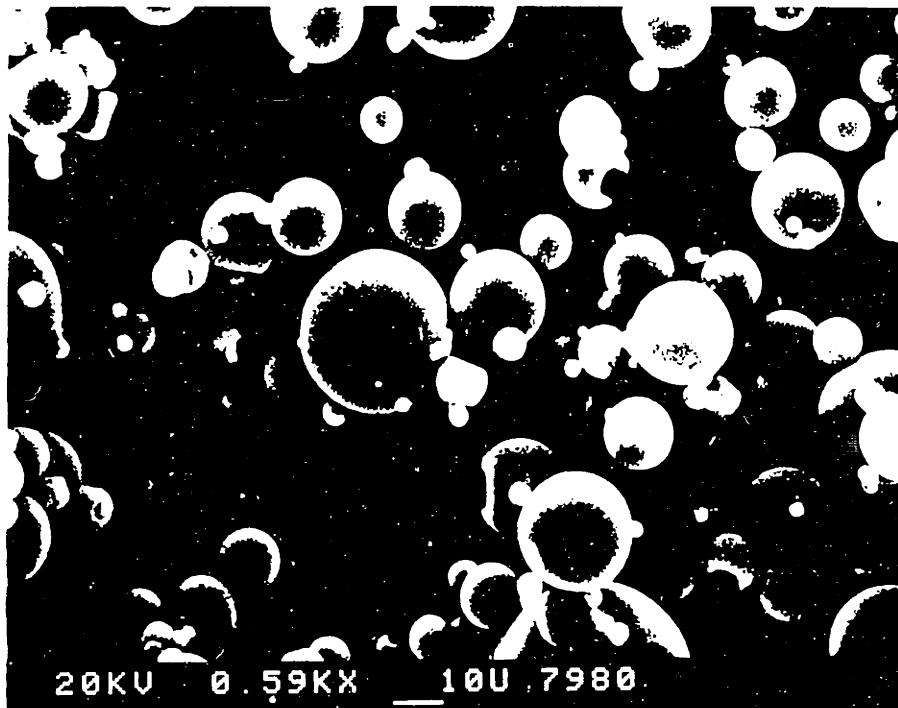
Figure 2.2: Scanning Electron Micrograph of Gentamicin Sulfate

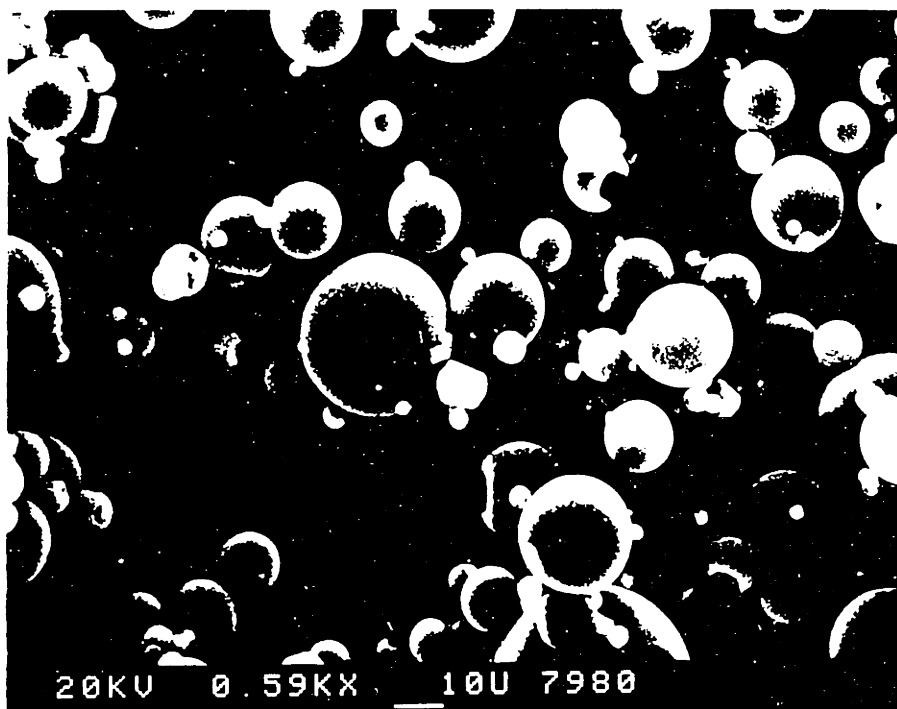Figure 2.3: Scanning Electron Micrograph of acetylsalicylic Acid

Figure 2.2: Scanning Electron Micrograph of Gentamicin Sulfate

Figure 2.3: Scanning Electron Micrograph of acetylsalicylic Acid
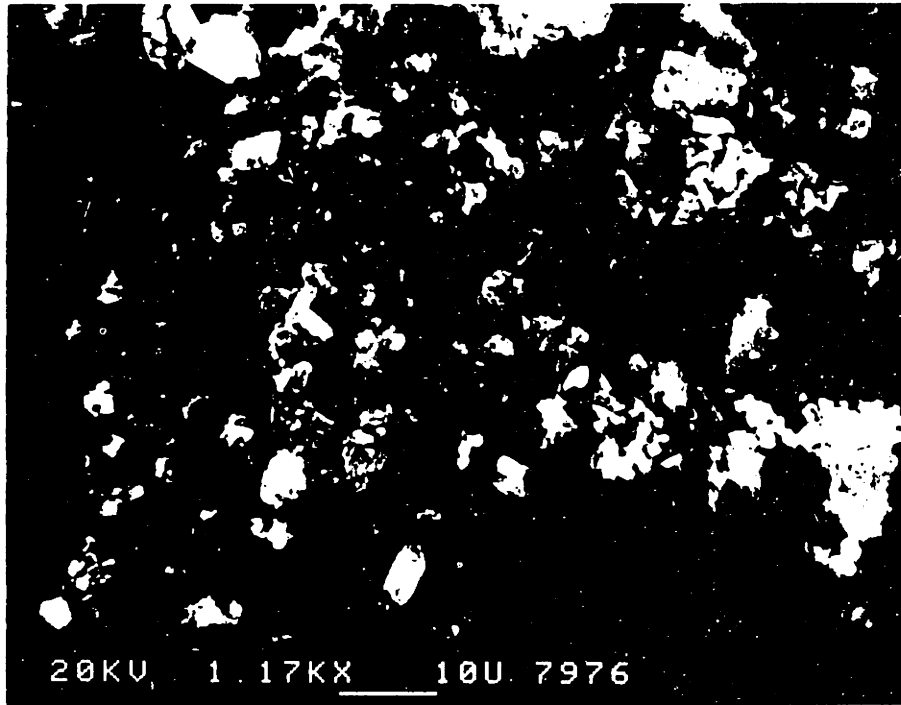
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Figure 2.4: Scanning Electron Micrograph of Cortisone Acetate

Chapter 3

Experimental

3.1 Suture Preparation

The wet-spinning technique requires both 'good-solvent' and 'poor-solvent' in order to dissolve the polymer and stabilize the shape after the suture was formed. Before actually making the sutures it was necessary to conduct certain experiments to find out the 'good-solvents', 'poor-solvents', the polymer solution concentration, and the amount of time that the sutures should be left in the coagulation bath.

'Good solvents' for the polymers were water, CHCl2, and CHCl2, respectively for alginic acid, polylactic acid, and polyorthoester. The appropriate 'poor-solvents' for the polymers were chosen by the trial and error method. The 'poor-solvents' chosen were; CaCl2 + hepes buffer, hexane, and ethanol, respectively. The concentration of the polymer solution was also found by the trial and error method. It was found that the sutures formed best at concentrations of 4.8 wt.% for the alginic acid, 20 wt.% for the polylactic acid, and 40 wt.% for the polyorthoester. It was found that best sutures would form with the above materials if the sutures were left in the coagulation bath for 6 minutes for alginic acid, 2 minutes for polylactic acid, and 4 minutes for polyorthoester. Coagulation is an important step because the suture

Table 3.1: Parameters for Preparing Polymer Sutures

POLYMER	'GOOD-SOLVENT'	'POOR-SOLVENT'	CONCENTRATION	COAGULATION TIME
Alginic Acid	Water	CaCl2 + Hepes Buffer	4.8 wt.%	6 Min.
Polylactic Acid	CH2Cl2	Hexane	20 wt.%	2 Min.
Polyorthoester	CH2Cl2	Ethanol	40 wt.%	4 Min.

will be too brittle if it was left in the bath for too long and will not harden if it was taken out too quickly. Table 3.1 summarizes the results of these experiments.

