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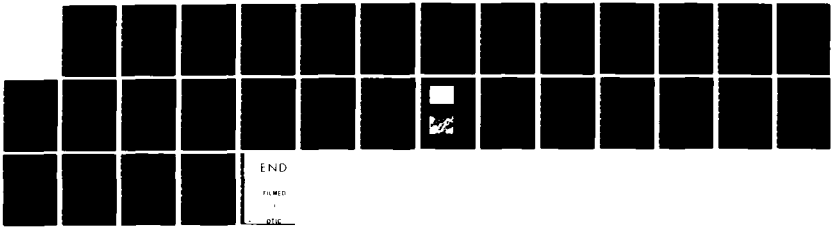

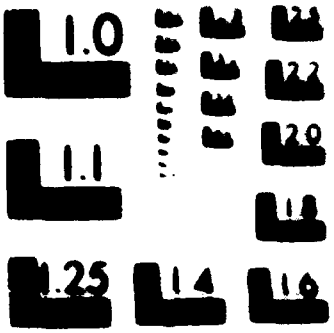
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# Research and Development of Wound Dressing in Maxillofacial Trauma

Annual Summary Report

David L. Williams, Ph.D.
James M. Kerrigan, B.S.

April 1981

Supported by

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

Contract No. DAMD17-80-C-0091

Biotek, Inc
Woburn, Massachusetts 01801

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Three kilograms of poly-L(-)lactide have been synthesized for this contract and for Contract No. DAMD 17-80-C-0110. This polymer has a viscosity [illegible] of 1.19 dl/g, a molecular weight ($MW_w$) of 45,700 and a polydispersity [illegible]. Material from a previous contract was used for preliminary experiments.

Avitene mat has been obtained from FMC which can be used as a collection element for the non-woven fabric. Povidone iodine [illegible] is insoluble in methylene chloride. Other grades [illegible]

D [illegible] 73

and also more readily cleared by the kidneys. However, a mixed solvent is required for material preparation.

Powders of polymer with lidocaine (HCl), etidocaine (HCl), benzocaine, and PVP-$I_2$ have been prepared using a hammer mill and dry ice. All composites contained 20% drug before and after comminution. Small particle sizes of powder containing the anesthetics released the drug rapidly. A 600-425 μm fraction containing 20% etidocaine released 20% of the drug in one hour, 48% in six hours, and 70% in 24 hours. Modifications of drug loading and drug form (e.g. free base, sulfate) are being considered.

PVP-$I_2$ is stable in the powder form, and 10% of the available iodine is found in the diffusion medium after one hour. However, a reaction occurs which removed iodine faster than it is released after the one hour measurement. This problem is under investigation.

Spraying a non-woven fabric of polymer and 20% lidocaine (HCl) caused corrosion of a copper tube. The equipment now has a spray gun (nickel plated), fluorocarbon gaskets, and glass and polyethylene connections. Fabric can now be produced; however, lidocaine diffusion is rapid from the present sample.

Samples of powder of each drug are being stored under six different conditions for stability studies.

TABLE OF CONTENTS


| | | Page |
|---|---|---|
| I | SUMMARY | 4 |
| II | ACCOMPLISHMENTS | 5 |
| | A Drug Materials | 5 |
| | 1 Povidone-Iodine | 5 |
| | 2 Incorporation of Avitene® into Fiber Matrix | 6 |
| | B Polymer Preparation | 7 |
| | C Fiber Mat Preparation | 12 |
| | D Powder Preparation | 16 |
| | E Drug Release Studies | 22 |
| | 1 Method of Measurement | 22 |
| | 2 Powder Assays | 22 |
| | 3 Powder Release Studies | 23 |
| | 3 Fabric Release Studies | 26 |
| | F Sample Storage | 28 |
| | REFERENCES | 28 |

## LIST OF TABLES


| | | Page |
|---|---|---|
| Table I | Polymers Prepared for Combined Program | 9 |
| Table II | Polymer Molecular Weight Distribution | 11 |
| Table III | Engineering Data on Spraying Systems Nozzles | 13 |
| Table IV | Summary of Preliminary Spraying Runs with 70:74 Polymer | 15 |
| Table V | Fabric Preparation Using 20% [illegible] in Polymer | [illegible] |
| Table VI | Percent of Powder in Various Size Fractions | 21 |
| Table VII | Percent Diffusion of Drug in One Hour or One Day | 24 |
| Table VII | Sample Storage Conditions | [illegible] |


## LIST OF FIGURES


| | | |
|---|---|---|
| Figure 1 | Photomicrograph of Non-Woven Fabric Containing [illegible] Lidocaine-HCl | 18 |
| Figure 2 | Sample of Non-Woven Fabric Shown in Figure 1 | 19 |
| Figure 3 | Lidocaine Release [illegible] | [illegible] |

# I. SUMMARY

Three kilograms of poly-L(-)lactide have been synthesized for this contract and for Contract No. DAMD 17-80-C-0110. This polymer has a viscosity (R.S.V.) of 1.19 dl/g, a molecular weight ($MW_w$) of 45,700 and a polydispersity of 2.14. Material from a previous contract was used for preliminary experiments.

