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DEVELOPMENT OF A SYNTHETIC POLYMER BURN COVERING.(U)
JAN 78 J B GREGORY, J D GRESSER, D L WISE N00014-73-C-0201
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DYNATECH R/D COMPANY

DEVELOPMENT OF A SYNTHETIC POLYMER BURN COVERING

Final Report on Contract N00014-73-C-0201
Dynatech Report No. 1704

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Sponsored by the Office of Naval Research
Contract Authority N00014-73-C-0201
Task No. NR 207-044/12-02-76(444)

Prepared by:
J.B. Gregory
J.D. Gresser
D.L. Wise

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Prepared for:

Director, Medicine and Dentistry Programs
Biological and Medical Sciences Division
Office of Naval Research
Department of the Navy
800 North Quincy Street
Arlington, Virginia 22217

Date Submitted:
January 17, 1978

a division of DYNATECH CORPORATION

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The objective of the program covered by Contract No. N00014-73-C-0201 is the development of a synthetic polymer burn covering which will reduce dehydration, sepsis, sodium loss, scar formation and mortality of burn patients.

Two approaches were successfully investigated. The first utilizes a solution of poly-ε-caprolactone (PCL) which when applied immediately after

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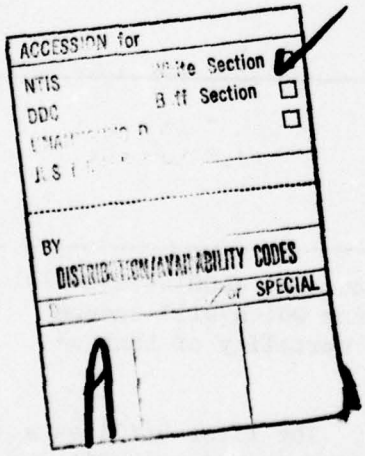
burn by wiping or brushing, leaves a protective film of PCL after the solvent evaporates. This film reduces water loss and trauma from the burn and promotes healing. U.S. Patent 3835308 was issued January 27, 1976 covering this development. Initial reports from pig tests at NMRI indicated that the best PCL wipe-on coating tested gave significant improvements in healing and reduction of scar formation.

The second approach involved the preparation of a synthetic temporary skin graft. This was made from a plasticized PCL film laminated to a cut plush fabric which in turn had been knitted from PCL fiber. The polymer for both film and fiber was high molecular weight PCL synthesized with the biocompatible initiator diethyl zinc. This laminate, particularly when cut on the bias, conforms well with minimum puckering to complex shapes such as a rat's back or a person's knee or elbow. A few days after application to full thickness excision wounds on rats the laminate can be removed with minimal damage to the new tissue formed beneath.

The grafts were dry to the touch and well tolerated by most of the rats. No unusual inflammation was noted other than occasional slight pockets of infection where the grafts did not adhere to the rat's back due to creases.

The PCL fabric laminate appears to have significant advantage over human skin and porcine skin with respect to infection and the incidence of rejection. Further investigation of both approaches is recommended since this will be clearly in the best interests of the Navy and the general public.



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Section 1

SUMMARY

The objective of the program covered by Contract No. N00014-73-C-0201 is the development of a synthetic polymer burn covering which will reduce dehydration, sepsis, sodium loss, scar formation and mortality of burn patients.

Two approaches were successfully investigated. The first utilizes a solution of poly-ε-caprolactone (PCL) which when applied immediately after burn by wiping or brushing, leaves a protective film of PCL after the solvent evaporates. This film reduces water loss and trauma from the burn and promotes healing. U.S. Patent 3835308 was issued January 27, 1976 covering this development. Initial reports from pig tests at NMRI indicated that the best PCL wipe-on coating tested gave significant improvements in healing and reduction of scar formation.

The second approach involved the preparation of a synthetic temporary skin graft. This was made from a plasticized PCL film laminated to a cut plush fabric which in turn had been knitted from PCL fiber. The polymer for both film and fiber was high molecular weight PCL synthesized with the biocompatible initiator diethyl zinc. This laminate, particularly when cut on the bias, conforms well with minimum puckering to complex shapes such as a rat's back or a person's knee or elbow. A few days after application to full thickness excision wounds on rats the laminate can be removed with minimal damage to the new tissue formed beneath.

The grafts were dry to the touch and well tolerated by most of the rats. No unusual inflammation was noted other than occasional slight pockets of infection where the grafts did not adhere to the rat's back due to creases.

The PCL fabric laminate appears to have significant advantage over human skin and porcine skin with respect to infection and the incidence of rejection. Further investigation of both approaches is recommended since this will be clearly in the best interests of the Navy and the general public.

Section 2

INTRODUCTION

The prompt treatment of major flesh burns to reduce shock and trauma caused by shipboard fire and explosions are of prime interest to the Office of Naval Research. The inability of burned skin to function as an effective barrier to evaporative water loss and sepsis contributes significantly to the mortality resulting from major burns. It has been shown that the average evaporative water loss for patients whose second- and third-degree burns range from 18 to 40 percent of the body surface is almost 3300 ml/24 hrs. for a 50 percent burn (Reference 16). This loss requires a compensating energy expenditure of approximately 1900 calories to maintain temperature, and to counteract this depletion, metabolic reserves are mobilized and muscle protein and fat losses occur unless heat is supplied artificially. In the short run this process can result in shock. In the long run any such losses contribute to the debility of the patient, delay wound healing, and increase the susceptibility of the patient to disease.