The procedure for the preparation of the suture is displayed in schematic form in figure 3.1 and summarized below. The polymer material is placed in a glass vial and the desired amount of solvent poured into the vial with a glass pipette. CHCl2 dissolves the aluminum lining and the glue of vial caps, therefore, such linings were discarded when CH2Cl2 was used. The polymer is dissolved in tightly capped vials after having been left overnight or shaken with a Vortex mixer. For alginic acid solution, stirring over a low heat was sufficient. If drug was needed it was added after all of the polymer has dissolved and mixed with the Vortex mixer to form a homogeneous solution.

After the polymer solution is prepared, the solution is sucked into a 5mm hypodermic syringe. An 18 gauge hypodermic adapter needle attached to the syringe is
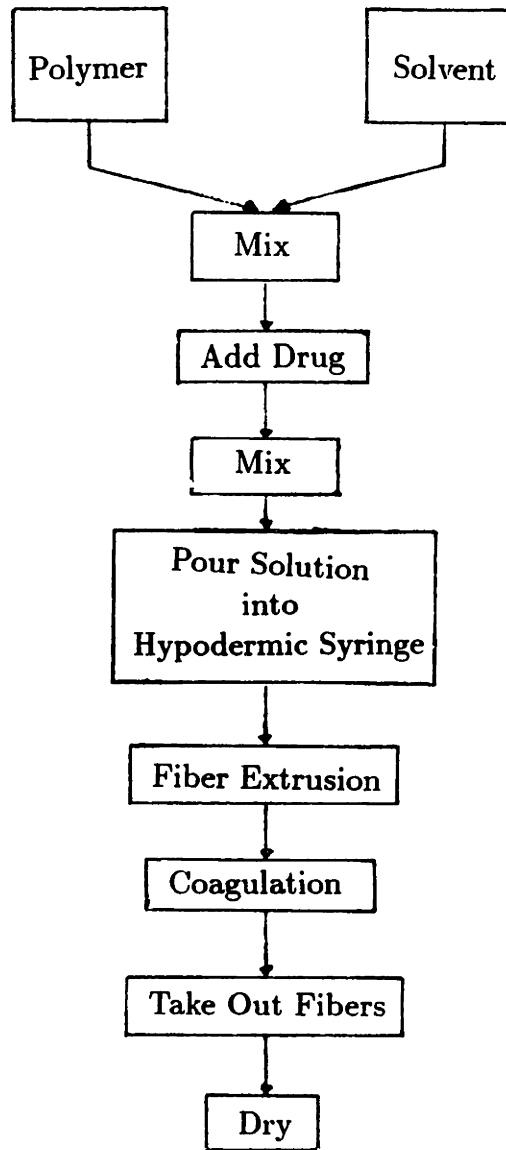
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Figure 3.1: Schematic of Suture Preparation Procedure

immersed into the 'poor-solvent' coagulation bath. The solution is extruded from the syringe as the syringe is moved inside the trough. This prevents suture fibers from sticking to each other. After an appropriate amount of time, the hardened sutures are taken out of the bath by with a forcep and hung to dry.

3.2   Drug Implantation

Using the technique described above fibers of various polymer material were made without drug or with 1 and 5 wt.% drug added. The relationship between composition and strength was examined and is discussed in section 3.4. Table 3.2 shows the different compositions of polymer sutures prepared. 4.8 wt.% alginic acid + 5 wt.% drug sutures were impossible to form because the chemical interaction between the drug and the polymer solution left the polymer solution too dilute to extrude. Also, 20 wt.% polylactic acid + 5 wt.% drug sutures were not prepared because the polylactic acid I was dealing with was no longer being produced. Figures, 3.2 - 3.8 show Scanning Electron Micrographs of the cross sections and the surfaces of the various sutures produced. The spherically-shaped gentamicin sulfate particles can clearly be seen in figures 3.5 and 3.8.

Table 3.2: Compositions of Drug Implanted Sutures

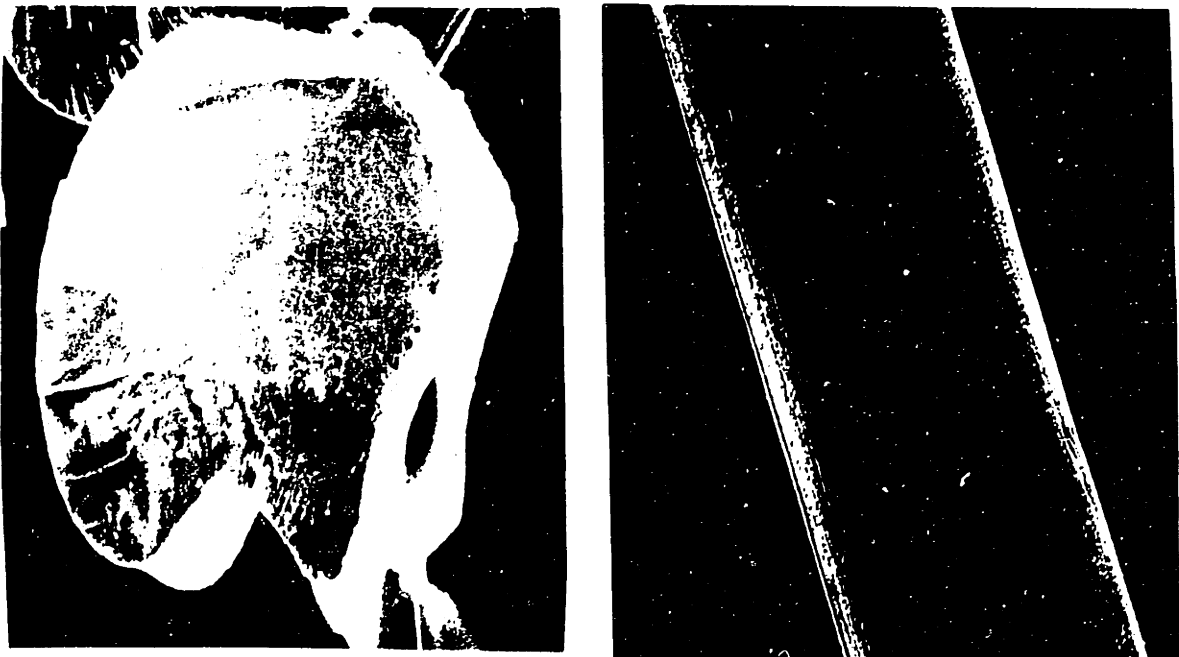|	
1.	4.8 wt.% Alginic Acid + 1 wt.% Gentamicin sulfate
2.	4.8 wt.% Alginic Acid + 1 wt.% Heparin
3.	20 wt.% Polylactic Acid + 1 wt.% Gentamicin Sulfate
4.	40 wt.% Polyorthoester + 1 wt.% Gentamicin Sulfate
5.	40 wt. % Polyorthoester + 5 wt.% Gentamicin Sulfate
6.	40 wt.% Polyorthoester + 1 wt.% Heparin
7.	40 wt.% Polyorthoester + 5 wt.% Heparin