Avitone mat has been obtained from FMC which can be used as a collection element for the non-woven fabric. Povidone-iodine ($PVP-I_2$) from Napp Co is insoluble in methylene chloride. Other grades from BASF are more soluble and also more readily cleared by the kidneys. However, a mixed solvent is required for material preparation.

Powders of polymer with lidocaine (HCl), etidocaine (HCl), benzocaine, and $PVP-I_2$ have been prepared using a hammer mill and dry ice. All composites contained 20% drug before and after comminution. Small particle sizes of powder containing the anesthetics released the drug rapidly. A 600-425 μm fraction containing 20% etidocaine released 20% of the drug in one hour, 48% in six hours, and 70% in 24 hours. Modifications of drug loading and drug form (e.g. free base, sulfate) are being considered.

$PVP-I_2$ is stable in the powder form, and 10% of the available iodine is found in the diffusion medium after one hour. However, a reaction occurs which removes iodine faster than it is released after the one hour measurement. This problem is under investigation.

Spraying a non-woven fabric of polymer and 20% lidocaine (HCl) caused corrosion of a copper tube. The equipment now has a spray gun (nickel plated), flurorocarbon gaskets, and glass and polyethylene connections. Fabric can now be produced, however, lidocaine diffusion is rapid from the present sample.

Samples of powder of each drug are being stored under six different conditions for stability studies.

## II. ACCOMPLISHMENTS

### A. Drug Materials

The selection of drugs and polymer were based on the result of the screening of the previous contract. However, povidone-iodine was added to replace iodine, and collagen (Avitene®) replaces gelatin (Gelfoam®) as the hemostatic agent. Slow release of the hemostatic agent is neither required nor possible. Slow release of active iodine could be advantageous, if the wound remains open to infection. Slow release of the anesthetic is highly desirable.

#### 1. Povidone-Iodine

The poly-L(-)lactide is soluble in methylene chloride and dioxane. Methylene chloride has been used in the previous contract for casting films and preparing non-woven fabrics. Iodine is soluble in methylene chloride, as is polyvinylpyrrolidone. However, the povidone-iodine complex is insoluble. This material was obtained from Napp Chemical Company, but they have an exclusive arrangement with GAF for their supply. Only one grade of PVP-$I_2$ is available, although several molecular weights of PVP are available through GAF.

Several alternative suppliers of PVP-$I_2$ were contacted. Our first choice would be for low molecular weight PVP, secondarily, we could use a less iodinated material. Schenck, Simak, and Haedicke (1979) describe the povidone-iodine binding as an $H^+ - I_3^-$ complex. Several low molecular weight complexes were also made by this BASF group.

A second possibility is to use a mixed solvent for preparation of poly lactide - PVP-$I_2$ materials. Methyl alcohol appeared to be the most probable second solvent for the drug and the polymer. A co-solvent for 10% polymer and 2% drug was needed. Therefore, a 15% polymer solution in methylene chloride was titrated with methanol and a 10% PVP-$I_2$ solution in methanol was titrated with methylene chloride. Considerable overlap exists and only a small quantity of methanol is required for PVP-$I_2$ solubility.

Letters were sent to nine suppliers of PVP-$I_2$. All of these suppliers are not necessarily manufacturers of the product. Samples were requested which could be tested for solubility in methylene chloride. A BASF Aktiengesellschaft sample (683-0493 Type 30/06) was received which had a greater solubility than the Rapp sample. However, it was significantly less than 2% soluble, which was our goal. Thus methanol was added to make a mixed solvent for particle composites of polymer and PVP-$I_2$. Very recently a PVP-$I_2$, Type 17/12 was received from BASF. This material complies with the Defense Medical Purchase Description (1/4/72). It is a low molecular weight material. This also conforms to the FDA concern on large wounds, only PVP-$I_2$ should be used of which the povidone portion can be eliminated from the body after possible resorption (BASF, 1980). The FDA considers this limit to be a molecular weight of 36,000. This is exceeded by less than 5% of the 17/12 material and about 50% of the standard K30 material. Based on this information we plan to use the BASF Type 17/12 for all future work. However, the material is also less than 2% soluble in methylene chloride.

In studying the literature on povidone-iodine (Schenck, Simak, and Haedicke, 1979; Noel and Sabelle, 1961) absorption spectra were found. Therefore, an analysis at 290 nm was attempted for solubility and later drug release studies. Unfortunately Beer's law was not obeyed (absorption proportional to concentration), presumably because the complex dissociates at concentrations useful for spectrophotometry. Therefore, iodine has to be titrated with thiosulfate, as in the previous contract.

2 Incorporation of Avitene® into Fiber Matrix

Avitene is a microfibril collagen which is normally teased and applied with dry forceps. Avicon Corporation was contacted and John Tenery, M.D., states that they have made webs from either alcohol or air suspension of the Avitene fibrils. Aqueous media impair the effectivenss of the collagen. Dr. Tenery graciously sent 24 grams of Avitene for our experiments.

