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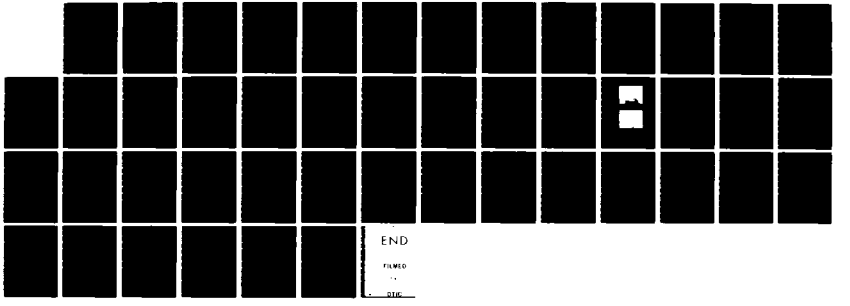

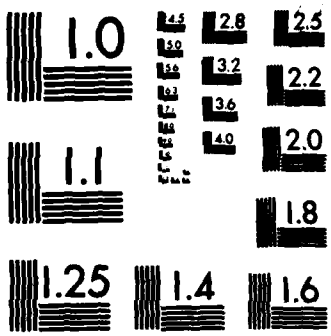

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Abcor Report No. 2679-F

Wound Dressing in Maxillo-facial Trauma

Final Summary Report

David L. Williams
Barron W. Tenney
James J. Dillion

October 1979

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD17-79-C-9020

Abcor, Inc.
Wilmington, Massachusetts 01887

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Biodegradable polymers of poly-L(-)lactide (R.S.V. = 0.3 and 1.3 dl/g), poly-DL-lactide and poly(lactide-co-glycolide) were prepared and blended with drugs for use in wound dressings. Three local anesthetics (procaine, benzocaine, and etidocaine), two antiseptics (iodine and cetylpyridinium chloride, CPC), an anti-inflammatory steroidal drug (hydrocortisone) and epinephrine were studied in non-woven fabric, film, and powder forms. Drug release was measured as a function of time for 45 different polymer-drug

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forms. Gelatine (Gelfoam®) and collagen (Avitene®) were studied as contact hemostatic agents, imbedded into the polymer surface.

Poly-L(-)lactide systems delivered anesthetics in the appropriate time frame. Fiber mats with procaine delivered 9% in one hour and 41% in one day. Films released similarly, and powders faster. Benzocaine and etidocaine were released more slowly. Benzocaine powder released 27% in one hour and 77% in one day, and etidocaine powder released 9% in one hour and 59% in one day. Iodine and epinephrine samples were labile and also quickly released their available drug. The quarternary ammonium antiseptic (CPC) systems were slower to release drug. The poly-L(-)lactide powder released 18% of the CPC in one hour and 23% in one day. Release from a similar system with hydrocortisone was 11% in one hour and 22% in one day. The copolymer film had the best release characteristics for hydrocortisone (7.5% in one hour and 60% in one day).

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FOREWORD

Abcor personnel involved with this project include: David L. Williams, Ph.D.; Barron W. Tenney, B.S.; James J. Dillon, B.S., and Kenneth R. St. John, M.S. We greatly appreciate the interest and direction afforded by the Project Officer, Colonel William R. Posey and by Colonel Duane E. Cutright, Commander, Institute of Dental Research.

I. INTRODUCTION

A. MILITARY RELEVANCY

Military problems of wound healing are unique in terms of the need to dress wounds under battlefield conditions. Controlled release of drugs from wound dressings should improve this primary wound care. Anesthetic, antiseptic, anti-inflammatory, and hemostatic agents may be needed to treat avulsive maxillofacial wounds. These drugs can be incorporated into bioabsorbable polymer matrices for use as wound dressings. Having the drug and dressing as a single items also has unique advantages under battlefield conditions.

B. MAXILLOFACIAL WOUND HEALING

Although there is no unique aspect of maxillofacial wound healing, facial wounds are of unique importance because of the facial features. These are relatively small anatomical organs, which break the epidermis at the mouth, nostrils, and eyes. Blood loss is also of special importance in maxillofacial wounds because of the increased danger of shock.

The distressing effect produced by a facial injury, no matter how small, is very pronounced. The loss of the tip of a nose, for example, can constitute serious disfigurement. Patients with facial deformities are crippled psychologically, socially, and economically.

Goldwyn and Rueckert (1977) published several accounts of natural healing of facial defects, and showed that the results were as good or better than might have been obtained using grafts or flaps. Furthermore, this procedure is more amenable to use at the military front line. The results are obtained with minimal pain, less confinement, greater safety and ease, and without donor site discomfort and scars.

Even if plastic surgery is required to correct maxillofacial avuslive wounds, a better wound dressing may allow the future surgery to be less extensive.

C. WOUND DRESSINGS

Wound dressings have been in use for centuries, and they are as common as adhesive bandages. Considerable industrial effort has been placed on these items and many commercial dressings are available (e.g., Remington's Pharmaceutical Sciences, 14th edition, Chapter 97). Topical drugs can be applied with, or under the dressing. These can be applied directly to the wound or to the dressing. Although solutions are often used, dusting powders and films may also be employed.

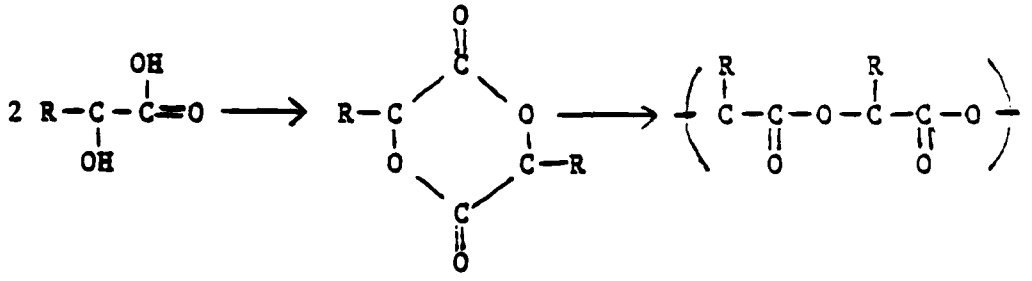
Dusting powders are usually inert dessicants. Materials include talc, magnesium and zinc stearate, and an absorbable starch-derivative dusting powder. In this contract, polylactide/drug powders were developed as absorbable dusting powders. Powders may be sprinkled on manually, sprayed as a micronized cream (Denny, Twoney, Hitchcock, 1978), or used with an insufflator or other powder blower device (Barrington, Williams, Mullins, Hitchcock, 1978). Powders may be applied directly to the wound or to the gauze dressing.

Films which are used as mechanical protectives include collodion and gelatin films. Flexible collodion and Vibesate are applied directly to the wound with an organic solvent. Gelatin systems are usually applied as pre-formed sheets or boots. Scribner (1973) developed a method for preparation of polylactide/polyglycolide/drug films. Methylene chloride was used as a replacement for chloroform in this contract, since methylene chloride is quite non-toxic (Chemical and Engineering News, July 24, 1978, p. 7).

Although films may be formed <u>in situ</u> using volatile solvents, considerable pain is associated with this method of application on open wounds. Aqueous films or gel may also be used and delayed release may be obtained (Nakano, Takikawa, and Takaichi). In this contract only pre-formed films were considered.

D. POLYLACTIDE/POLYGLYCOLIDE SYSTEMS

Lactic and glycolic acids are natural metabolic products. Polymers of these hydroxy acids can be made by rearrangement of cyclic dimers, which are formed by condensation, with removal of water. The reactions are:



where "R" is "H" for the glycolide and "CH_3" for the lactide. Lowe (1954) described these materials almost twenty-five years ago. In 1966, Kulkarni and co-workers investigated tissue reactivity. Much of the work since that time has emphasized use as sutures and drug delivery devices.

Polylactide drug systems were first described by Boswell and Scribner (1973). Surgical dressings were described by Schmitt and Polistina in 1975. These authors used medicaments in polyglycolides in 1976, with projected usage in sutures, clips, and storage pellets. Sprayable films for wound coverings were described by Scribner (1973). Polyglycolide as a dusting powder was described by Ramsey and DeLapp (1970).

Abcor has been involved in this effort since 1973 with polylactide in drug delivery systems, and since 1971 in implantable devices. Cutright and co-workers at USAIDR, WRAMC have studied this material primarily for hard tissue replacement. Sinclair at Battelle has collaborated in this effort (Contract No. DADA 17-72-C-1053).

Extensive testing has shown that these materials are completely absorbed and do not cause any untoward tissue reaction during disintegration.

Factors of importance to this program include: rate of bioabsorption, hardness (or flexibility), ease of preparation of composites with drugs, and the rate of release of these drugs. For this reason, we evaluated four types of polymers. In general, these polymers increase in hardness, decrease in solvent solubility, and decrease in bioabsorption rate as the molecular weight (reduced specific viscosity) increases. Bioabsorption rates decrease from L(-), to DL, to copolymer at the same molecular weight; however, solubility in solvents decreases from copolymer, to L(-), to DL polymers. Solvents, at room temperature, decrease in solvating power from hexafluoroisopropanol, to methylene chloride and dioxane.

Polymer molecular weights are evaluated by viscosity measurement (0.1% in dioxane at 25±0.1°C). Figure 1 shows the relationship which is based on the Mark-Houwink equation.