Figure 3.2: Cross Section and Surface of 4.8 wt.% Alginic Acid Blank Suture

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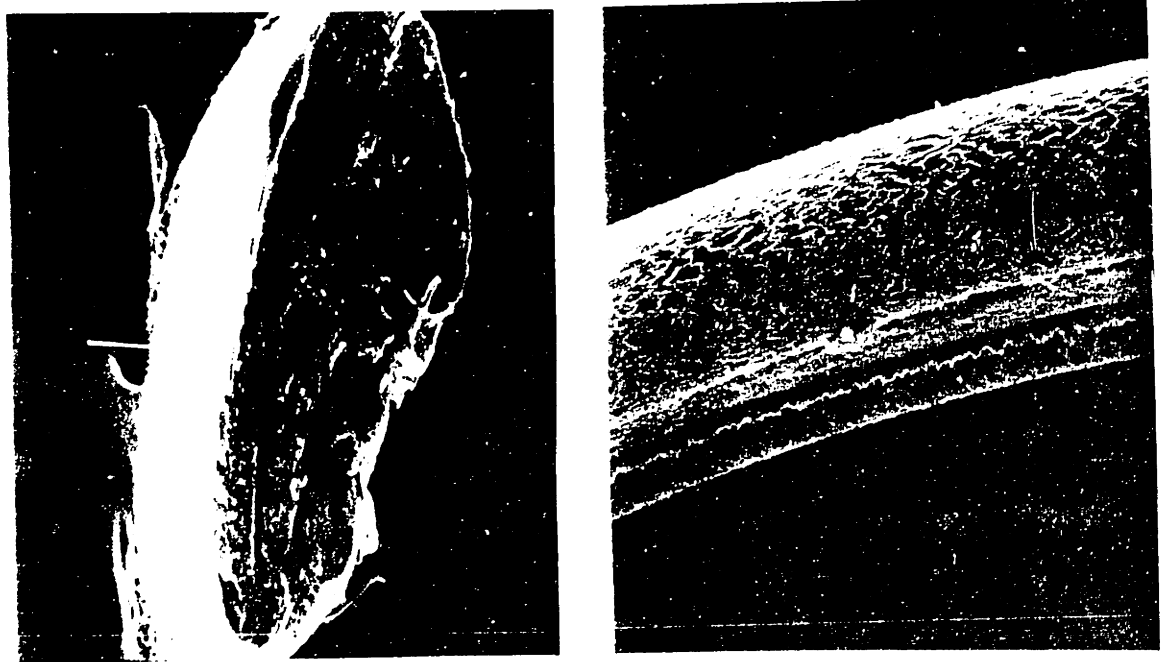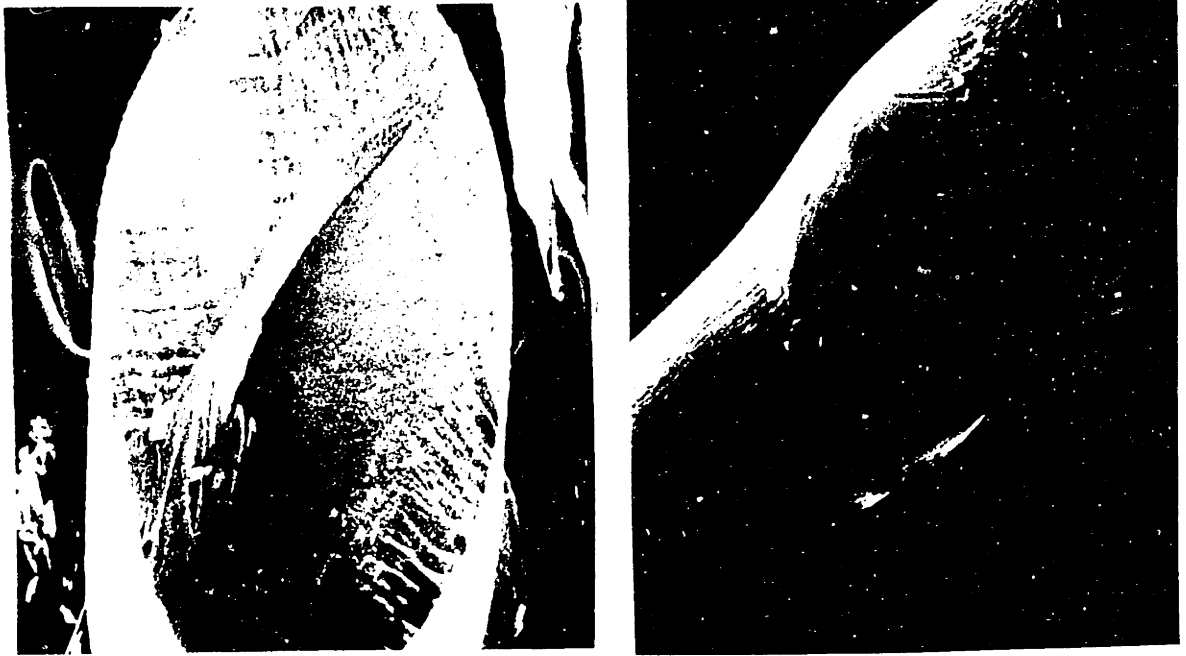Figure 3.3: Cross Section and Surface of 4.8 wt.% Alginic Acid + 1 wt.% Gentamicin Sulfate Suture

Figure 3.4: Cross Section and Surface of 20 wt.% Polylactic Acid Blank Suture

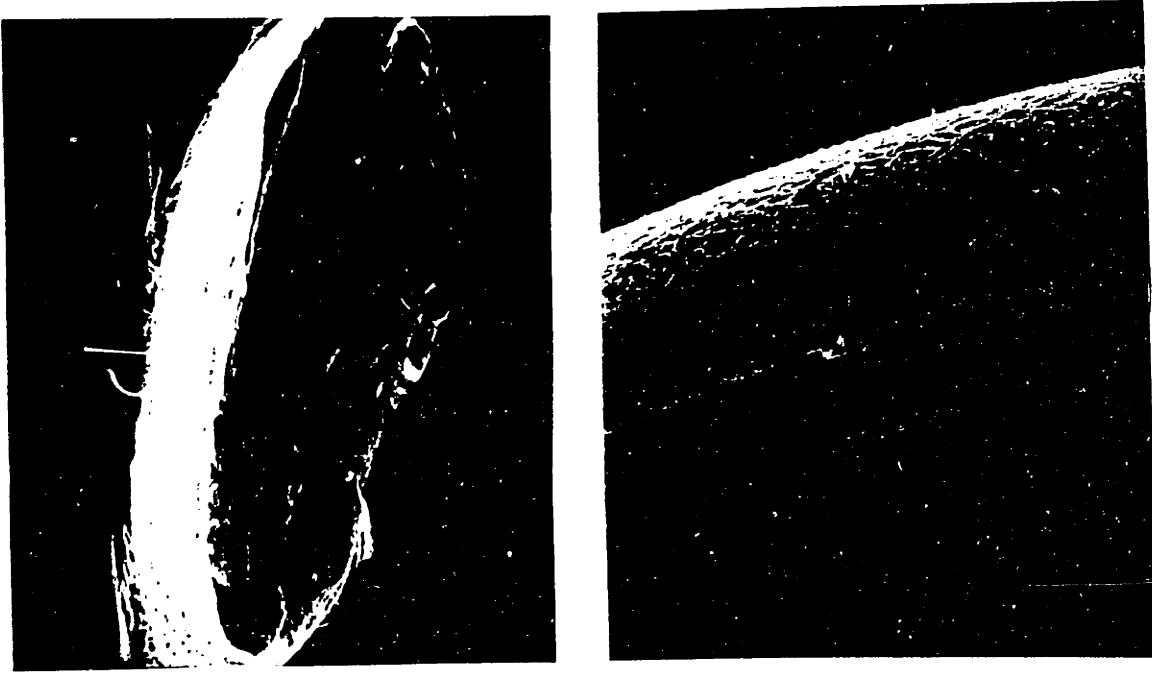Figure 3.3: Cross Section and Surface of 4.8 wt.% Alginic Acid + 1 wt.% Gentamicin Sulfate Suture