Hugo Stange, Ph.D., was contacted at FMC Corporation. They prepare a non-woven fabric mat using an air-laid device. They normally separate layers with glassine paper. The final product is approximately 1 mm thick, after being compressed about 6-fold. A sample of this material was graciously supplied by Fred Sorrevallo, Ph.D. of FMC.

Use of an FMC product as the collection element for the polylactide-drug non-woven fabric appears to be the method of choice. However, a thinner and less dense Avitene mat would probably be quite adequate. The uncompressed material would also be more likely to collect and hold the polymer-drug fibers. We are using gauze in our present experiments.

B. Polymer Preparation

Poly-L(-)lactide of a reduced viscosity of about [illegible] dl/g has been prepared and used by us for several government contracts. This was the polymer used for powder, film, and fabric preparation on the previous contract DAMD [illegible]. It was also used for the preparation of lidocaine microcapsules by the Wurster process under Contract No. DAMD 17-79-C-9019. Finally, it is the polymer used for much of the steroid encapsulation work performed under Contract No. N01 HE [illegible]. The preparation of this polymer was described in detail in the annual report. The same method was used in the present contract.

The preparation of the polylactide was performed as follows. The lactide dimer was obtained from Boehringer-Ingelheim through Henley and Company. This dimer was purified by repeated recrystallizations from ethyl acetate shortly before use. Reagent Grade solvents were used for all operations. The lactide dimer was heated in a [illegible] bath while stirring the melt, in vacuum, for 30 minutes to remove traces of volatile materials. Dry nitrogen was then introducted to release the vacuum. Next the bath temperature was raised to 180°C. To this mixture was added 0.2 ml of stannous octoate catalyst which is 6% in mineral oil. Within about 15 minutes after the catalyst addition, the polymer mixture reaches a maximum temperature. After about 30 minutes, the reaction is stopped by removing the mixture from the [illegible]

bath, and the polymer is allowed to cool to room temperature. The polymer block is dissolved in methylene chloride and the solution is decanted and treated with three volumes of isopropanol, by slow addition to a stirred solution.

Two kilograms of poly-(L-)lactide which has a reduced specific viscosity (R.S.V.) between 1.0 and 1.5 dl/g are required for this contract. A parallel contract (DAAD 17-80-C-0110) also required an equivalent amount of polymer of the same R.S.V. To improve the characterization and reproducibility of both programs, it was decided to combine the requirements of both programs in one blend of a number of batches of polymer.

Approximately 1,200 grams of poly-(L-)lactide (R.S.V.=1.0 to 1.2 dl/g) was available from a previous contract (DAAD 17-79-C-9020). This material was used for preliminary experiments on both contracts to quantify operating parameters.

Because of the narrow range of the specified R.S.V. and the excessive heat generated in large batches, preparation of this quantity of polymer was a lengthy process. A total of 12 batches (see Table I) of dimer have been polymerized for these two contracts. Four of these were in the right range and eight were not. Five of the eight batches were too high and three were too low. Two of the out-of-range batches were exchanged with a similar project which had two batches which fell within our range but which were out of range for that application.

All six batches of polymer were blended together after dissolving in methylene chloride. A total of 19.3 liters of this polymer solution was precipitated by slow addition of isopropyl alcohol in the ratio of 3 to 1 (57.9 liters IPA). Due to the large volumes this had to be carried out in three batches.

TABLE I

POLYMERS USED FOR COMBINED PROGRAM

| Polymer No. | Starting Grams Dimer | Approximate R.S.V. |
|---|---|---|
| 5-6-6 | 574 | 1.25* |
| 5-6-10 | 649 | 1.02* |
| 5-6-15 | 582 | 0.57 |
| 5-6-18 | 600 | 2.91 |
| 5-6-19 | 400 | 3.0 |
| 5-6-21 | 665 | 1.08* |
| 5-6-23 | 617 | 3.0 |
| 5-6-25 | 637 | 2.23 |
| 5-6-27 | 500 | 0.72 |
| 5-6-29 | 500 | 2.08* |
| 5-6-30 | 500 | 1.57* |
| 5-6-31 | 300 | 0.92 |
| 7-12-2 | 500 | 1.40* |
| 7-12-7 | 500 | 1.29* |
| TOTAL | 7,524 | |

* used in blend (total of 3,386 gm.)

* exchanged with NIH program for last two polymers or [illegible]

After precipitation, the polymer was removed from the [illegible] by vacuum filtration, the pieces were pressed with rubber dam material in the Buchner funnel to remove most of the solvent. The polymer was then placed under vacuum to remove the residual solvent. Due to the low volatility of isopropanol and the large volume of polymer, the drying process took two weeks. When the polymer chunks were sufficiently dry, they were ground in a blender to a uniform size, shaken in a large bag and again placed under vacuum to complete the drying. Three random samples of this final mixture were taken and their viscosities determined in duplicate. The viscosity was found to be 1.9±0.03 dl/g and the total polymer obtained was 3,048 grams which was a 90% yield.

The polymer is presently being stored under argon in the freezer. The polymer was placed in plastic bags into one-gallon cans which are tightly sealed (paint cans). The air was removed by vacuum and replaced by argon, just prior to sealing. As mentioned in the proposal, this procedure has been standardized, but is presumably much more stringent than necessary to prevent polymer degradation.