E. DRUG SELECTION

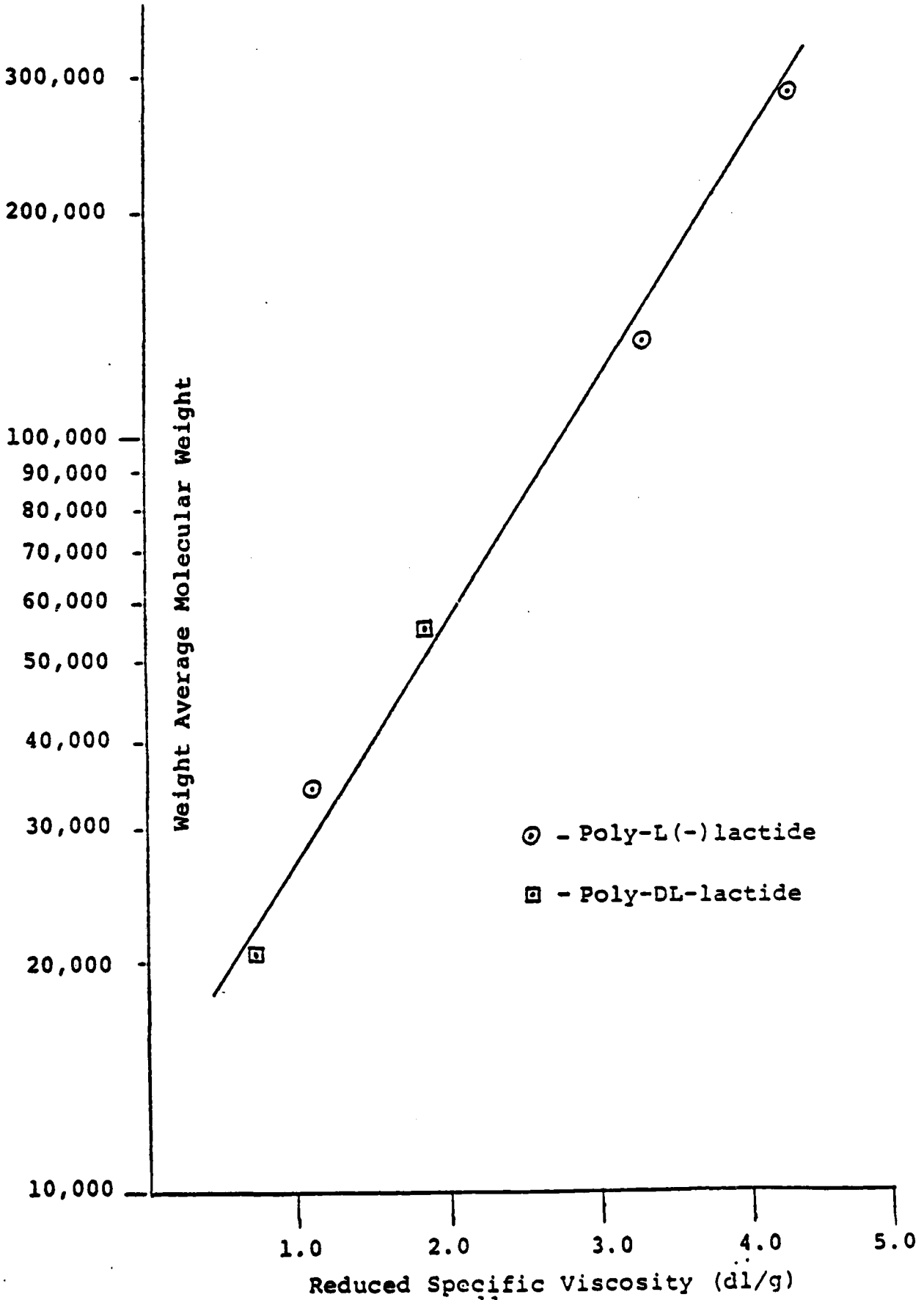
Materials to be incorporated in the polymer matrix were chosen from standard drugs for local anesthetic, antiseptic, anti-inflammatory, and hemostatic action.

1. Anesthetic Agents

Local anesthetics are advantageous in wound dressings, and their slow release from a polymer matrix would be an added advantage. Relatively insoluble local anesthetics are often used for topical application since their effect is longer lasting. However, they are general y less effective than the soluble compounds. There is no effective anesthetic with an action commensurate with the duration of most wound dressings.

Figure 1

Correlation Between Weight Average Molecular Weight of Polylactides (GPC-Waters, Assoc. and Reduced Specific Viscosity-Abcor)



The local anesthetic of comparison is procaine · HCl (Novocaine®, Winthrop). It is also one of the least toxic anesthetics. It is normally injected as the hydrochloride. Both the hydrochloride and the free base forms were available commercially. Because of the higher solubility in methylene chloride, the free base (Sigma P 9754) was used for release studies.

Benzocaine is less soluble in water, but more soluble in the polymer solvents. It has a long history of use in wounds, ulcers, and mucous surfaces.

Etidocaine · HCl (Duranest®, Astra) is a newer, longer-lasting anesthetic which is generally similar to lidocaine (Xylocaine®, Astra). Both the hydrochloride and base forms were available for investigational use from Astra Pharmaceuticals (Worcester, MA). The base form was used for all experiments in this contract.

2. Antiseptic Agents

Antiseptic agents with surgical dressings have been used for centuries. With the advent of antibiotics and cleaner surgical procedures, the addition of antiseptic agents has decreased. However, its use in military situations is still advantageous. Slow release of these agents from a drug-polymer matrix would be useful, although some antimicrobial activity will be needed immediately.

Iodoform is the classic form of antiseptic gauze, but its release of iodine is too slow and would be even slower if incorporated into a polymer matrix. Elemental iodine, however, remains one of the best, all-around antiseptics. Its solubility in chloroform indicated that it would be readily incorporated into polylactide matrices for sustained release. The sustained release should eliminate the possibility of iodine burns. Formation of complex ions such as the povidone or tri-iodide ions, or the use with alcohol, might be advantageous in some applications (e.g., to penetrate intact skin). However, for dressing an open wound, protein complexation of iodine released from the polymer matrix should be sufficient.

In a meeting with Colonels Cutright and Posey, an iodine-polyvinylpyrrolidone complex was suggested (povidone-iodine M.I. 7499, Betadine®, Isodine®, etc.) as an alternative to iodine. A sample of the solid compound was received from Napp Chemicals, Inc. (Lodi, NJ). However, it was not possible to test this material under the present contract.

There is a large class of surface active compounds which are used as antiseptics. Cetylpyridinium chloride was chosen as a representative of this class. It is a clearly defined chemical compound which had already been encapsulated at Abcor under Contract No. NO1-DE-52448. Figure 2 shows the release of 53-105 micron cetylpyridinium chloride microcapsules. These micro-

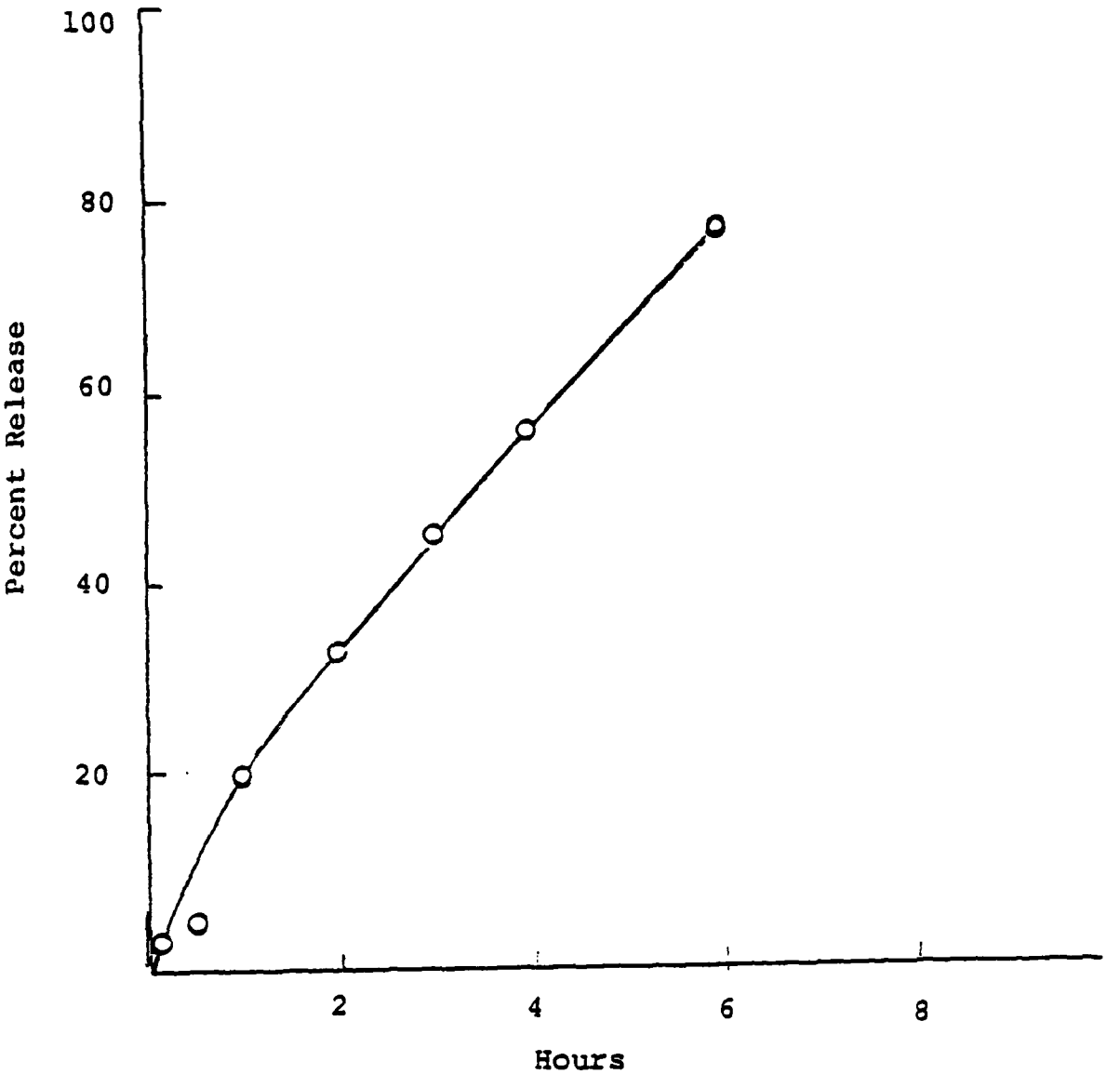


Figure 2 Release of Cetyl Pyridinium Chloride from Ethyl Cellulose Microcapsules (53-105 μm particles, 42% drug, Abcor/NIDR contract).

capsules were formed by a coacervation process at Abcor. Cetylpyridinium chloride is also used for prophylactic antisepsis of wounds (Remington's Pharmaceutical Sciences, 14th edition, p. 1176). Benzalkonium chloride is more widely used (e.g., Zephiran®), but its alkyl constituent is of random length. Chlorohexidine was suggested as a more effective antiseptic agent than cetylpyridinium chloride. This material was requested from ICI Americas, Inc. (Wilmington, DE) but was not received.

Many other antiseptic agents are highly toxic and have been replaced by antibiotics. Antibiotics are much more selective antimicrobial drugs. However, their use was already under investigation by the USAIDR.

3. Anti-Inflammatory Drugs

Inflammation of wounds is a cause of pain and should be controlled, if possible. However, the inflammation may be caused by bacteria, and an antimicrobial agent should be administered with the anti-inflammatory agent.