Figure 3.4: Cross Section and Surface of 20 wt.% Polylactic Acid Blank Suture
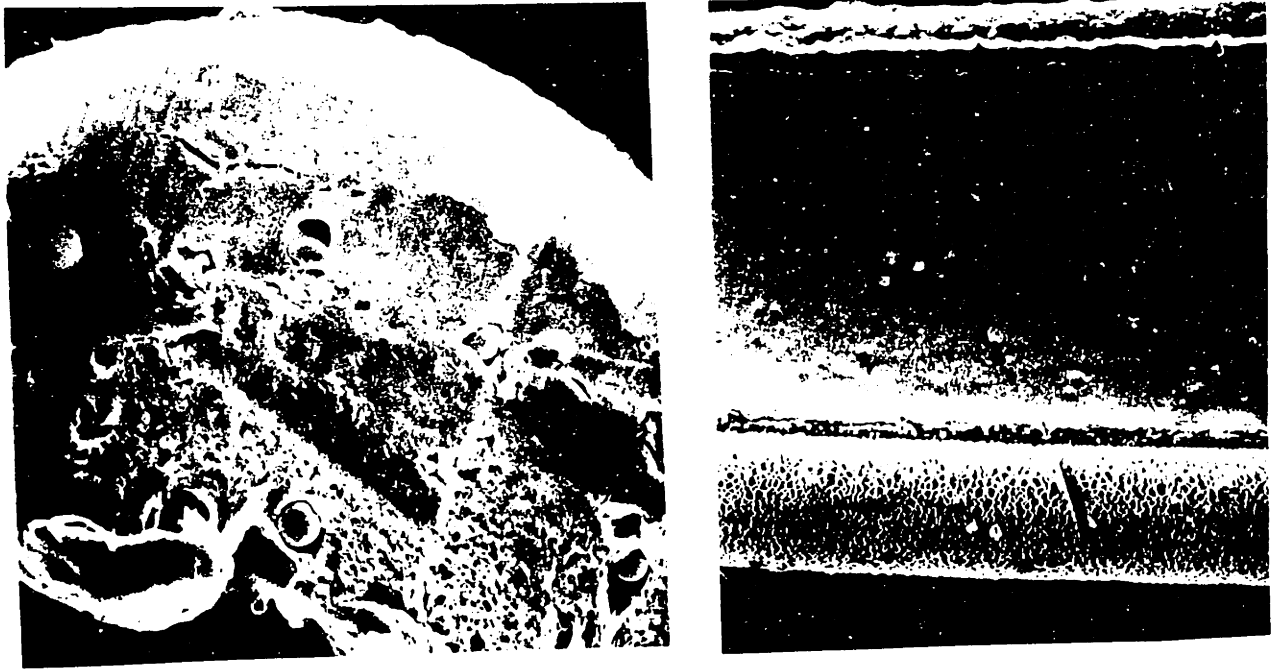
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Figure 3.5: Cross Section and Surface of 20 wt.% Polylactic Acid + 1 wt.% Gentamicin Sulfate Suture

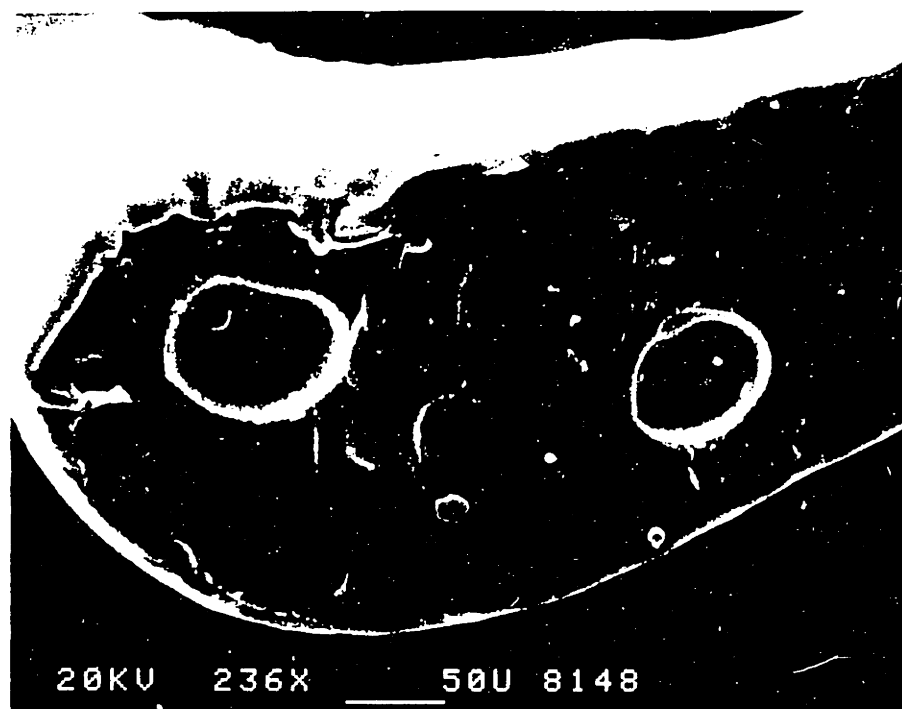Figure 3.6: Cross Section of 40 wt.% Polyorthoester Blank Suture

Figure 3.7: Cross Section of 40 wt.% Polyorthoester + 1 wt.% Gentamicin Sulfate Suture
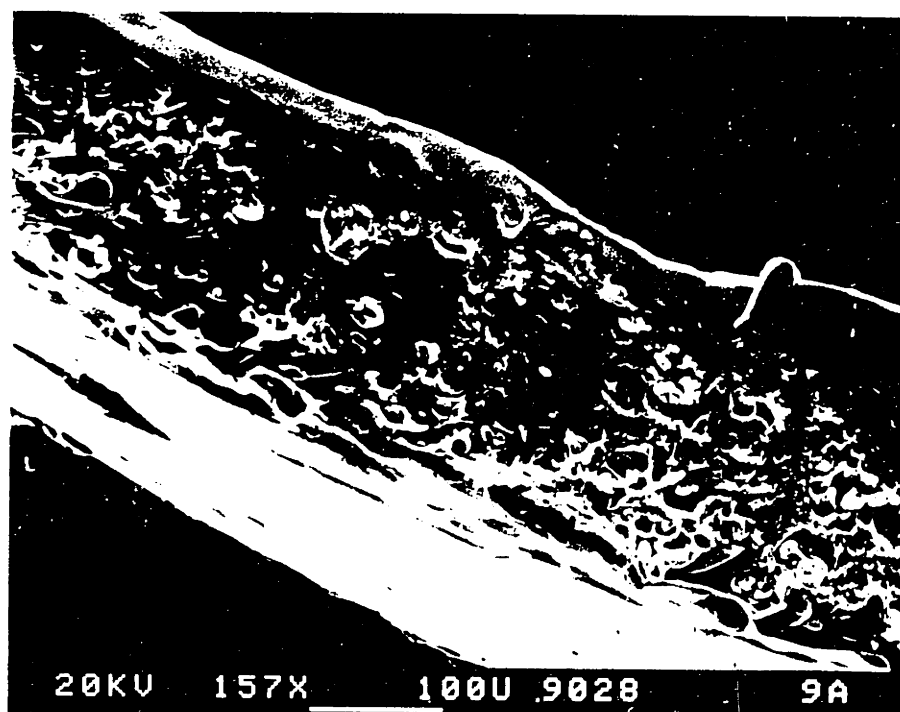

Figure 3.8: Cross Section of 40 wt.% Polyorthoester + 5 wt.% Gentamicin Sulfate Suture

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3.3 Drug Release Test

The release of gentamicin sulfate from the suture strands was followed by means of bacterial clearing in an agar plate. The sutures were cut into segments of 1cm's each and placed on agar plates whose surface had been spread with a dilute solution of staphilococous aureus. Each of these plates was kept in an incubator for approximately 24 hours. The antibiotic killed bacteria surrounding the suture. Each of the zone of clearance corresponded to the local concentration of gentamicin sulfate until all of the drug was released from the suture. Suture segments were transferred onto a new agar plate each day. The area of the zone and the amount of polymer material remaining were recorded daily.