A sample of polymer was sent to Cambridge Analytical Associates for determination of molecular weight distribution by gel permeation chromatography. Samples were dissolved in hot trichlorobenzene. Duplicate injections were run 12 hours apart to determine whether the high temperature analysis would degrade the polymer. After 12 hours, no evidence of polymer degradation was evident. A series of μ-Styrage columns (10⁶, 10⁵, 10⁴Å) from Waters Associates were used at 45°C. The flow rate was 1.5 ml/min and the change of refractive index was used for detection. The molecular weight determination was made by reference to polystyrene standards.

Data from the chromatograms of the polymer were reduced by standard methods. The results are shown in Table II. The weight average molecular weight of 45,700 is higher than expected for this viscosity of polymer (Kumayser, et al., 1976). However, provided later experiments are repeated with the same technique, any degradation can be quantified.

TABLE II

POLYMER MOLECULAR WEIGHT DISTRIBUTION

| | |
|---|---|
| Sample Poly-(L-)lactide (R.S.V. [illegible] dl/g) | |
| Number Ave. MW $MW_n$ | [illegible],500 |
| Weight Ave. MW $MW_w$ | 45,[illegible]00 |
| $(n_1M_1^2/n_1M_1)$ $MW_z$ | 60,[illegible]00 |
| Polydispersity $MW_w/MW_n$ | [illegible]4 |

C. Fiber Mat Preparation

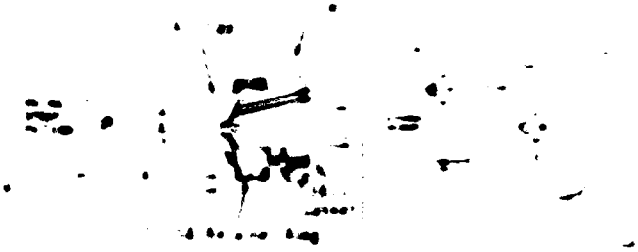
The fiber mat is being prepared in a manner similar to that of the previous contract work. About a 5% weight-to-volume solution of the polymer is prepared using methylene chloride as the solvent. The appropriate amount of drug is added to this system to obtain the appropriate drug/polymer ratio (e.g. 2.0%). This solution is poured into a tank which is connected to the liquid inlet of a Spraying Systems air atomizing nozzle using a piece of tubing.

The air inlet is connected to a tank of inert gas and the gas outlet pressure is set at about 4 psi. The polymer solution is fed into the nozzle body under gravity (e.g., 1 meter head) and fine polymer-drug fibers are formed as the solution leaves the nozzle. The fibers are collected on a piece of surgical gauze.

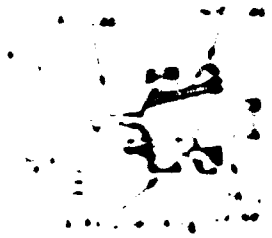
The previous method was reviewed with a representative of Spraying Systems Company. Materials were changed from stainless steel and rubber gaskets to nickel-plated brass and Teflon gaskets. An atomizing gun was obtained to facilitate shut-down. A clean-out needle assembly was included for the gun. Spraying nozzles are comprised of separate fluid and air caps, and all parts are readily interchangeable. Components were purchased for a round spray, as used previously (Set-up 2A) and two flat spray set ups (F1 and F2C). The materials can also be assembled as Set-up 2 (see Table IIB), which had also been used previously. The use of the gun, Teflon gaskets and flat spray head were significant improvements.

The Spraying Systems gun, with appropriate nozzles, was mounted, inverted, on a clamp. A straight 1/8" copper tube, one meter in length was attached to the fluid inlet. On top of this tubing was attached a series of gas pipe reducers. This formed a reservoir to give a constant hydrostatic head for spraying.

## SET UPS FOR [illegible] Round Spray



## SIPHON SPRAY SET UPS FOR [illegible] Flat Spray



It was decided to use Parke-Davis sterile gauze as backing material [illegible] to spray the polymer. This material is held at a fixed distance from the gun nozzle and is attached to an embroidery hoop to keep it taut. Thus air passes through the wound dressing to facilitate drying of the solvent.

A 10% polymer solution in methylene chloride was made with previously synthesized polymer (#70-74) which had a recently measured viscosity (R.S.V.) of 1.18 dl/g. The Spraying Systems atomizing gun (nickel plated brass with teflon gaskets) with various combinations of air caps and fluid caps was tried at various pressures. In all cases the nozzles plugged either immediately or shortly after the spraying started.

The 10% solution was diluted with methylene chloride to 5% and to 2.5%. The 2.5% continued to spray but did not deposit much material on the gauze. The 5% polymer solution was used with various combinations of air caps, fluid caps, air pressure, and distances of gauze from the nozzle. Table [illegible]

Using 5% polymer solution with fluid cap 2850 and air cap 73420 (flat spray setup F1 in catalogue), the nozzle clogged after some collection at [illegible] psi and immediately at 3.75 psi pressure. At 2.5 psi, fiber was collected at 22 cm from the nozzle.