Corticosteroids are known to mitigate inflammatory reactions. Hence, these drugs are used with antibiotics in dermatosis and in some surgical procedures (Protofoam-HC for episiotomy). A PDR list of corticoids and antibiotics gave fourteen preparations. Half of these used hydrocortisone or its acetate. Four other corticoids were also used. The relative anti-inflammatory to adrenal cortex activity was suggested as a reason for choice of corticosteroid. Beta- and dexamethasone were found to be best by this criteria (Goodman and Gilman, 1975), and letters were sent to manufacturers of these drug products. Dr. Howard at Schering discussed the subject by telephone and two other informative replies are included in the Appendix. White, et al (1978), recently studied methylprednisolone and found that it did not alter the clearance of E. coli from the peripheral blood of dogs. They also summarize the reports of potentiation of infection by corticosteroids and MP's use in septic and endotoxic shock. This is an area of considerable research and controversy. We originally proposed to study hydrocortisone (cortisol), and further investigation did not change this decision.

4. Hemostatic Agents

Application of a non-medicated dressing is often sufficient to stop the bleeding of a wound. Upon contact with most surfaces, platelets disintegrate, thereby liberating thromboplastin. The higher the surface area, the greater the effect. Specific drugs for hemostasis include those involved with the clotting mechanism (e.g., fibrinogen and thrombin), astringents that initiate clotting by precipitating proteins (ferric subsulfate), and substances which restrict blood flow (epinephrine). Specific agents studied in this contract were: Avitene® (Avicon, Inc.) Gelfoam® (Upjohn, Co.), and epinephrine.

Avitene® is a microfibrillar collagen hemostatic agent. It is bioabsorbable; although its absorption requires months, and its action is required in minutes. It is usually applied as a dry powder, but might be better utilized in the field as part of a wound dressing. As stated in the proposal, drug release modification would be inappropriate since the action of contact is catalysis and is required immediately. The material is also insoluble in any solvent for the polymer.

Gelfoam® is an absorbable gelatin powder. It was more amenable to incorporation into a wound dressing because it was not fiberous. In other respects it is similar to Avitene®

As a hemostatic agent, epinephrine is used mostly in dental surgical procedures. Gingi-Pak® (Gingi-Pak Laboratories) is a dental retraction cord which is available with epinephrine impregnated into the absorbant cord. Epinephrine has the added advantage of restricting the loss of other drugs to the systemic circulation. Its use in wound dressing is therefore indicated as a hemostatic agent, and as a potentiator for anesthetic or bacteriostatic drugs. Epinephrine is often incorporated into local anesthetic formulations.

Continuous release of epinephrine may also slow the healing process by decreasing the blood flow which normally increases in the area of the wound.

II. POLYMER SYNTHESIS

The polymers for this program are all prepared by the ring opening polymerization of the corresponding cyclic dimers using stannous octoate as a catalyst at a temperature above the melting point of the dimers. Table I summarizes the polymer synthesis effort.

A. Polylactides

Lactide compounds purchased commercially are not pure enough for synthesizing the polylactide required for this program. The crude material must be purified by repeated recrystallizations from ethyl acetate. The purified lactide is kept in a dry, cool environment until ready for use. A.C.S. Reagent Grade solvents are used for all operations.

Polymerization is carried out batchwise in bulk (500-700 gram batches). Larger batches are nonhomogeneous and too difficult to control due to the exothermic nature of the reaction. The general preparation procedures for the polylactides used are described below.

1. Poly-L(-)lactide Synthesis (RSV = 1.3 dl/g)

Five hundred grams of purified L(-)lactide and a Teflon-coated magnetic stirring bar are placed in a 1000 ml flask provided with a thermowell. The lactide is heated in a 120°C oil bath while stirring the melt in vacuum for 30 minutes for removing traces of volatile materials. Dry nitrogen is introduced to release the vacuum. The bath temperature is raised to 180°C. To the mixture is added 0.2 ml of stannous octoate catalyst (6% in mineral oil) with vigorous stirring. Within five minutes the mixture viscosity increases to a point where the stirrer moves slowly. About two minutes later the stirrer stops. About fifteen minutes after the catalyst addition, the polymer mixture reaches a maximum temperature. After a total of thirty minutes of reaction (since the introduction of catalyst), the mixture is taken out of the oil bath and allowed to cool to room temperature.

The polymer remains a tough solid which adheres to glass tenaciously. The flask containing the polymer is shattered. The glass/polymer mixture is taken out of the cooling bath and dissolved in methylene chloride to remove the glass. The solution is decanted and treated with three volumes of 2-propanol by slow addition to a stirred solution. The precipitated polymer is washed with 2-propanol, broken up into smaller pieces, and dried.

After this initial drying (room temperature), the polymer is ground into a coarse powder and vacuum dried for an additional four hours at 25°C. The polymer is packaged in 50 gram lots (mason jars) and sealed under an atmosphere of argon. The material is subsequently frozen to further inhibit any additional degradation prior to use.

Table I

Polymer Inventory

	Batch No.	R.S.V. (dl/g)	Grams
Poly-L(-)lactide			
RSV ≈ 1.0 dl/g	70-74	1.33	429
	185-24	1.35	430
	70-70	1.43	438
Weight Average		1.37	1297
RSV ≈ 0.3 dl/g	70-49	0.37	79
	70-60	0.43	429
	638	0.43	208
	508F	0.50	30
	529	0.48	476
Blended	228-4	0.27	975
Poly-DL-lactide			
RSV ≈ 0.3 dl/g	228-5	0.24	275
	228-5A	0.38	480
	228-5B	0.41	450
Weight Average		0.35	1205
Poly-DL-lactide-co-glycolide			
RSV ≈ 0.3 dl/g	337-19	0.51	14

A yield of about 80% of fractionated polymer with a reduced viscosity of about 1.3 dl/g was obtained in three reactions.

2. Poly-L(-)lactide Synthesis (RSV = 0.3 dl/g)

In the course of preparing polymers that fall into narrow viscosity ranges, a large amount of out-of-specification material has been prepared. Thus, 1 kg of 0.3 dl/g poly-L(-) lactide was prepared by solution blending of appropriate polymers. Five batches of polymers are charged into a 4 liter flask to give a total weight of 1214 g with a weighed average RSV of 0.44 dl/g. Two liters of reagent grade methylene chloride are added to the flask, and the contents are stirred until the polymer goes into solution. The solution is then filtered under gravity through Whatman #4 filter paper. The polymer is precipitated with six liters of 2-propanol, filtered, and allowed to dry. A total of 975 g of a white, powdery material were recovered with an RSV of 0.27 dl/g (in 1,4-dioxane at 0.1%, 25°C).

3. Poly-D,L-lactide Synthesis (RSV = 0.3 dl/g)

Six hundred grams of once-recrystalled D,L-lactide (recrystallization from ethyl acetate) were vacuum dried at 60°C for two hours. The crystals were then charged into a one-liter, round-bottom flask along with a one-inch, Teflon-coated stirring bar. One drop of 6% stannous octoate in mineral oil is added for every ten grams of dimer as the catalyst. The flask is then fitted with a gas outlet tube and evacuated and filled with dry nitrogen three times to rid the flask of any lingering water vapor. With the flask under a blanket of nitrogen, it is lowered into a 200°C preheated silicone oil bath. At the end of three hours, the flask is removed from the bath and allowed to cool. The pale orange polymer is then broken into small pieces and dissolved in boiling dichloromethane. The polymer is precipitated from solution with -40°C 2-propanol. The polymer retains a large amount of solvent and must be dried at 90°C under vacuum. The final product is a white, extremely hard material. An average yield of 70% was obtained in the three experiments (1205 g).

4. Poly-D,L-lactide-co-glycolide

Lactide-glycolide copolymers have been prepared at Abcor for fabricating readily absorbable devices, such as intervasal stents and phigs. The composition is 55.5% D,L-lactide and 44.5% glycolide, which is a 1/1 molar ratio. Unfortunately, no material was available from stock; therefore, this copolymer was synthesized for this program.

a. Glycolide Preparation

Since the dimer of glycolic acid is not commercially available, it is synthesized by the two-step process described by Sorenson and Campbell (1968).

Glycolic acid was heated slowly to 185°C under vacuum (water aspirator). After the free and bound acid was removed, the system was cooled and the low molecular weight polymer was formed.

The glycolide polymer was depolymerized using 1% antimony trioxide at 280°C with a vacuum of 12-15 torr. The dimer was collected in dry ice traps. This product was recrystallized from ethyl acetate until a melting point of 82-84°C was obtained.

b. Copolymerization

D,L-lactide from Clinton Corn Products was recrystallized to a melting point of 127-128°C and blended with the glycolide dimer. Stannous octoate catalyst was added and the system was evacuated and flushed with nitrogen.

The temperature was raised to 165°C for two hours and the system was stirred for 55 minutes, at which time the material was too viscous to be stirred. After the system cooled, dioxane was added and refluxed until the polymer dissolved. The polymer was reprecipitated from this solution using isopropyl alcohol.

The product yield was 70% and the reduced specific viscosity was 0.51 dl/g.

B. POLYMER ANALYSIS

Several polymer properties of the polylactide have been determined in previous contract work. These include molecular weight determinations by gel permeation chromatography, infrared spectra, nuclear magnetic resonance spectra, differential thermal analysis, polymer sticking temperature, optical rotation, and density. Since composition and spectral analysis are fairly similar for various polylactides, the only important variable is the molecular weight. This affected the mechanical and physicochemical properties of the polymer. For routine purposes, only the reduced specific viscosity (R.S.V.) of each batch of polymer prepared is determined. The R.S.V. is a good indicator of molecular weight.

According to the Mark-Houwink equation, the polymer molecular weight is related to the intrinsic viscosity in the following manner:

$$[\eta] = KM^a$$

where "M" is the molecular weight, "η" is the intrinsic viscosity, and "K" and "a" are constants for a particular polymer solvent system. For most polymers, the value of "a" has been found to be approximately 0.7.

The intrinsic viscosity is calculated from the experimental values as follows:

t_o = flow time of solvent through a viscometer

t = flow time of dilute polymer solution through the same viscometer.

η_{rel} = relative viscosity = $\frac{t}{t_o}$

η_{sp} = specific viscosity = $\eta_{rel} - 1 = \frac{t - t_o}{t_o}$

C = concentration in grams per deciliter

$\eta_{sp/C}$ = reduced specific viscosity (R.S.V.)

$[\eta]$ = intrinsic viscosity = $\lim_{c \to o} \frac{\eta_{sp}}{C}$

In practice, intrinsic viscosity is obtained by plotting the reduced specific viscosity versus concentration at low concentrations and extrapolated to zero concentration. Since a very low polymer concentration (0.1%) was used for our polylactide, the R.S.V. approximated the intrinsic viscosity.

The reduced specific viscosity of polylactide synthesized in our laboratory is determined in a 0.1% dioxane solution at 25±0.1°C, and is expressed in deciliters per gram (dl/g).