The objective of the program covered by contract no. N00014-73-C-0201 is the development of a synthetic polymer burn covering which will reduce dehydration, sepsis, sodium loss, scar formation and mortality in burn patients. The target material is to be producible at low-cost and in large quantities so as to be immediately available in event of large-scale disasters.

From the inception of the program on February 1, 1973, work has been concentrated on two approaches. First is the development of a solution of a plastic that can be applied immediately after the burn by wiping or spraying it onto the burned area. After evaporation of the solvent, the protective film left limits water loss from the burned area and reduces the trauma from the burn. The second approach is the development of a covering

to be applied to the burned area after debridement and excision of the burned tissue. This coating is meant to be temporary. It should prevent dessication and promote the formation in the underlying wound bed of a viable, well-vasculated interface free of sepsis which will be suitable for the application of skin grafts taken from other areas of the patient's body.

Human and porcine skin have been successfully used in the treatment of major second and third-degree burns. However, major problems with availability, expense and handling have made apparent the need for a synthetic burn covering that is easily manufactured in large quantity and can be stored for long periods without freezing or other specialized methods (References 17, 18, 19).

Many materials and composites have been tried -- polyurethane foam laminated to films of silicone rubber or to films of polypeptides, collagen or polyvinyl-alcohol. A variety of forms -- foams, film, velours, and sponge -- have been investigated (References 20, 21, 22, 23). At the present time, there is no satisfactory replacement for natural skin, human or porcine, in the treatment of major skin wounds.

The desirable characteristics of any synthetic covering are listed in Table 2.1.

Table 2.1

DESIRABLE CHARACTERISTICS OF SYNTHETIC SKIN SUBSTITUTE

(Reference 24)

Nonantigenic
Nontoxic to viable tissue
Exclude exogenous bacteria
Thin, pliable, and elastic, but resistant to linear and shear stress
Semipermeable to H_2O vapor
Rapidly adherent
Porous undersurface with firm intimate bonding to wound
Prevent bacterial proliferation and promote bacterial reduction at wound interface
Inexpensive with indefinite shelf life and minimal storage requirements.

The specific tasks proposed for the fifth year are quoted below:

Task 1 - Continued Testing and Evaluation of Immediate Post-Burn Wipe-On Treatment System.

Close communications and assistance with the pig testing at NMRI will be an integral part of the program. Techniques will be used to quantify the results on animal testing such as resistance hygrometry, use of ^{14}C labelled proline to measure quantitatively the rate of wound healing and of ^{14}C-poly-ε-caprolactone for evaluation of possible polymer up-take. A practical applicator for wipe-on fluid will also be developed.

Task 2 - Complete Preparation and Evaluation of Poly-ε-caprolactone Fabric/ Laminate Burn Covering.

Work on this task will continue, but at a substantially reduced level. Special attention will be given to the completion of all polymer, yarn and fabric preparation during this present contract year. Evaluation of selected fabric/laminates on animals will be carried out, including adherence measurements and determination of ^{14}C labelled proline ingrowth into the fabric.

Task 3 - Supply Samples and Coordinate Work with NMRI.

The Contractor shall maintain close coordination between work at NMRI on swine and the burn covering testing and evaluation at Dynatech. Samples will be supplied to NMRI and results using this material on smaller animals and other tests will be well documented.

Task 4 - Evaluation of Burn Covering Materials in Anticipation of Clinical Trials.

Standard sterilization procedures will be evaluated and tested on both the wipe-on and the fabric/laminate burn treatment systems. Radiation sterilization and ethylene oxide sterilization will be evaluated.

Appropriate FDA staff will be contacted to determine potential requirements. Communications with FDA staff on other biomaterials development programs have proved to be valuable in anticipating regulatory requirements.

This final report covers the progress during the period January 1, 1977 through December 30, 1977. The prior work is summarized and previous reports are referenced for details. The work on the wipe-on treatment system is covered in Section 3; that on the poly-ε-caprolactone (PCL) fabric-PCL film laminates is covered in Section 4. Section 5 lists previous reports on this project, all publications and references pertinent to this final report. Copies of patent disclosures and U.S. Patent 3,935,308 which issued as a result are given in Appendix A.

Section 3

DEVELOPMENT OF SOLUTIONS FOR IMMEDIATE POST-BURN TREATMENT

3.1 Introduction

During the first year of this program, it was found that a 20% solution of poly-ε-caprolactone (PCL) in tetrahydrofuran, when wiped onto burns on rats, significantly reduced insensible water loss for up to 10 days and had good adherence. Films made by applying two or more coats did not adhere as well as those made by applying only a single coat. (References 1, 2, 3, and 4).