In another combination, fluid cap 2850 was used with air cap 70 (round spray). This setup (2 in the catalogue) was tested at 2.5 and 5 psi at distances of 22, 30, and 38 cm from the nozzle. All runs with the round spray air cap gave fabric that looked like films with varying amounts of shot (Table IV).

Based on the results of the preliminary runs the best fibers were produced with the flat spray air cap No. 73420 and the fluid cap No. 2850 using a 5% polymer solution. These fabrics appear similar to those prepared under the previous contract.

TABLE IV

SUMMARY OF PRELIMINARY SPRAYING RUNS WITH 70-74 POLYMER (5% SOLUTION, FLUID CAP 2050)

| Run | Microscopic Evaluation | Air Cap | Distance From Nozzle Cm | Air Pressure PSI | Comments |
|---|---|---|---|---|---|
| 1 | Films with holes | 70 | 22 | 5 | |
| 2 | Mostly fibers/some shot | 73420 | 22 | 5 | Clogged soon |
| 3 | Mostly shot/some fibers | 73420 | 22 | 2.5 | |
| 4 | A few fibers (little product) | 73420 | 22 | 3.75 | Clogged immediately |
| 5 | Mostly shot/some film | 70 | 30 | 2.5 | |
| 6 | Usual shot and film | 70 | 30 | 5.0 | |
| 7 | Mostly film/some shot | 70 | 38 | 5.0 | |

When the final contract polymer became available, the system was re evaluated using 20% lidocaine (HCl) with 80% polymer. The system was modified to measure air flow rather than tank pressure. Samples are being prepared in a laboratory hood. When the hood is on the air draft pulls air through the fabric and also affects the overall spray pattern.

The results are shown in Table V. In the first series of tests with lidocaine·HCl (101-104), the fabric turned green with time indicating a leaching of the copper. The copper was replaced with polyethylene tubing and a glass (separatory) funnel. The lidocaine (HCl) polymer fabric is now white again. From several of these tests it appears that low polymer (and drug) concentrations produce a low density product. However, this product is primarily discreet particles, similar to snow or whipped cream. High polymer concentrations produce more fibrous material. However, film formation and nozzle plugging can occur. Less film formation occurs as the distance from nozzle to collector increases.

All of the recent samples have been photographed and catalogued. For comparison, photomicrographs of a fibrous (409) and non-fibrous (301) samples are shown in Figure 1. A sample of material (409) is attached as Figure 2. The photographs are deceiving because of the lack of depth of field. Sample 409 has been sent to Col. Tsaknis (USAIDR) for scanning electron microscopy.

D. Powder Preparation

In the previous contract work, powders were prepared by comminution of material prepared as a film, by grinding at liquid nitrogen temperature. Both mortar and pestle and micro-mill apparatus was employed. Since these methods cannot be readily scaled up to common pharmaceutical equipment, different methods were employed in this contract work.

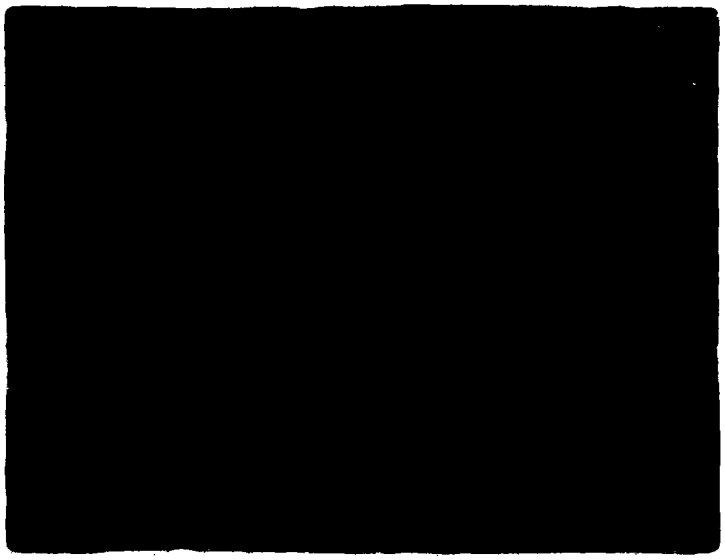
TABLE V

FABRIC PREPARATION USING 20% LIDOCAINE HCl IN POLYMER

(Fluid Cap 2850, Air Cap 70)