III. PREPARATION OF POLYMER/DRUG COMPOSITES

An estimate is needed of the amount of drug needed per area of wound. This is difficult to assess, especially for a slow release system. Estimates were made based on dosages used for wound treatment (Remingtons Pharmaceutical Sciences, 1970). Thus it was estimated that the drug release rate for the composites should be in the hundreds of milligrams per day for all the drugs except for epinephrine and cetylpyridinium chloride. Epinephrine should be released at the tens of micrograms per day level, and cetylpyridinium chloride at the tens of milligrams per day level. For wounds that require changes of dressing more often, the delivery should perhaps be greater. Since drug delivery will be greater with fresh dressings, and with greater fluid exudate, the dressing change frequency can be readily used to adjust the medication dose.

This is a considerable loading of drug since the weight of a 250 μm (0.010") film is 31 mg/cm^2 (density ∿1.25 gm/cm^3). The fiber mat weighed about 17 mg/cm^2 for a 1 mm fiber depth (uncompressed). Thus, composites were prepared that contained 20% drug, for all drugs except epinephrine, provided composites could be made at this concentration.

A. FIBERS

A ten or twenty percent w/v solution of the polymer along with a known weight of drug is prepared using methylene chloride as the solvent. The twenty percent polylactide (R.S.V. = 1.3 dl/g) solution has a Brookfield viscosity at room temperature of 70 cps. The solution is then filtered under pressure through a 3 μm Teflon Millipore filter to remove any solid contaminants. The solution is then poured into a glass vessel which is connected to the liquid inlet of a Spraying Systems air atomizing nozzle (Type Number 2A) using a piece of latex tubing.

The air inlet is connected to a tank of inert gas of either nitrogen or argon. With the gas outlet pressure set a 4 psi and the polymer solution feeding into the nozzle body under gravity, fine polymer drug fibers are formed. The fibers are collected on a piece of surgical gauze. The fibers have a diameter of approximately 14 μm with a bulk density of ∿175 mg/cm^3.

B. FILMS

Polymer drug films are prepared by solution casting. A polymer drug solution is prepared as described above. The ten percent polylactide solution is then poured onto a clean glass plate and the solvent is allowed to evaporate. The thickness of the resulting film is controlled by varying the amount of polymer solution.

C. POWDERS

Powders are prepared by grinding the above composites. Liquid nitrogen temperatures are required for non-brittle films.

Some experiments were performed in which the drug-polymer solutions were sprayed and the solvent evaporated prior to the particle contacting the collecting surface. This method did not reproducibly produce discrete particles using the laboratory-size equipment.

D. SUSPENDED DRUG COMPOSITES

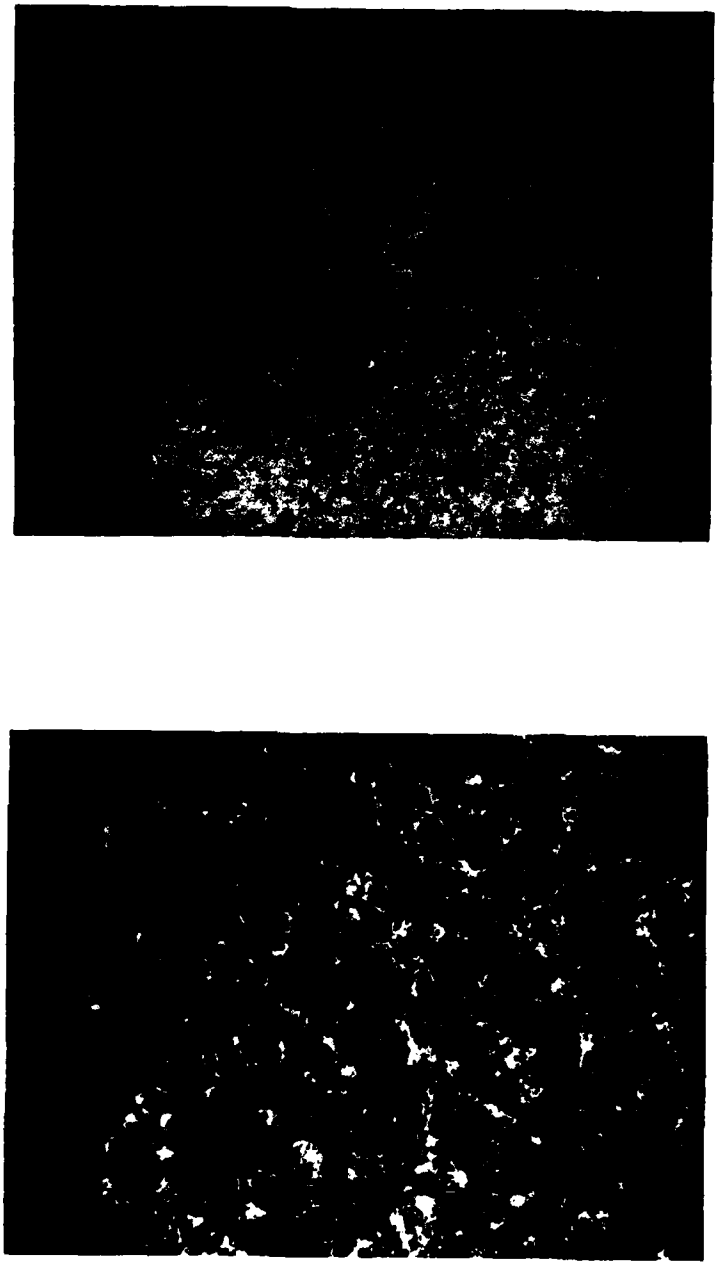
If the drug is insoluble in methylene chloride, the composite will be comprised of discrete particles of drug in a polymer matrix. Also, as the solvent evaporates, the drug may come out of solution first. Molecularly homogeneous systems (solid solutions) are likely to form only when the drug and polymer are similar in solubility and in chemical nature.

When the drug does not dissolve at two percent in methylene chloride (for 20% in polymer using 10% polymer in a solvent), it is used at 0.2% (for 2% in polymer). Only epinephrine was insoluble in methylene chloride at 0.2%. Although much lower concentrations of epinephrine would be effective, measurement of drug release from lower concentrations was a problem. Therefore, epinephrine was suspended in the polymer-methylene chloride solution and maintained (suspended) in this viscous solution while the solvent was removed with a rotary evaporator. This method of preparation caused more aggregation than casting on a flat plate. Hence flat-plate cast samples were prepared for all drugs.

Hemostatic agents which depend on blood contact for efficacy should be slightly imbedded into the polymer matrix. Drug diffusion or particle release is not required.

Microfibular collagen (Avitene®) proved to be very intractable, because of its fibrous nature. It could not be suspended as single strands in methylene chloride, or in 50/50 methylene chloride/ethanol. No acceptable method was found to suspend Avitene in a vehicle which would soften the polylactides or copolymer. Because of fiber attraction, it also could not be successfully sprayed as a dry powder from a powder blower onto a softened polymer surface. Attempts to grind Avitene to a powder were not successful by hand or in a micro-mill.

Powdered gelatin (Gelfoam® powder) was more easily managed. A suspension of Gelfoam in methylene chloride could be produced, but could not be uniformly sprayed onto a polylactide surface, using small mechanical sprayers. However, better results were obtained by softening the surface of the film with a fine spray of methylene chloride and then spraying the Gelfoam powder onto the softened polymer with a De Vilbiss powder blower (No. 288). Figure 3 shows



1 mm

Figure 3. Poly-L(-)lactide film (R.S.V. 1.3 dl/g) before (a) and after (b) irradiation of 60 Mrad.

the particles of Gelfoam attached to a poly-L(-)lactide film of R.S.V. = 1.3 dl/g. Figure 3A shows the surface characteristics of the film, without Gelfoam.

E. COPOLYMER-DRUG COMPOSITES

The lactide-glycolide copolymer was insoluble in methylene chloride; hence films were cast from dioxane. These films were ground to powder using liquid nitrogen and the micro-mill. However, dioxane is not sufficiently volatile to allow fibers to be produced by the method described above. Hence, fibers were not made with the copolymer and the various drugs. Also, dioxane did not dissolve cetylpyridinium chloride (<0.2%); hence the copolymer-CPC films and powders were non-homogeneous.

F. LOW MOLECULAR WEIGHT POLYLACTIDE COMPOSITES

The low molecular weight polylactides (R.S.V.$\sim$0.3 dl/g) did not have sufficient cohesive strength to make intact films. Hence neither the poly-L(-)lactide nor poly-DL-lactide composites of R.S.V.$\sim$0.3 dl/g were tested as films. The poly-DL-lactide composites were tested as a fiber network, which formed by slow evaporation of the solvent (film preparation method). The poly-L(-)lactide composites were ground to powders and tested as such.

IV. DRUG RELEASE MEASUREMENTS

A. DRUG RELEASE MECHANISMS

Two general types of drug/polymer systems exist. These are the drug-core/polymer-wall type and the dispersed drug in polymer type. The ideal drug-core/polymer-wall systems generate constant drug release, regardless of whether the system is planar (film), cylindrical (fiber), or spherical (powder). In homogeneous systems, drug diffuses most rapdily from near the surface of the film, fiber, or particle. As the drug near the surface is depleted, the rate of drug release decreases.

Baker and Lonsdale (1974) present theoretical curves for homogeneous systems, from which Figures 4 and 5 are excerpted. In Figure 4 the rate of release of a dissolved drug is shown in time units which are proportional to the diffusion coefficient (e.g., $D/r^2 = 1$). Different curves are obtained depending on whether linear, cylindrical, or spherical coordinate geometry is appropriate. Figure 5 shows a similar set of curves for drug particles uniformly dispersed in the polymer matrix.

In both the reservoir and homogeneous systems, the smaller the particles, fiber diameter, or film thickness, the faster is the fractional drug release. Hence, there are many variables that can be independently controlled to achieve the required release of a drug.

B. METHOD OF MEASUREMENT

Drugs were purposely chosen for this contract which were amenable to ultraviolet monitoring, or a simple titration analysis (iodine). A known area of film or fiber (17 mm diameter, 2.27 cm^2 area) is cut with a punch. The weight and thickness are then measured. The fiber mat is examined under the microscope. Powders are weighed out directly. These samples are then placed in an L-shaped diffusion cell (Figure 6) to which is added 40 ml of pH 7.4,0.1 molar phosphate buffer. The solution does not completely fill the bottom of the cell and good mixing is therefore obtained using a metabolic shaking bath. The temperature is maintained constant (37°C) in this system. Samples of the solution are taken after 1, 2, 4, 6, and 24 hours of contact, for appropriate drug analysis. Most of the drugs in this program are very soluble in water or buffer; hence, the concentration gradient can be expected to remain essentially constant, until all of the drug dissolves from the matrix. This is not necessarily true of solid solution of drug in polymer.