A constant decrease in drug release from the 4.8 wt.% alginic acid + 1 wt.% gentamicin sulfate loaded sutures was observed up to the fifth day (figure 3.9). At that time, drug release stopped and more than half of the polymer material had degradated away. Gentamicin sulfate release was observed for the longest time when it was loaded at 1 wt.% in 20 wt.% polylactic acid. The suture was still releasing at a constantly decreasing rate even after the twelfth day (figure 3.10). In addition, there was almost no change in the shape and amount of the material over this period of time. In contrast, the same amount of gentamicin sulfate placed in 40 wt.% polyorthester sutures released at a constantly increasing rate until the third day. From then on release was virtually undetectable despite the fact that the shape of the suture did not change substantially during the testing period (figure 3.11).
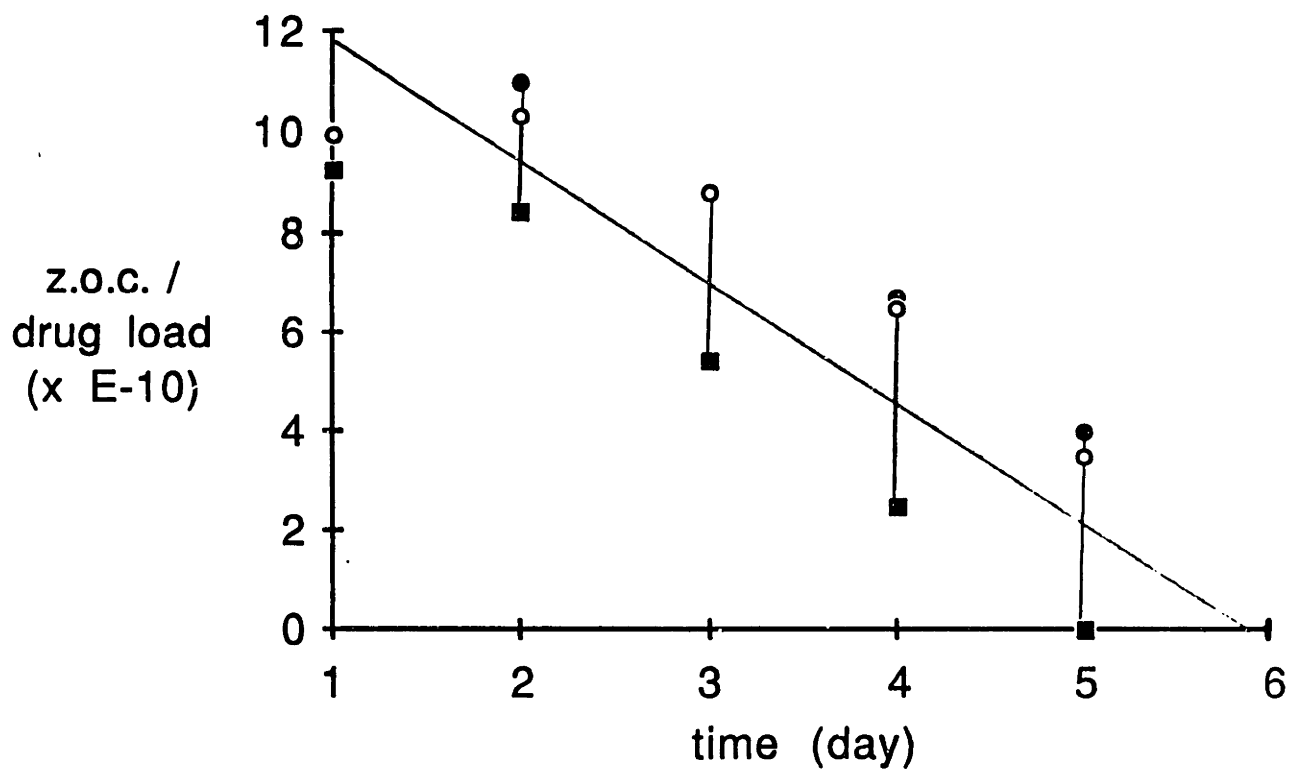
Figure 3.9: Plot of Zone of Clearance/Drug Load vs. Time for the Drug Release of 4.8 wt.% Alginic Acid + 1 wt.% Gentamicin Sulfate Sutures
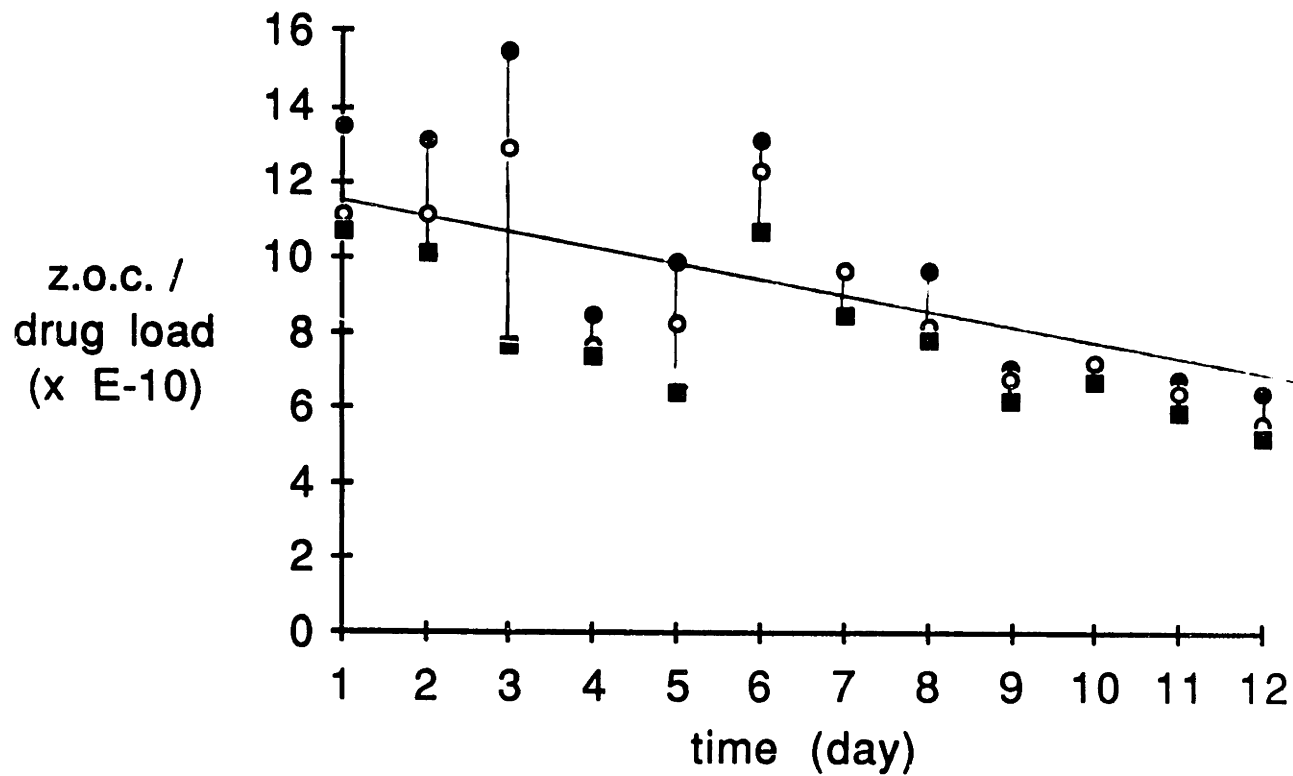
Figure 3.10: Plot of Zone of Clearance/Drug Load vs. Time for the Drug Release of 20 wt.% Polylactic Acid + 1 wt.% Gentamicin Sulfate Sutures
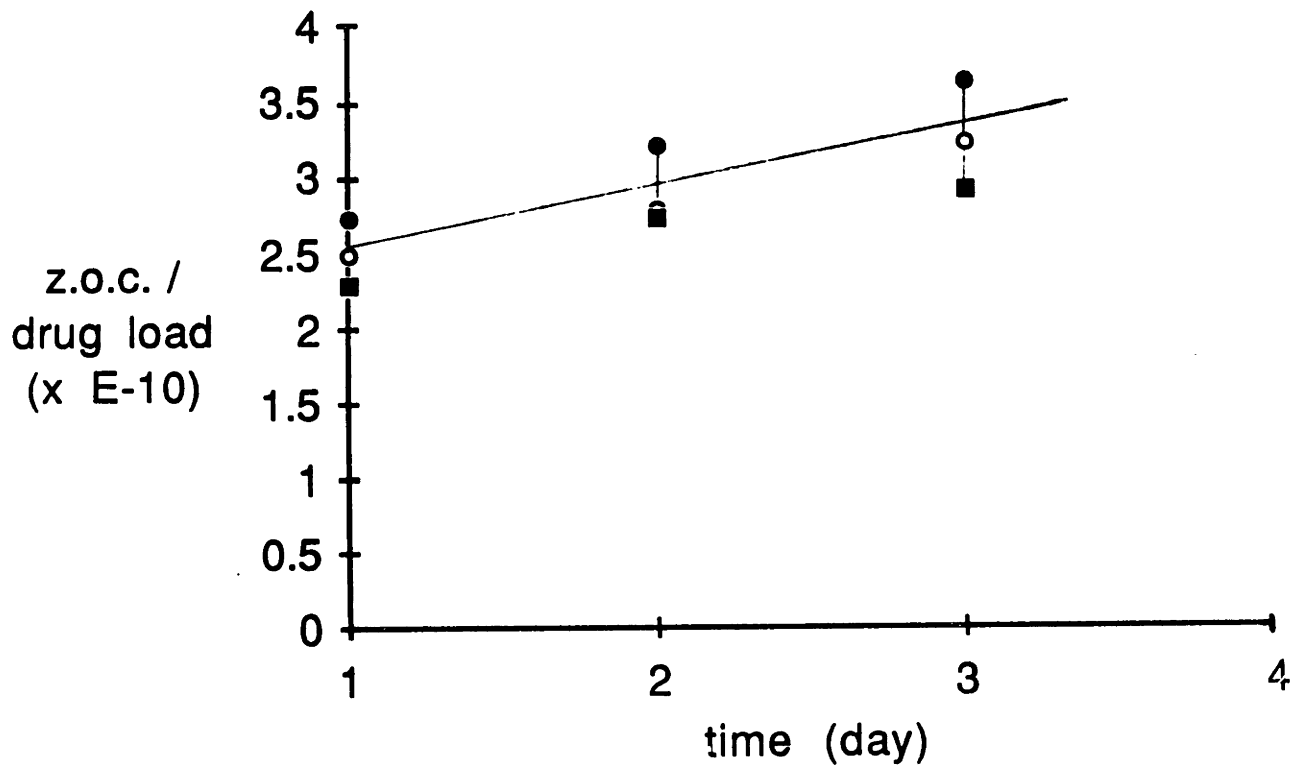
Figure 3.11: Plot of Zone of Clearance/Drug Load vs. Time for the Drug Release of 40 wt.% Polyorthoester + 1 wt.% Gentamicin Sulfate Sutures