| Test No. | Charge ml | Charge % Polymer | Soln Head m | Gas Flow SCFH | Nozzle to Collector cm | Hood Off - On + | Spray Continuous + Intermittent - Stationary o Moving - | |
|---|---|---|---|---|---|---|---|---|
| 101 | 30 | 5 | 1.1 | 50 | 30 | | + | o |
| 102 | 30 | 5 | 1.1 | 20 | 30 | - | + | - |
| 103 | * | 5 | 1.1 | 30 | 45 | - | + | - |
| 104 | 50 | 5 | 1.1 | 50 | 45 | - | + | - |
| 201 | 50 | 5 | 1.1 | 25 | 33 | + | + | - |
| 202 | 30 | 5 | 1.1 | 35 | 47 | + | + | - |
| 203 | 30 | 5 | 1.1 | 30 | 58 | + | + | - |
| 204 | * | 5 | 1.1 | 20 | 40 | + | + | - |
| 205 | 30 | 5 | 1.1 | 10 | 40 | + | + | |
| 206 | 30 | 5 | 1.1 | 15 | 50 | + | + | |
| 207 | 30 | 5 | 1.1 | 20 | 55 | - | + | - |
| 208 | 30 | 5 | 1.1 | 20 | 40 | - | + | - |
| 209 | 30 | 5 | 1.1 | 20 | 55 | - | + | - |
| 210 | 50 | 2.5 | 1.1 | 20 | 55 | | + | - |
| 211 | 50 | 2.5 | 1.1 | 30 | 40 | - | + | - |
| 301 | 90 | 5 | 1. | 20 | 50 | + | + | - |
| 302 | * | 5 | 1.0 | 40 | 50 | + | + | - |
| 303 | 100 | 2.5 | 1.5 | 40 | 50 | + | + | - |
| 304 | * | 2.5 | 1.5 | 40 | 75 | + | + | - |
| 401 | 50 | 10 | 1.5 | 40 | 38 | + | + | - |
| 402 | * | 10 | 1.5 | 40 | 75 | + | + | - |
| 403 | * | 10 | 1.5 | 40 | 75 | + | + | - |
| 404 | 50 | 10 | 1.5 | 30 | 90 | - | + | - |
| 405 | 50 | 10 | 1.5 | 30 | 90 | + | + | - |
| 406 | 50 | 10 | 1.1 | 30 | 90 | + | + | - |
| 407 | * | 10 | 1.5 | 30 | 45 | + | + | - |
| 408 | * | 10 | 1.5 | 40 | 60 | + | | - |
| 409 | * | 10 | 1.5 | 40 | 75 | + | + | - |

* continuation of same charge



A

Particulate Foam (30)

B

Fibrous Mat (40X)

FIGURE 1 PHOTOMICROGRAPH OF NON-WOVEN FABRIC CONTAINING 20% LIDOCAINE HCl

FIGURE 2 SAMPLE OF NON-WOVEN FABRIC SHOWN IN FIGURE 1B

Since the previous powders which showed good drug delivery had sizes of 50 to 250 microns, it was important to maintain this approximate size distribution. Thus micronization in a fluid energy mill would presumably not be advantageous.

Felmeister (1970) describes the common apparatus and methods of producing powders for the pharmaceutical industry. Of the intermediate pulverizers described, the hammer mill is the most applicable to the present materials. We, therefore, sent samples of films to Dr. S.B. Roy at Massachusetts College of Pharmacy (Boston, MA) for hammer milling under cold conditions. A cooled mill would be most appropriate for large scale production. For small scale production the sample was sent through a standard mill with dry ice.

Solutions of 20 grams of drug and 80 grams of polymer were prepared using 700 ml of methylene chloride. For povidone-iodine 20 grams of Napp povidone-iodine (USP, Lot 9104) was dissolved with 80 grams of polymer, using 800 ml of methylene chloride and 40 ml of methanol. Films were cast into seven flat glass vessels of 400 $cm^2$ area, and hence the average thickness was about 350 $\mu m$. These films were cut with scissors into squares of approximately 5 x 5 mm. These pieces could be fed with the auger into the hammer mill.

A Mikro-Pulverizer C.F. (18,000 RPM, Pulverizing Machinery, Div. Slick Industrial Co., Summit, N.J.) was used. The mill was assembled with the hammer edge of the rotor facing the direction of rotation. A 20 mesh (841 $\mu m$) classifier screen was used at the bottom of the mill. The feed and comminution chamber were pre-cooled with 500 grams of dry ice. Next the sample was sent through the mill, mixed 1 to 10 with dry ice (i.e., 90% $CO_2$). A final charge of 100 grams of dry ice was sent through the mill to increase the yield from the chamber. The mill was dismantled, washed, dried, and re-assembled for each drug run.

The resulting powders were sieved with the Sonic Sifter at BIOTEX and the results are shown in Table VI.

TABLE VI

PERCENT OF POWDER IN VARIOUS SIZE FRACTIONS

(20% drug)

| Size (μm) | Lidocaine | Etidocaine | Benzocaine | Povidone-Iodine |
|---|---|---|---|---|
| > 600 | 17.7 | 9.0 | [illegible] | 11.7 |
| 600-425 | 28.5 | 27.0 | 27.[illegible] | 46.1 |
| 425-300 | 7.0 | 5.5 | 18.8 | 9.9 |
| 300-212 | 9.4 | 10.9 | 13.1 | 7.0 |
| 212-150 | 13.2 | 17.1 | 12.5 | 7.4 |
| 150-106 | 13.6 | 15.1 | 17.0 | 7.5 |
| 106-74 | 3.0 | 12.1 | 4.7 | 3.9 |
| 74-38 | 4.1 | 3.1 | 4.4 | 6.0 |
| < 38 | 0.2 | 0.2 | 0.2 | 0.2 |
| Milling Recovery | 68% | 67% | 89% | 86% |