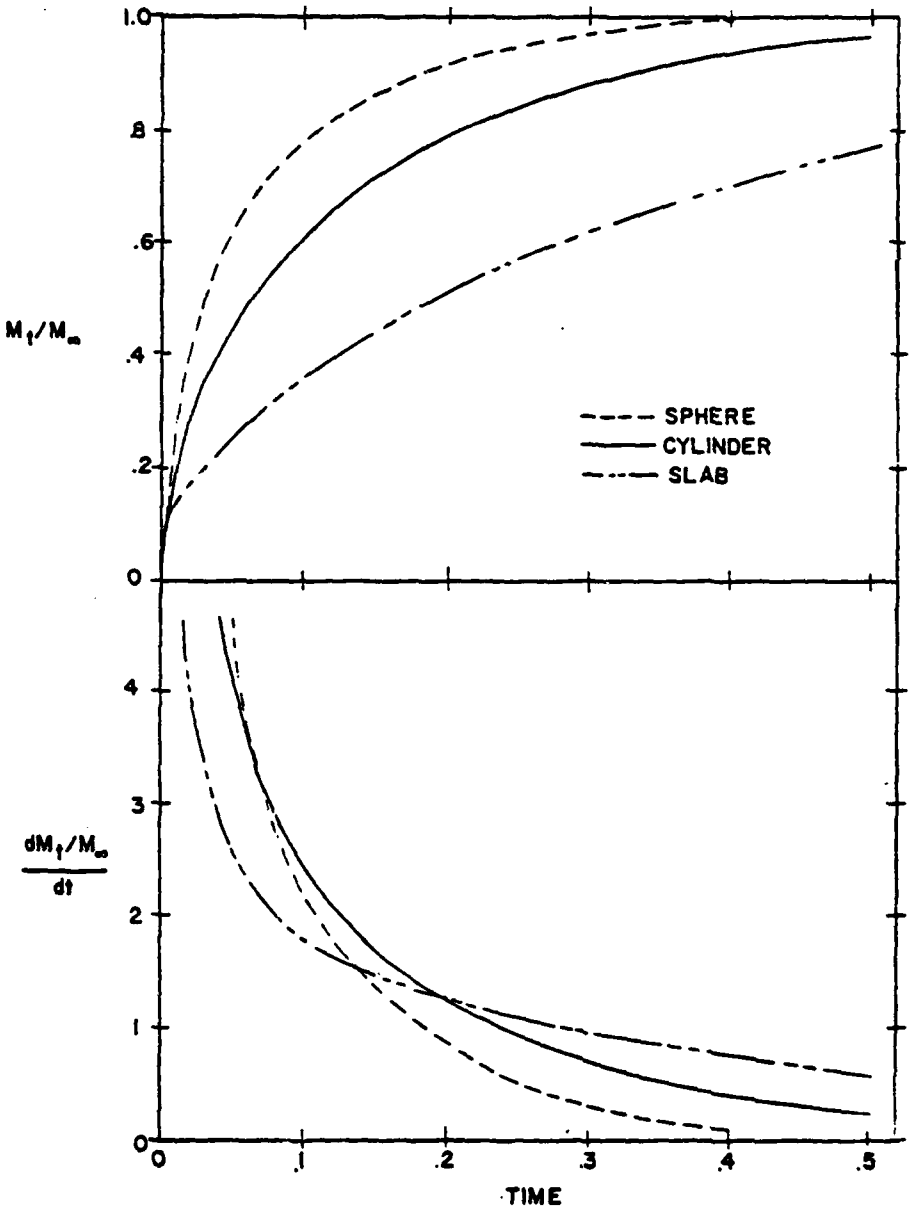


Figure 4 Fractional release and release rate vs. time for drug dissolved in a slab, cylinder, and sphere. (d/l^2 or $D/r^2 = 1$ from Baker and Lonsdale, 1974).

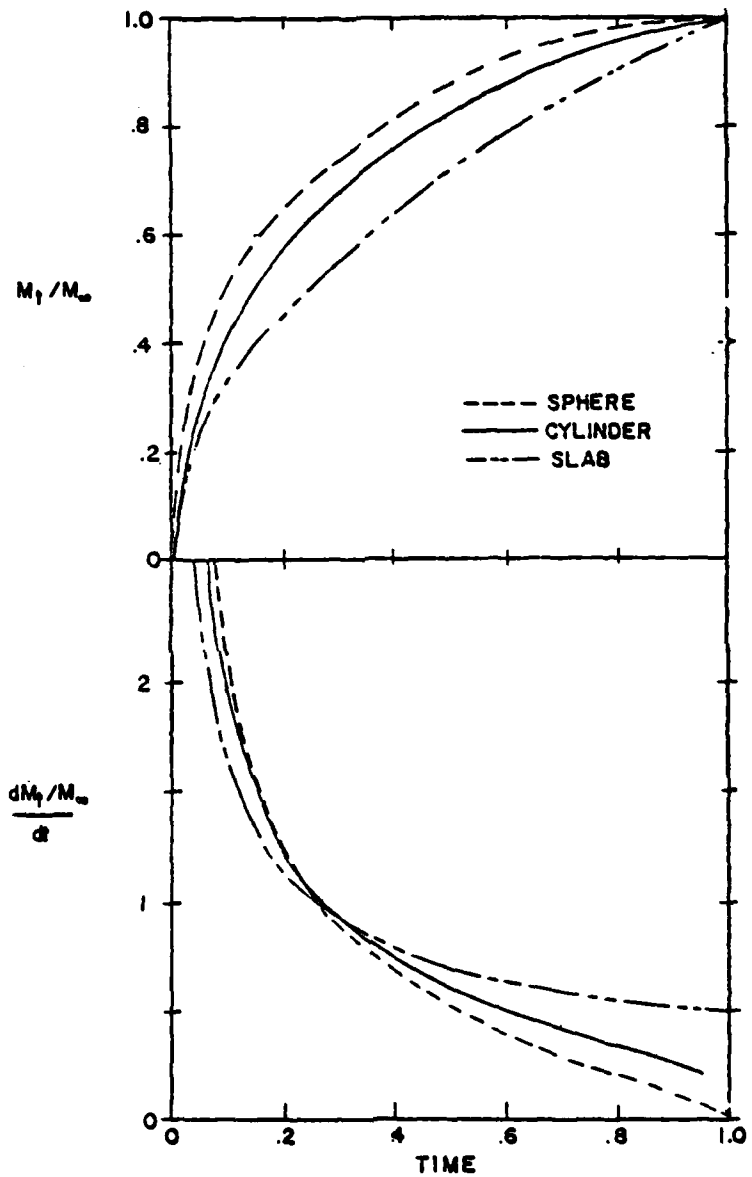
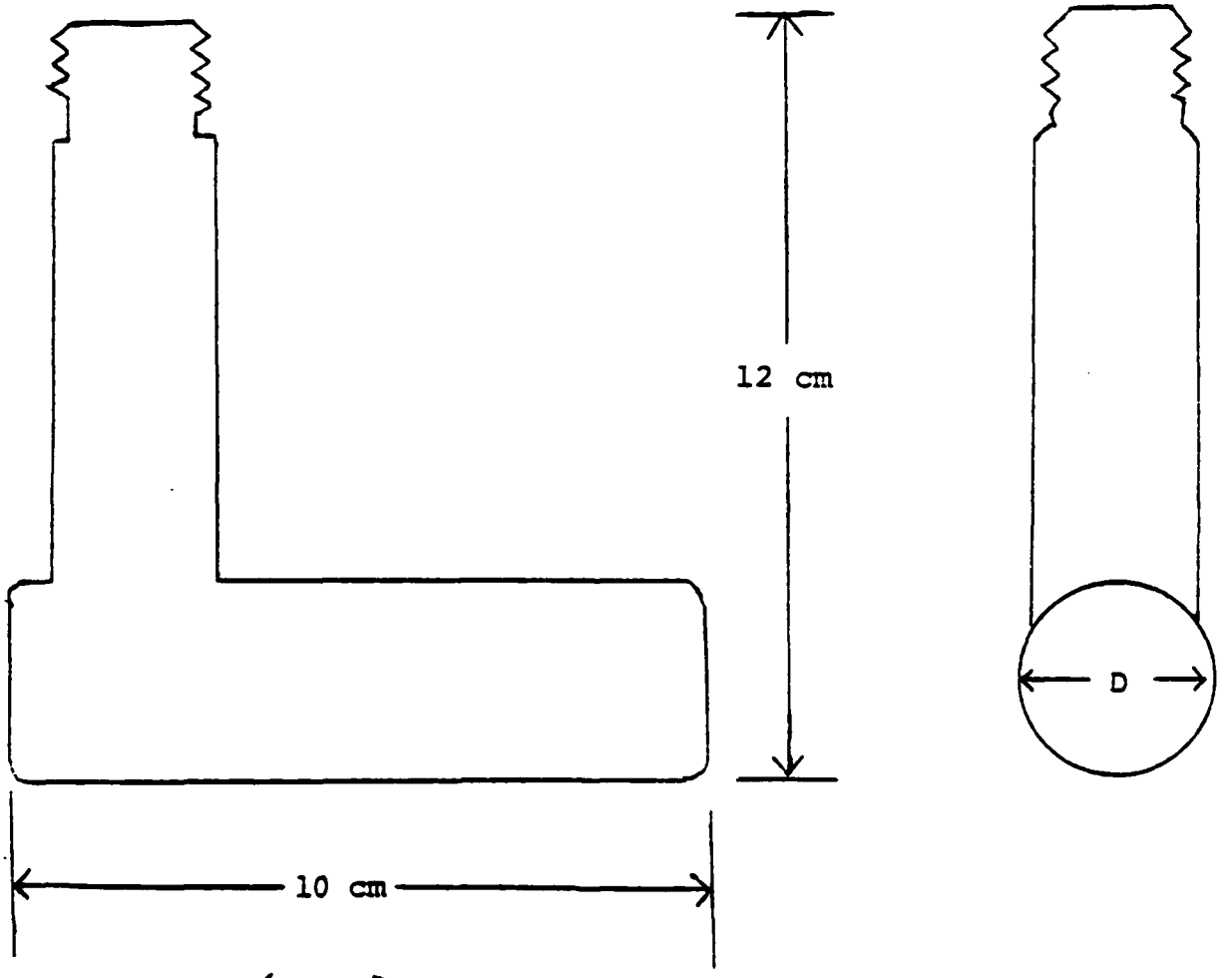


Figure 5 Theoretical fractional release and release rate vs. time for a dispersed drug in a slab, cylinder, and sphere (from Baker and Lonsdale, 1974).