Table 3.3: Sutures Used for Strength Test

1.	Polyorthoester + 0 wt.% Drug
2.	Polyorthoester + 1 wt.% Gentamicin Sulfate
3.	Polyorthoester + 5 wt.% Gentamicin Sulfate
4.	Polyorthoester + 1 wt.% Heparin
5.	Polyorthoester + 5 wt.% Heparin

3.4 Strength Test

The strength of polyorthoester sutures implanted with different kinds of drugs at different concentrations was compared using standard strength of material techniques. Blank polyorthoester sutures were used as a standard. The compositions of sutures studied are shown in table 3.3.

The stress on a polymer fiber induced by a controlled load can be measured precisely and used in a measure of its material strength. The stress is equal to the applied load divided by the cross sectional area of suture fiber. The maximum and breaking loads were measured with an Instron at a constant strain rate.

Sutures were then cut into 3 inches and glued onto 1/32 inch polyvinylchloride grips with an epoxy and sealed with silicone rubber (figure 3.12). The mounted samples were dried for at least three days before the instron tests to make sure that the sutures don't slip out when the grips are pulled. For the instron test, Instron Model 1122 was used at a 1 % full scale of 1,000 pounds. The actual Cross Head Speed and the chart speed varied depending on the sample. However, a typical cross head speed and a chart speed of 1 mm/min and 100 mm/min, respectively, were used. Figure 3.13 shows an example of an instron chart. After the instron
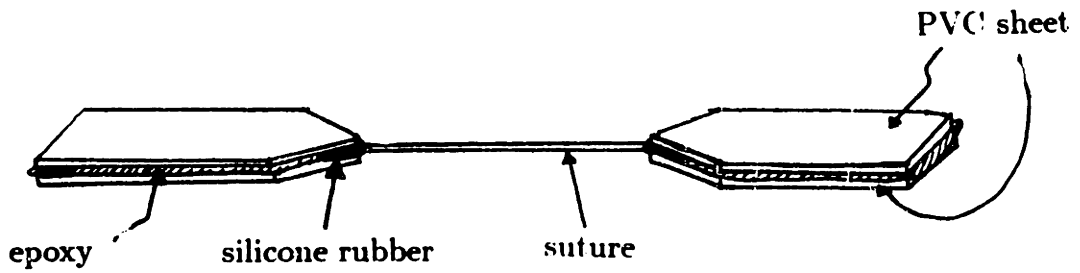
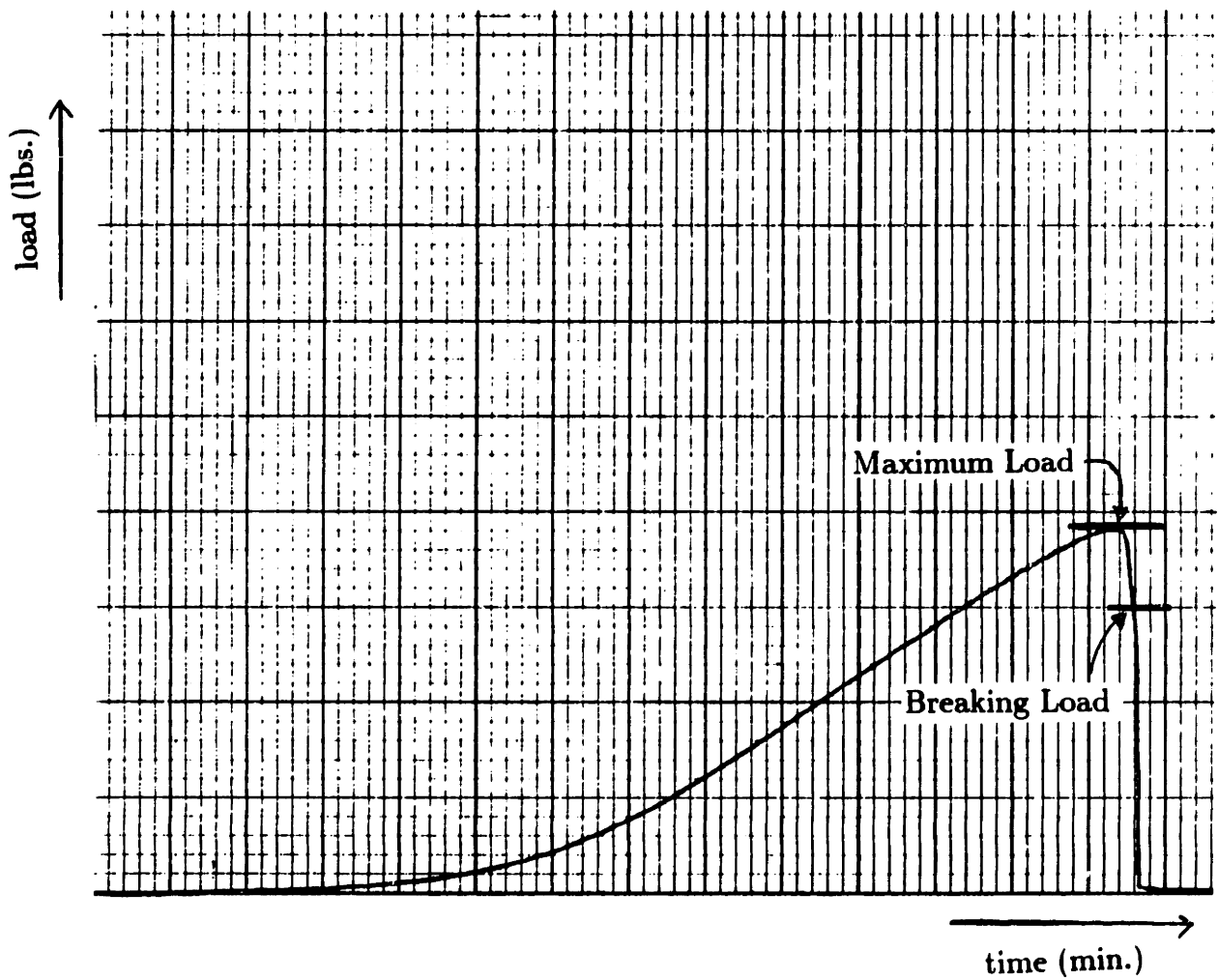Figure 3.12: An Instron Grip Made Out of 1/32 inch PVC Sheet.