## E. Drug Release Studies

### 1. Method of Measurement

Drug release is measured in a manner similar to the previous contract work. Ultraviolet absorption is used to measure the amount of anesthetic released and a titration is used to measure the amount of available iodine released from povidine-iodine. A known area of non-woven fabric is cut (17 mm diameter, 2.27 $cm^2$), and the sample is weighed after removing the gauze backing. Powders of various size ranges are weighed out directly. These samples are placed in 44 μm mesh heat-sealed bags. These sample bags are then placed in L-shaped diffusion cells to which 40 ml of pH 7.4 phosphate buffer has been added. Good mixing is assured and the temperature is maintained at 37°C in this system. As in the previous work, solutions are analyzed after 1, 2, 4, 6, and 24 hours of sample contact. Fortunately all of these drugs are quite soluble and relatively stable in this buffer. As in the previous contract work, etidocaine samples are acidified before being measured by ultraviolet absorption. Also, as in the previous contract, iodine is analyzed by titration with sodium thiosulfate, using a starch end point for the diffusion sample.

Standard curves are generated from the pure drugs and a least-square equation is used for determining drug weights. Calculations, involving assay values and sample loss due to etidocaine acidification, are performed by computer. Drug assays are performed in methylene chloride, using a calibration curve in the same solvent.

### 2. Powder Assays

As expected, drug assays of particles were identical to the initial 20% drug loading for the anesthetics. This was true regardless of particle size. For povidone-iodine-polymer particles, some degradation may occur. Instead of 20.0%, 18.7% was recovered using a thiosulfate titration procedure in 50/50 $CH_2Cl_2/CH_3OH$.

3. Powder Release Studies

The drug release results of the first set of milled particles are shown in Table VII. Since most of the available drug was released in the first hour, the data for 2, 4, 6, and 24 hours is practically identical. Hence only the 1 and 24 hour data are tabulated. In this test, using a sample submerged in moving buffer, release is too fast for delayed drug action. Drug release is faster than observed in the previous contract work for etidocaine and benzocaine. Larger size particles will be tested since it is possible that the slow release in the previous work was due to a few large particles in the unsieved powder. In a recent test, the hypothesis was confirmed that larger particles would release drugs significantly more slowly. A sample of 425 to 600 μm powder was studied and the results are shown in Figure 3.

Comparing iodine samples of the previous contract with the present povidone-iodine samples, PVP-$I_2$ is much more stable. Iodine from PVP-$I_2$ is not released to the air, discoloring even the sample containers. PVP-$I_2$ does not appear to react significantly with polylactide during film and powder formation. However, a loss of available iodine during the release studies remains unexplained. An assay titration of the spent particles (after release study) showed no significant residual iodine in the particles.

It may be unnecessary to have a slow release of antiseptic agents such as PVP-$I_2$. Iodine kills bacteria instantly on contact (Bogash, 1956), and PVP-$I_2$ releases active iodine within milliseconds after dissolution (Schlezinger, Mahinka, and Levin, 1979). Once a wound is antiseptic and bandaged, continued release of antiseptic agent may be unnecessary. However, it is important that active iodine be released from the wound dressing. We, therefore, propose studies to measure release of active iodine by addition of soluble starch to the solution (Schlezinger, et al, 1979) and be determination of bacteriocidal effectivess of the wound dressings.

TABLE VII

PERCENT DIFFUSION OF DRUG IN ONE HOUR OR ONE DAY

| Particle Size (μm) | Lidocaine | | Etidocaine | | Benzocaine | | Povidone-Iodine | |
|---|---|---|---|---|---|---|---|---|
| | Hour | Day | Hour | Day | Hour | Day | Hour | Day |
| 300-212 | 67 | 80 | 44 | 75* | 41 | 59 | 10.5 | 10.5 |
| 212-150 | 75 | 79 | 56 | 56 | 32 | 48 | 8.0 | 10.2 |
| 150-106 | 65 | 69 | 49 | 69 | 31 | 48 | 10.7 | 13.1 |
| 106-74 | 69 | 71 | 73 | 76 | 32 | 52 | 9.8 | 9.8 |
| 74-38 | 64 | 71 | 71 | 71 | 30 | 50 | 12.0 | 12.0 |