FIGURE 6

Diagram of Diffusion Cell



Inside Diameter "D" = 2.8 - 3.0 cm

Iodine is quite insoluble in water, but is readily complexed by many components of blood and tissue. To eliminate concentration polarization in the in vitro diffusion test, potassium iodide (4.15 g/l) was added to the buffer in the diffusion cells.

Etidocaine samples were acidified after removal from the diffusion cells, since the assay which was recommended by Astra personnel included this step.

Iodine samples were titrated with 0.01 N sodium thiosulfate. A starch endpoint was used for diffusion samples. Assays were performed by dissolving the sample in methylene chloride, adding water, and titrating to the colorless methylene chloride endpoint.

All other diffusion samples were measured as they came from the diffusion cells. Assays of the composites were performed by extraction of the drug into the aqueous layer from a methylene chloride solution of the composite.

Calculations were performed using a Hewlett Packard 9825A computer, and results printed on an HP 9871A printer. Standard curves for most drugs were used to develop a least-squares equation for absorbance versus weight of drug. This data is presented in Table II. Absorbance diffusion values (triplicates) and assay values were entered and percent release was calculated and plotted. Epinephrine and iodine data was reduced manually because of differences in the calculation methods for these drugs (see below).

Table II

Data for Drug Analysis

Drug	Supplier	λ (max) nm	(Abs)[1]=m (μg/ml)+b m	b
Procaine (base)	Sigma	288	0.08245	0.0048
Benzocaine	Sigma	278	0.10195	0.0008
Etidocaine (base)[2]	Astra	271	0.00089	-0.0102
CPC	Hexcel	259	0.01156	-0.0015
Hydrocortisone	Sigma	242	0.04085	0.0013
Epinephrine	Sigma	292	0.00120	0.0000

[1] Absorbance in pH 7.4 phosphate buffer at λ max.

[2] Assayed in acid form; λ, m and b for hydrochloride.

C. DRUG RELEASE RESULTS

The summary of the diffusion results is shown in Table III. The data from the spectral analyses is shown in Figures 7-11 .

1. Procaine

The results of procaine diffusion experiments are shown in Figure 7 . The release of procaine from the high molecular weight poly-L(-)lactide was in the desired range for timed release of an anesthetic. As expected, the powder released drug more rapidly than the film (77.6% vs 8.0% in one hour). The non-woven fabric material released at a rate similar to that of the film (8.8% in one hour and 40.6% in one day). Since the samples are totally submerged and agitated at 37°C, the release in a wound dressing application might be considerably slower.

The low molecular weight poly-L(-)lactide did not have sufficient cohesive strength to be used as films or fabrics. The release of procaine from the powder was similar to release from the composite powder which was made with the higher molecular weight polymer.

The poly-DL-lactide material, which formed as an extremely porous film or fiber network, was very slow to release procaine. This formulation would probably not be useful as a wound dressing.

The copolymer was insoluble in methylene chloride, and therefore could not be used to form non-woven fabric by the standard technique. The film material released procaine in a range of probable interest. The powder released most of the available drug within one hour.

2. Benzocaine

Benzocaine-polymer composites were somewhat similar to the corresponding procaine-polymer composites. The high and low molecular weight poly-L(-)lactide composites released benzocaine more slowly than they released the more hydrophilic procaine.

The network formed by evaporation of solvent from the poly-DL-lactide-benzocaine system released drug more rapidly than the procaine system. However, this release is still comparatively slow.

The copolymer-benzocaine systems again release the drug more slowly than the corresponding procaine systems.

3. Etidocaine

Etidocaine ($C_{17}H_{28}N_2O$) is a hydrophilic drug which is larger

Table III

PERCENT RELEASE OF DRUG FROM POLYMER SYSTEMS

TIME (hrs.)		1	24	1	24	1	24	1	24	1	6	1	24	1	24
POLYMER SYSTEM		DRUG													
No.[1]	Type, RSV[5], Form	Procaine 20%		Benzocaine 20%		Etidocaine 20%		Iodine 20%		Epi-[2]nephrine 2%		CPC 2%		Hydrocortisone 2%	
1	L(-), 1.3, fiber	8.8	40.6	2.5	22.6	2.6	3.6	0	0	-		5.6	5.6	4.8	6.9
2	L(-), 1.3, film	8.0	51.6	4.3	22.7	7.6	37.1	32	32	34.5	39.1	7.1	11.4	0.9	2.7
3	L(-), 1.3, powder	77.6	93.6	26.9	77.1	9.0	59.2	31	31	-		18.3	32.9	11.4	22.1
4	L(-), 0.3, powder	82.1	93.0	45.2	87.3	14.3	17.8	84	84	>100 [4]	>100	8.1	15.4	21.9	38.9
5	DL, 0.3, network	1.4	7.1	3.2	18.6	0	0	6.5	8.2	20.3	21.3	10.2	13.6	3.3	9.8
6	L/G[6], 0.5, film	40.7	75.1	6.1	22.6	6.5	18.6	1.2	2.8	12.7	15.9	13.3	28.7	7.5	59.6
7	L/G[6], 0.5, powder	85.7	88.2	38.5	69.4	>100	>100	2	2	-		56.6[3]	77.2	17.5[3]	25.8

[1] Number used for graphs.

[2] Corrected for decomposition.

[3] Single sample data, insufficient material for triplicates.

[4] Assay value was low (0.53%, 108% release in 1 hour).