Figure 3.13: An Inston Chart of 40 wt.% Polyorthoester + 5 wt.% Heparin Suture; 1 % Full Scale of 1,000 lbs., 1 mm/min Cross Head Speed and 100 mm/min Chart Speed.

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tests have taken place, Scanning Electron Microscopy photographs were taken in order to calculate the cross section areas of the sutures. Finally, maximum stress and breaking stress values were calculated using the datas obtained from the experiments and figures 3.14 to 3.17 show the results of the strength test by plotting stress vs. % drug. The maximum stress of gentamicin sulfate sutures ranged from about 0.4 to 0.8 MPa and the maximum stress of heparin sutures ranged from about 0.8 to 2.2 MPa. The stress at break for gentamicin sulfate sutures ranged from about 0.3 to 0.6 MPa and the stress at break for heparin sutures ranged from about 0.5 to 1.3 MPa.

The blank polyorthoester fibers were stronger sutures than fibers loaded with gentamicin sulfate at 1 wt.% and 5 wt.%. Increasing doses of heparin decreased the tensile strength but paradoxically the blanks were weakest of all. This is probably because the 1 wt.% and 5 wt.% heparin strength tests and the 0 wt.% suture strength tests were conducted at different times. Another reason for this might be that the extent that the sutures were dried before the strength tests might have been different since 1 wt.% and 5 wt.% heparin sutures were prepared later than 0 wt.% suture.
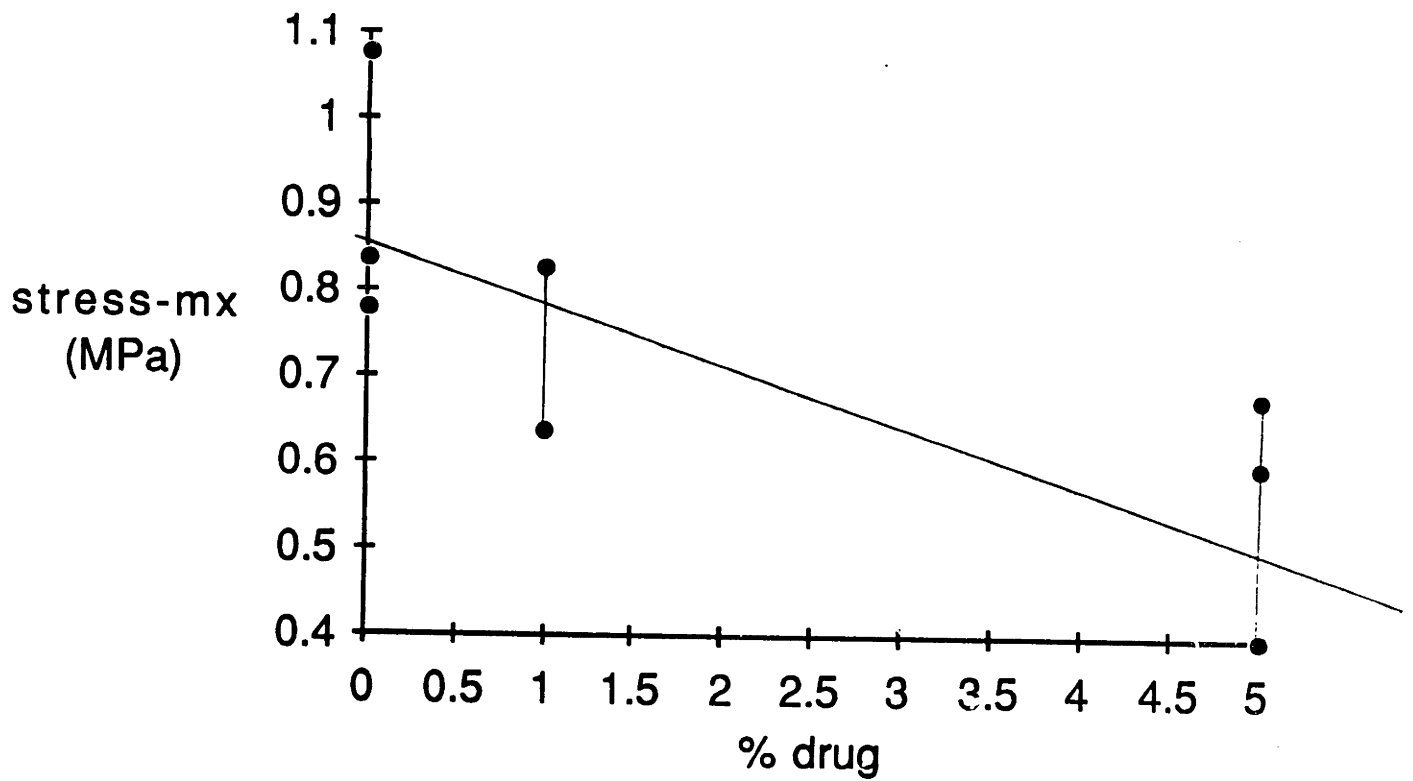
Figure 3.14: Maximum Stress Values of Polyorthoester Sutures vs. % Gentamicin Sulfate Implanted in the Sutures.
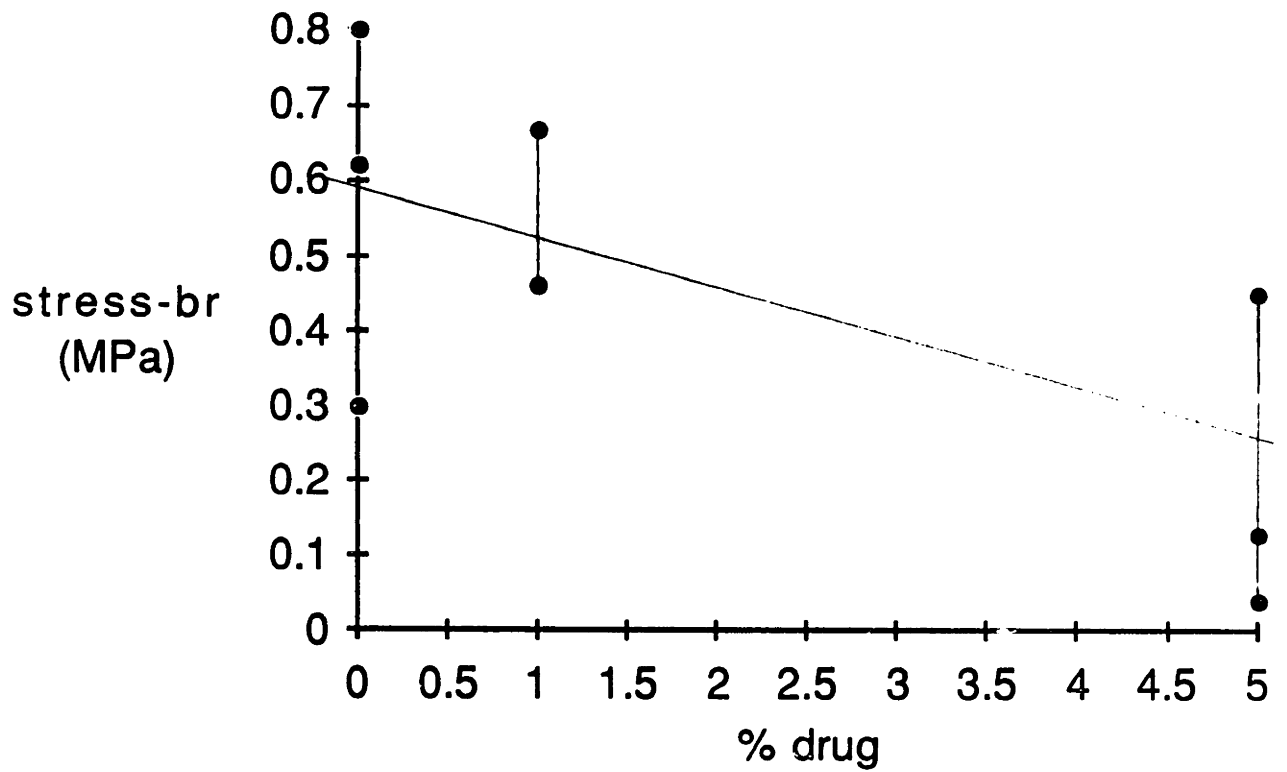
Figure 3.15: Breaking Stress Values of Polyorthoester Sutures vs. % Gentamicin Sulfate Implanted in the Sutures.
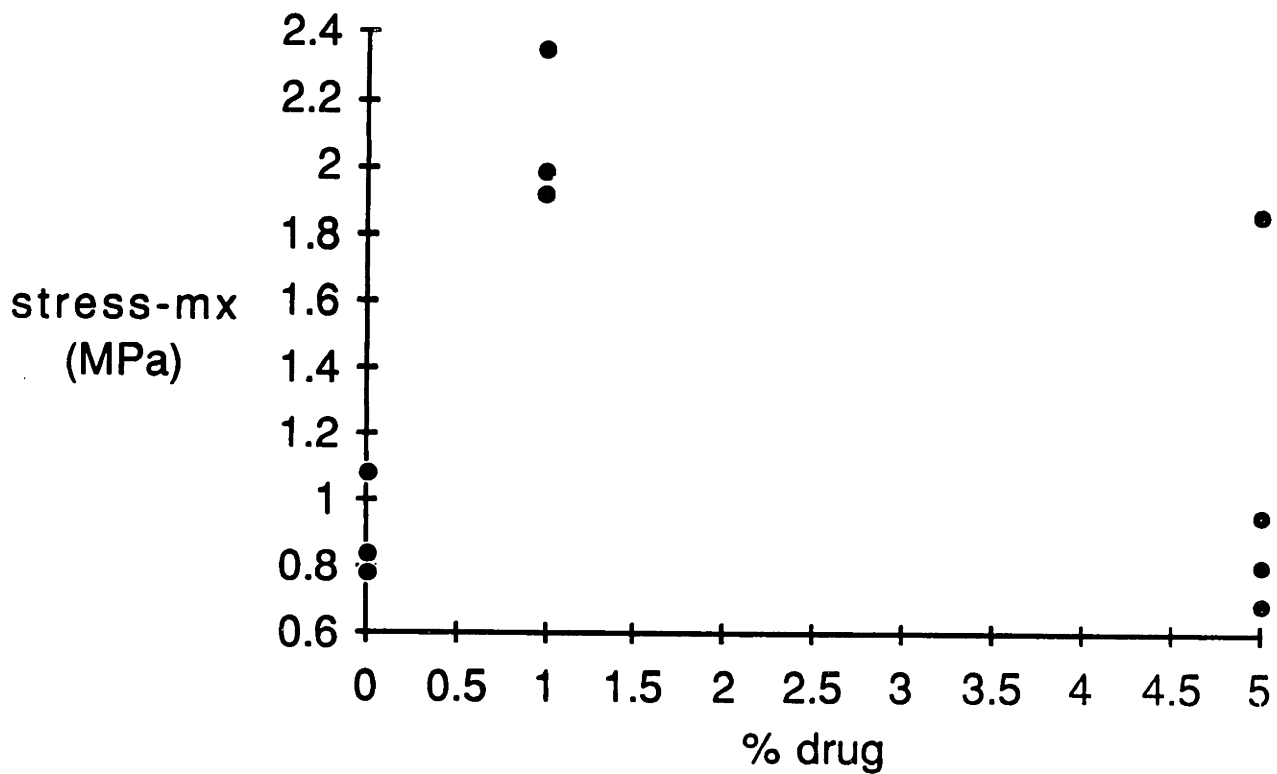
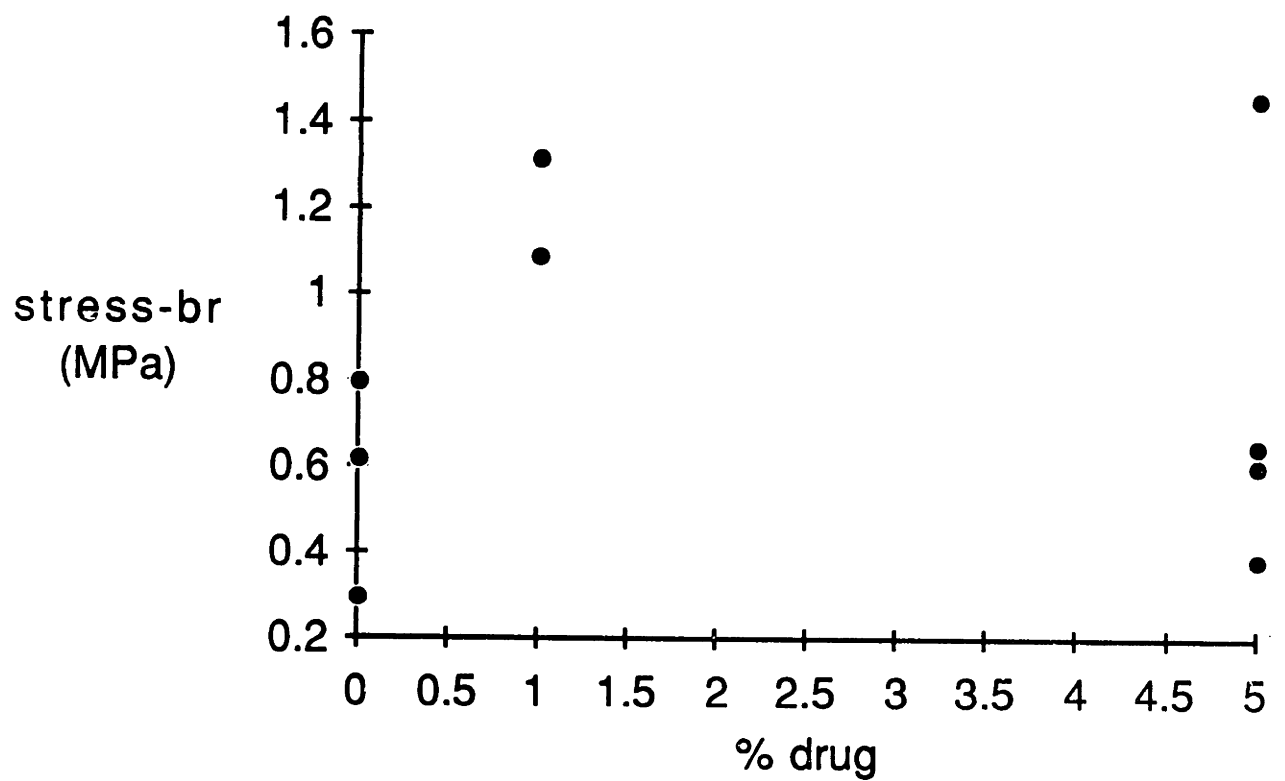Figure 3.16: Maximum Stress Values of Polyorthoester Sutures vs. % Heparin Implanted in the Sutures.