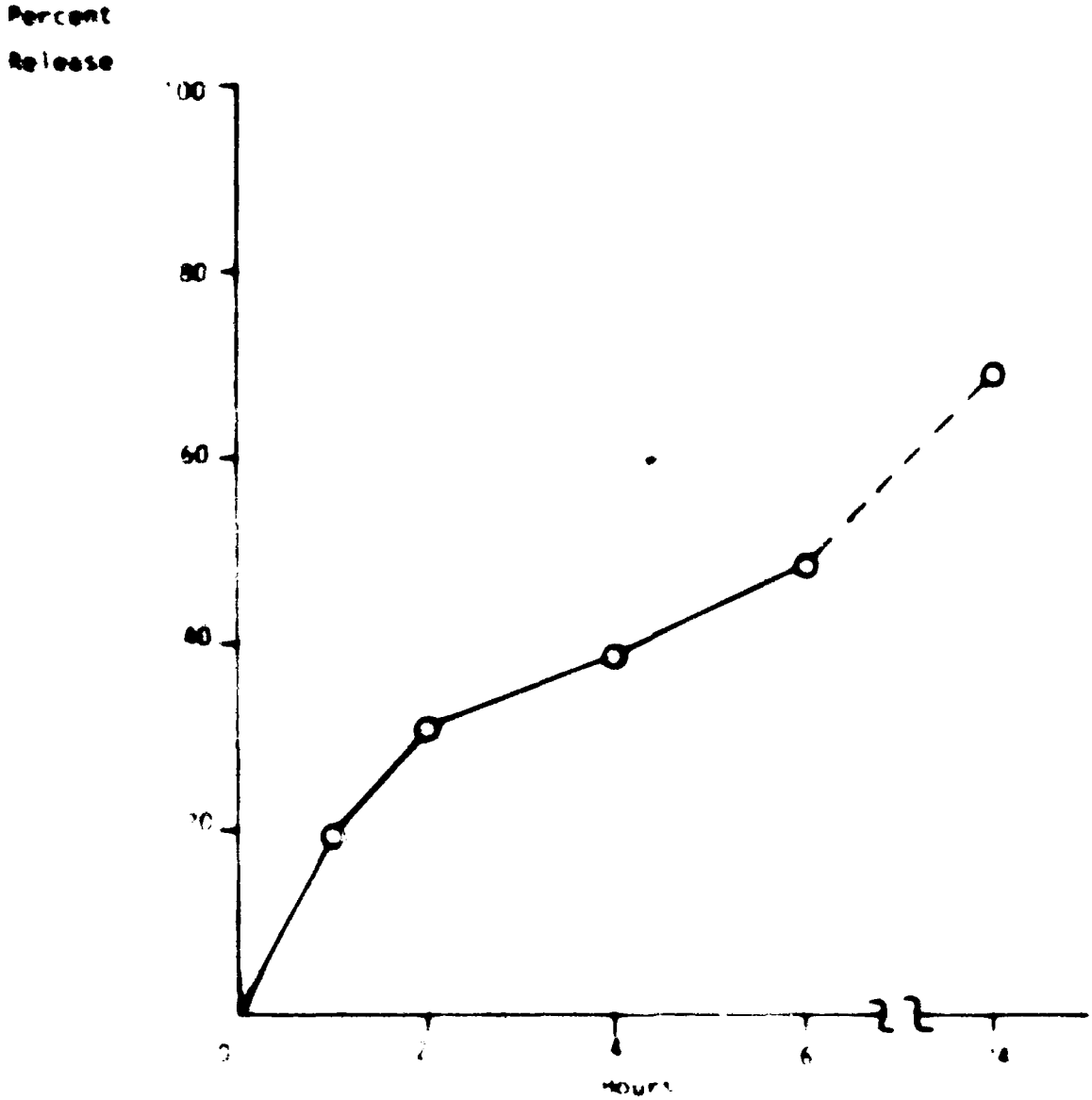



FIGURE [illegible] LIDOCAINE RELEASE FROM [illegible] PART [illegible]

Lidocaine particles were washed with various solutions and dried, in an attempt to eliminate the initial burst of drug release. A 5-minute water rinse was attempted which should dissolve the drug on the outside of the particles. Unfortunately this water rinse removed 82% of the drug. A diffusion analysis on the remainder of the drug was inconclusive. Five minute rinses with 0.1 M NaOH, 0.1 M $Na_2SO_4$ and 0.05 M phosphate buffer (pH 7.4) were performed in an attempt to precipitate the drug on the outside of the particle. The base form of lidocaine and the sulfate and phosphate forms are less soluble than the hydrochloride. Again the water removed most of the drug (78-84%), and an analysis of the remaining drug release was inconclusive. Slower release is more likely to be achieved by preparing new samples which incorporate these less soluble drug forms in the polymer matrix, and/or by preparing samples which have lower drug loadings.

4. Fabric Release Studies

Only preliminary studies have been performed on lidocaine-polymer non-woven fabric. No significant (>1 hour) delayed release was observed.

5. Sample Storage

Particles of 300 to 212 μm of lidocaine, etidocaine, benzocaine, and povidone-iodine have been prepared for storage under the six conditions which were proposed (Table VIII). Two separate containers of each drug are being prepared. One container will be opened at the end of the contract year for assay and release testing. The other container holds twice as much material and will be held for two later analyses. American Can Company has graciously supplied sufficient M-1173 61-0 93004 heat-sealable bags for dessicant storage. Pouches consist of Bartuf Poly/Foil/L.D.P.E. Ambient moisture is achieved in bottles capped with glass wool. Absence of light is achieved with black tape. Temperatures are 40°C (chemical oven), ambient (laboratory), 4°C (refrigerator).

TABLE VIII

SAMPLE STORAGE CONDITIONS

| CONDITION | TEMPERATURE | HUMIDITY | LIGHT |
|---|---|---|---|
| 1 | 40°C | Ambient | None |
| 2 | 40°C | Desiccate | None |
| 3 | Ambient | Ambient | None |
| 4 | Ambient | Ambient | Ambient |
| 5 | 4°C | Ambient | None |
| 6 | 4°C | Desiccate | None |

## III. [illegible]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