[5] Reduced Specific Viscosity

[6] Polylactide-co-glycolide

Figure 7 Procaine Release from Polymer Composites

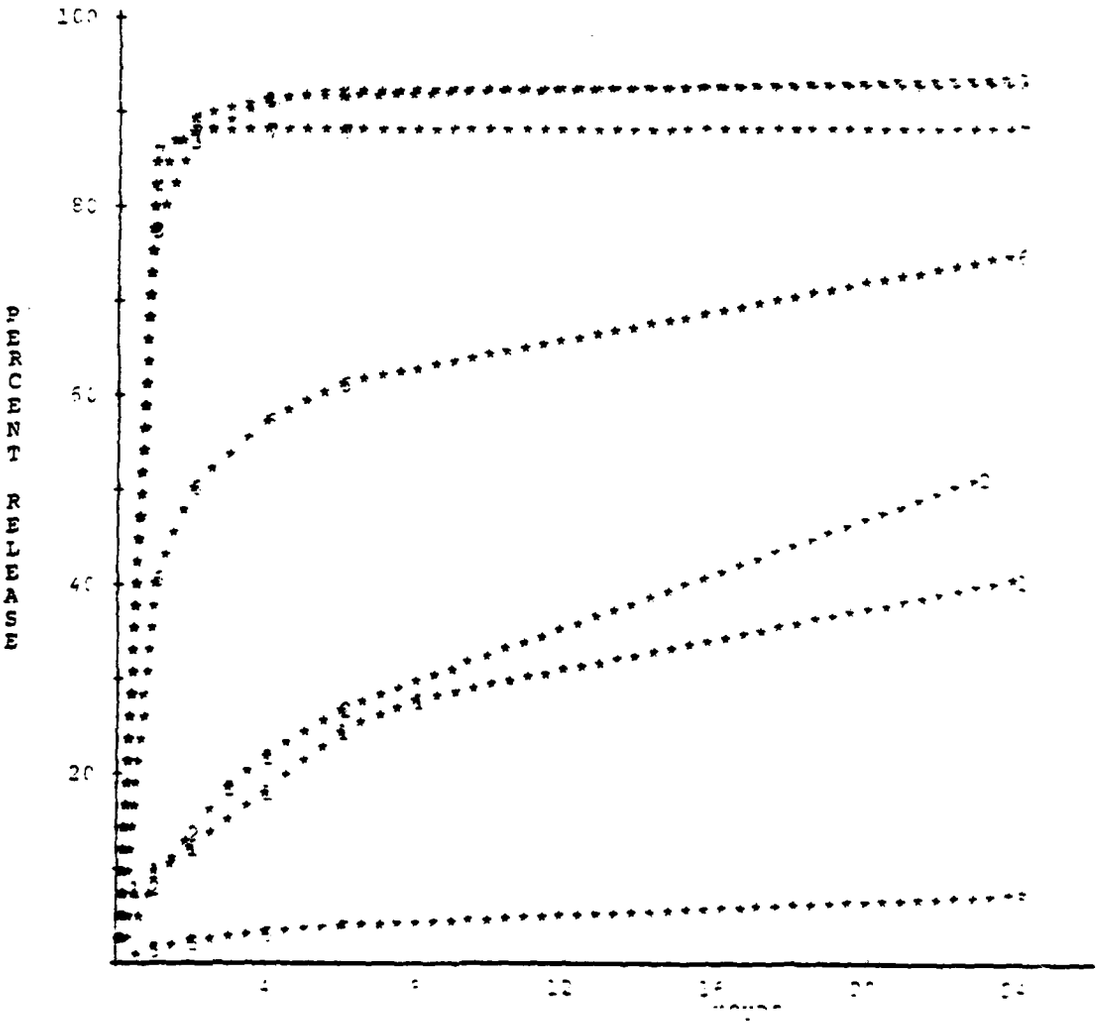


Figure 8 Benzocaine Release from Polymer Composites

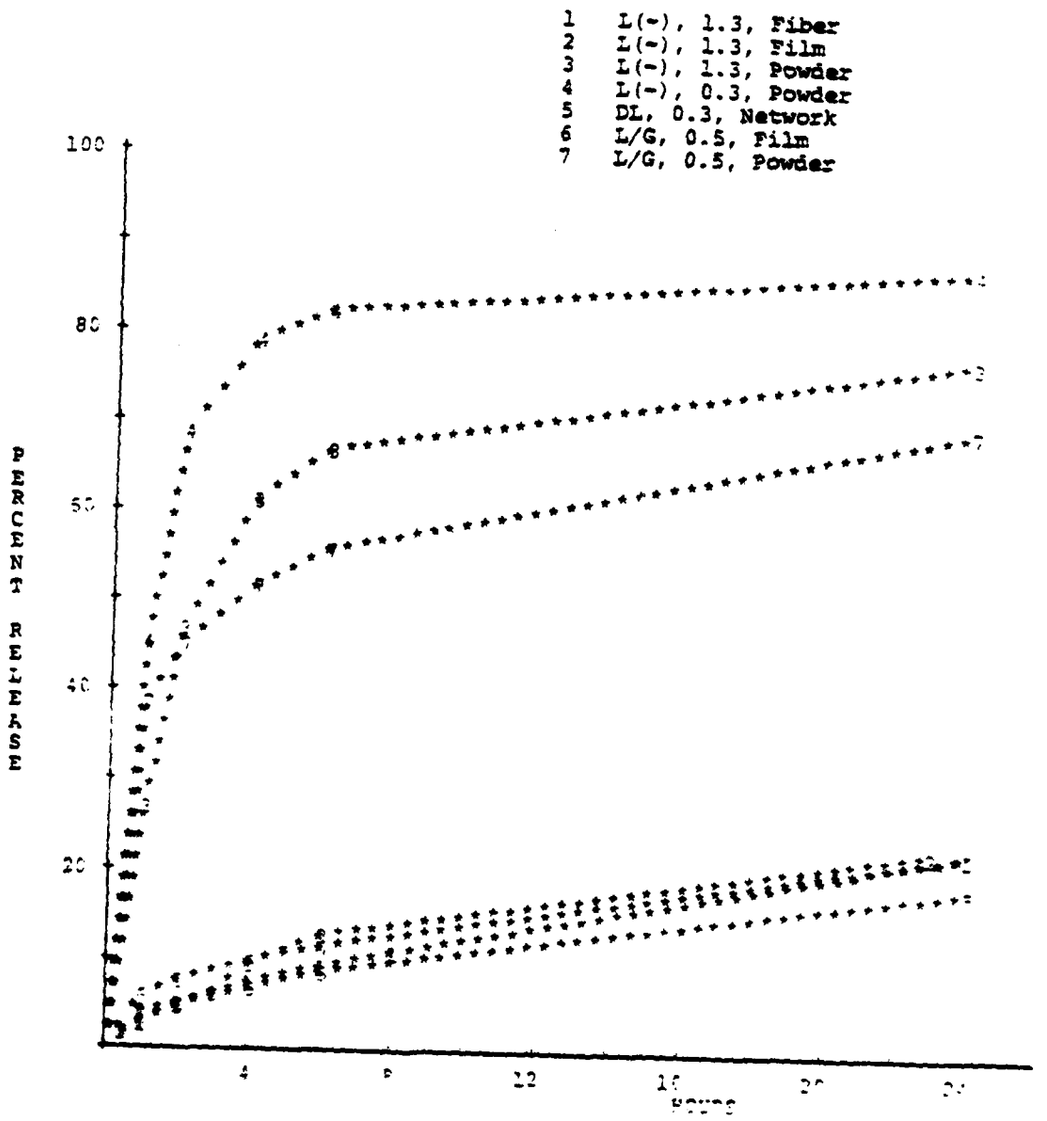


Figure 9 Etidocaine Release from Polymer Composites

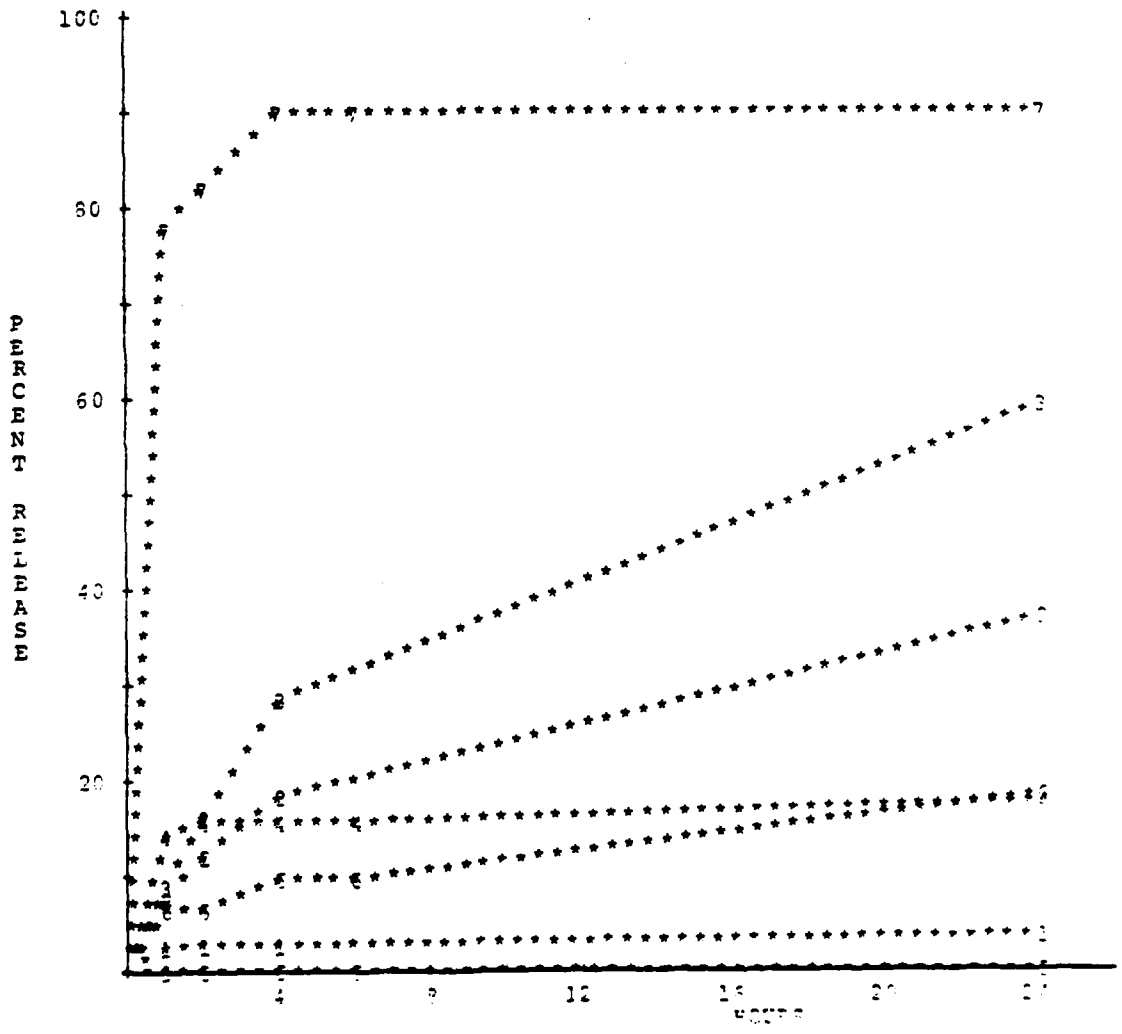


Figure 10 Cetyl Pyridinium Chloride Release from Polymer Composites

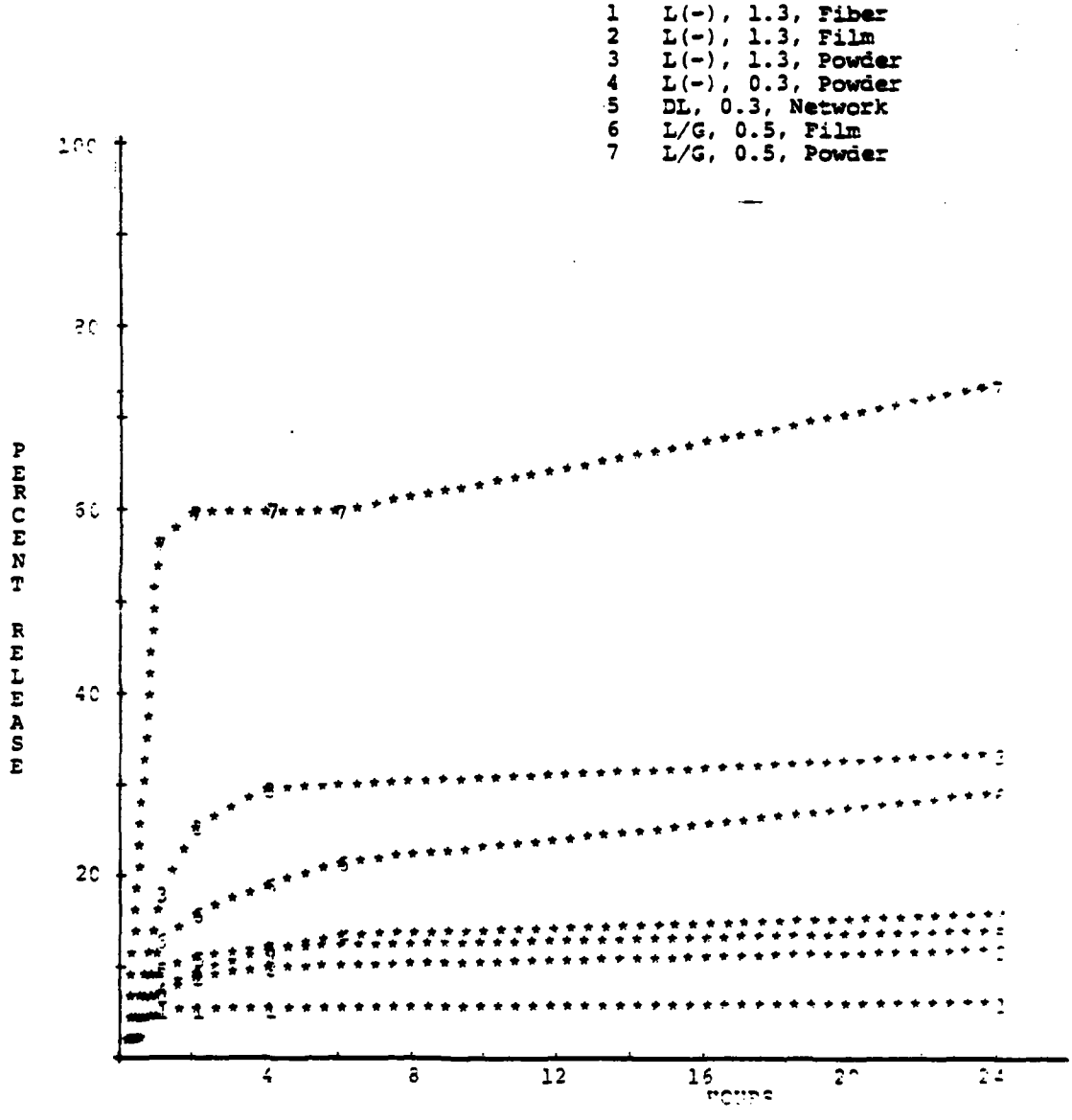
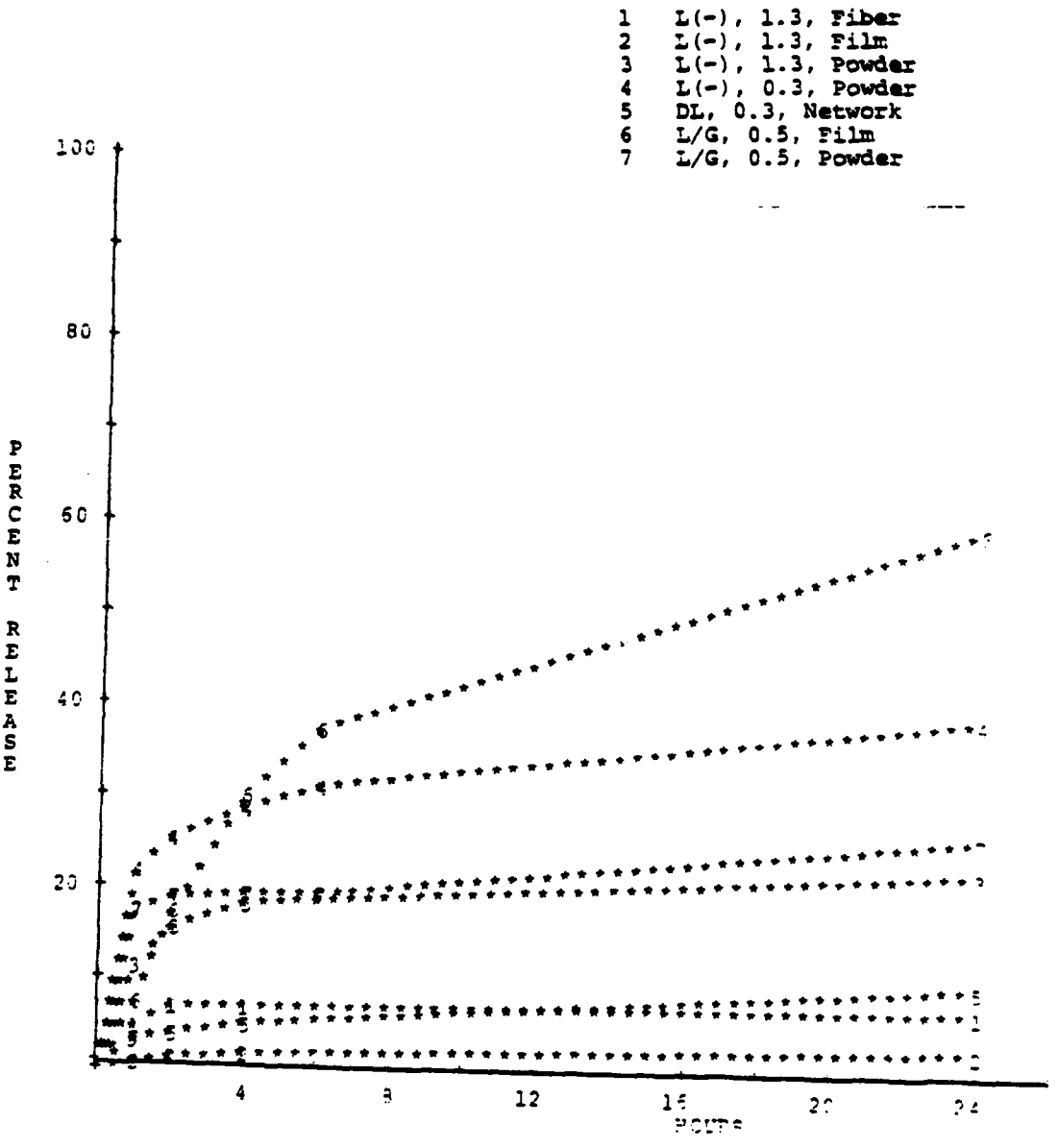