Figure 3.17: Breaking Stress Values of Polyorthoester Sutures vs. % Heparin Implanted in the Sutures.

Chapter 4

Conclusion

Polymer sutures with different amounts of gentamicin sulfate and heparin were prepared and tested.

The 1 wt.% gentamicin sulfate release tests showed the following results: alginic acid sutures released drug at a constantly decreasing rate for about five days, poly-lactic acid sutures at a constantly decreasing rate for more than twelve days, and polyorthoester sutures at a constantly increasing rate for about three days. It was also found that alginic acid suture degraded rapidly as drug was released. From these results it can be concluded that alginic acid and polyorthoester sutures can be used for a wound which is expected to heal in about three to five days and the polylactic acid sutures can be used for a more long term healing.

The uniaxial tensile strength testing of the polyorthoester sutures show different ranges of strength for different drug loads and different drugs. For both gentamicin sulfate and heparin sutures, strength of sutures decrease as more drug is implanted. Also, heparin sutures seem to be stronger than the gentamicin sutures.

Chapter 5

Suggestions for Further Work

For the further research in this work, it might be a good idea to prepare sutures with materials other than the ones used in this work to make sure that the results agree with this work. It is also suggested that drugs other than the ones used in this research used in order to verify the conclusion from the suture strength tests. Lastly, it will be interesting to compare the drug release of different drugs as well.

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