Figure 11 Hydrocortisone Release from Polymer Composites



and more stearically hindered than procaine ($C_{13}H_{20}N_2O_2$). Etidocaine is also structurally similar to lidocaine ($C_{14}H_{22}N_2O$), but slightly more stearically hindered. Etidocaine release should therefore be similar, but slower than procaine release.

As expected, etidocaine release from poly-L(-)lactide composites was slow. Release from the high molecular weight powder was surprisingly constant, and was in the desired range. Unfortunately, laboratory set-up problems prevented 6-hour data being taken on several of these samples.

No release of etidocaine from the poly-DL-lactide composite could be observed. Some release might be observed as the wound dressing biodegrades, but this is likely to be too slow for the wound dressing application.

Release of etidocaine from the copolymer film was slow, but release was much more rapid from the powder which was comminuted from the film sample. An error on assay or a sample weight caused the etidocaine powder values to exceed 100%. Relative values are plotted in Figure 9 , and the release is rapid.

4. Iodine

A 2.5% iodine and 10% polymer solution could be prepared in methylene chloride and dioxane. However, sublimation of iodine resulted in low assay values for iodine, especially from the dioxane system. Loss of iodine also occurred from the final solid composites, even when stored in separate polyethylene bags. For the copolymer film only 25% of the added iodine was found in the sample at the time of analysis. Less than one percent of the original iodine was released to the KI-buffer solution. About 65% of the added iodine was found in the poly-DL-lactide sample. The poly-L(-)lactide-iodine samples were the first to be prepared and were not immediately isolated. Less than 50% of the iodine was available when these were assayed.

In addition to the problem of the vapor release of iodine, most of the samples that did release iodine to the KI solution released it immediately. The use of an iodine complexer, such as povidone, might therefore be useful in these composites.

5. Epinephrine

Epinephrine was also very labile, and its decomposition products had high absorbance at the wavelength for epinephrine anaylsis. Epinephrine decomposition is catalysed by many factors, including light, especially untraviolet radiation. Due to the decomposition and the physiological effects of this quantity of epinephrine (2% in polymer), non-woven fabric was

not prepared. One powder was prepared, carefully. However, the assay value was low (0.53%) and the sample used for release testing released most of its drug within one hour (108% of the assay value).

Release was studied over a 24 hour time period. However, decomposition precluded analysis of the 24 hour data points. A solution of epinephrine was measured as a function of time under standard conditions of the release test, and all analyses were performed one hour after the sample was taken. Data at 4 and 6 hours was then corrected for the amount of decomposition, assuming that all of the epinephrine was in solution for one additional hour.

Based on these corrected values, most of the epinephrine is released very rapidly. This may be the release required for hemostatic action. The utility as a vasoconstrictor in wound dressing is questionable, and the duffusion analysis indicates it is unlikely tc be improved by incorporation into the polymer composite.

6. Cetylpyridinium Chloride

Cetylpyridinium chloride (CPC) was only slightly soluble in methylene chloride or dioxane. Hence the polymer-drug composites were heterogeneous, and somewhat non-uniform. Delayed release of this bacteriostat was evident from many of the composite systems. For example, the poly-L(-)lactide powder of R.S.V. = 1.3 dl/g released 18% of the CPC in one hour and 23% in one day. Other quarternary ammonium salts might be expected to exhibit similar release patterns.

Assay values were close to the expected 2% value. Hence considerable CPC was apparently never released from most of these composites. This was rather unexpected, based on previous coacervation systems. Again the non-woven fabric system released very little drug.

7. Hydrocortisone

Hydrocortisone was only slightly more soluble than CPC in the methylene chloride and dioxane and the final samples were usually inhomogeneous. As expected from Abcor progesterone work (Contract No. NO1-HD-3-2738), the steriod is released slowly from polylactide systems.

Films and non-woven fabrics of the high molecular weight poly-L(-)lactide released hydrocortisone too slowly. The drug was also slowly released from the poly-DL-lactide porous film. Excellent release characteristics were shown by the three copolymer films (7.5% in one hour and 60% in one day). It is surprising the powdered sample did not display similar or more rapid release. This sample was very difficult to obtain and the assay value or weight may be in error.

It is expected that other steroidal antiinflammatory agents will release similarly. Also faster release would be expected from higher drug loadings.

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VI. APPENDIX

Letter from Merck, Sharp and Dohme

Letter from Warner-Lambert

MSD
MERCK
SHARP&
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DIVISION OF MERCK & CO., INC., WEST POINT, PENNSYLVANIA 19486 • TELEPHONE (215) 699-5311

June 11, 1979

David L. Williams, Ph.D.
Program Manager
ABCOR, INC.
850 Main Street
Wilmington, MA. 01887

Dear Mr. Williams:

Thank you for your letter of May 23, 1979.

As you may know, used topically or systemically, DECADRON (Dexamethasone, MSD) is an excellent anti-inflammatory agent. Its anti-inflammatory affect is approximately 25 times that of hydrocortisone and it has no, or almost no, mineralocorticoid effect.

Any topically used corticosteroid can be absorbed through the skin and cause systemic side effects. If used in suffient doses, for a long enough period of time, or under occlusion, the absorption of corticosteroid may actually cause adrenal suppression and result in adrenal insufficiency. Dexamethasone is thought to be better absorbed into the skin than is hydrocortisone. The absorption of DECADRON is less than that of triamcinolone and less than that of betamethasone and fluocinonide; (Sutton et al., "Vasoconstrictor Potency of Corticoids: Intradermal Injection," The Journal of Investigative Dermatology, Volume 57, No. 6, 371-376, 1971).

Not knowing the details of your study or the medical information, or the individuals involved, I am not in a position to recommend our product for use in your protocol. I am, however, providing product information regarding DECADRON for your convenience and your review.

Thank you for your inquiry. If we can be of any further assistance to you in the future, please feel free to contact us.

Sincerely,

Frank M. Krakowski, M.D.
Professional Information

mb

Enclosure

Warner-Lambert COMPANY
Pharmaceutical Division
Parke-Davis Warner/Chilcott Texas Pharmacal

June 18, 1979

David L. Williams, Ph.D.
Program Manager
Abcor, Inc.
850 Main Street
Wilmington, MA 01887

Dear Doctor Williams:

Thank you for your recent letter telling us of your research in wound dressings.

Betamethasone benzoate is an excellent topical anti-inflammatory agent. With betamethasone benzoate, the relative anti-inflammatory/sodium retention ratio should improve.

We have not done clinical trials combining antibiotics or antiseptic agents with the betamethasone benzoate.

As with any potent fluorinated topical corticosteroid preparation, betamethasone benzoate also reduces capillary permeability, vasoconstricts, inhibits new capillary growths, reduces phagocytosis of polys and histiocytes, and inhibits fibroblasts and ultimately scar tissue formation. These effects, coupled with the possibility of epidermal and dermal atrophy, as well as the impeded wound healing, seem to make the fluorinated corticosteroids less than ideal.

If you can give us more specific details as to the type of wounds, type of dressings etc., we may be able to give you more specific answers.

Doctor Williams, thank you for your interest in our dermatologic products.

Sincerely,

Frank W. Deanovic, M.D.
Medical Director of Dermatologics

FWD:hs

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