During the second year, more extensive work with this wipe-on system showed that the PCL film stiffened and did not conform well to the animal's back and its movements. Some of the solution was packaged in an aerosol container so the film could be applied to the burned area by spraying rather than by swabbing or brushing. (References 5 and 6).

During the third year of the project, work concentrated on the development of a synthetic covering to be applied to debrided and excised wounds, and no work was done on the solutions for immediate post-burn treatment. (References 7 and 8).

During the fourth year, it was found that one coat of a wipe-on coating containing 10% by weight of poly-ε-caprolactone (PCL) dissolved in a 4/1 by volume mixture of acetone and methylene chloride significantly reduced insensible water loss (IWL) from burned and abraded areas on the backs of rats. The coating also appeared to promote healing especially of abraded areas. (References 9 and 11).

During the fifth year which is covered by this final report further study of PCL coatings have been carried out on pigs at NMRI under the supervision of Captain Burgoon D.V.M. (USAF). Progress has also been made in the formulation, testing and packaging of PCL wipe-on coatings.

3.2 Study of Plasticized PCL Films

Initial data on plasticized PCL films was given in Section 3.4 of the Fourth Annual Report (Reference 11). This work has been continued and the results of the current and past work are summarized in Table 3.1.

For the latest PCL wipe-on coating submitted for trial by Captain Burgoon (see Section 3.5), a formulation containing 33 PHR of the plasticizer, triethyl citrate was selected as PCL films containing this amount of triethyl citrate appear to have ample strength for a wipe-on coating with a minimum increase in water vapor transmission compared to films of unplasticized PCL.

Similar films were used in making the film-fabric laminates discussed in Section 4 of this report.

To duplicate the water vapor transmission (WVT) of full thickness normal human skin which is about 83g mm/24 hr.-m^2 (see reference 4, page 16), a PCL film having a WVT of 8.5g-mm/24 hr.-m^2 should be about 0.1 mm thick (4 mils). The thickness of a one coat application of the wipe-on solutions being tested by Captain Burgoon (see Section 3.5) is 0.02 to 0.04 mm (1 to 2 mils). Since the eschar over the traumatized area is also a moisture barrier, evan though not as good as normal skin, the water loss from a burned area covered by both the wipe-on coating and eschar should be close to that of normal skin.

3.3 Solvent for PCL Wipe-On Solutions

The first PCL wipe-on solution tested was made by dissolving PCL in tetrahydrofuran. Aromatic solvents are not suitable for this application because of their toxicity. A number of solvent combinations were tested using their solubility parameters as a guide but no satisfactory combinations of low boiling oxygenated straight chain hydrocarbons were found.

Table 3.1

STUDY OF PLASTICIZED FILMS

PHR Plasticizer (1) by weight	PCL Polymer (1)	Nature of Plasticizer (1)	Tensile Strength (3) k Pa	Tensile Strength (3) psi	Elongation at Yield (3) %	Young's Modulus (3) psi x 10-4 k Pa x 10^{-4}	Young's Modulus (3) psi x 10-4 psi x 10^{-4}	WVT (4) g mm/24 hrs m^2
0	A	-	7720	1120	2	52	7.5	4.62
4.5	A	A	11031 ± 4137	1600 ± 600	4.2 ± 2.	39 ± 8	5.6 ± 1.1	----
4.5	A	B	12548 ± 3723	1820 ± 540	4.2 ± 1.2	36 ± 16	5.2 ± 2.3	----
9	A	A	13376 ± 4482	1940 ± 650	6.3 ± 2.3	32 ± 8	4.7 ± 1.1	----
9	A	B	11721 ± 4757	1700 ± 690	5.5 ± 2.0	30 ± 12	4.3 ± 1.7	----
18	A	A	11652 ± 1172	1690 ± 170	10.3 ± 1.4	21 ± 0.7	3.0 ± 0.1	5.06
18	A	B	12824 ± 2344	1860 ± 340	7.8 ± 2.0	25 ± 3	3.6 ± 0.4	6.62
25	A	B	9253 ± 1055	1342 ± 183	3.4 ± 0.3	32 ± 47	4.6 ± 6.8	7.6 ± 0.3
33	(5)	B	5516 ± 738	853 ± 107	3.8 ± 0.5	19 ± 6	2.8 ± 0.9	8.5 ± 0.5
50	B	B	3820 ± 827	554 ± 120	3.5 ± 0.2	10 ± 3	1.4 ± 0.5	28.2 ± 0.2

NOTES:

(1) A basic solution was made up containing 50 grams of PCL polymer 22392, 100 mls of methylene chloride and 400 mls of acetone giving a 10% by weight solution of PCL. PHR = Parts by weight per hundred parts of resin. Two different polymers were using polymer A, 22392 molecular weight 135K and polymer B, 26311 molecular weight 152K.

(2) The amounts of plasticizer to give the parts by weight indicated of plasticizer based on 100 parts of polymer were added to the base solution. A = triacetin (Eastman Kodak Co.); B = triethyl citrate (Charles Pfizer and Co. Citroflex 2).

(3) Films of the solution were cast on release paper using a film caster set at 0.64 mm and allowed to air dry and then evacuated for 24 hrs. giving a dry film thickness of about 25μ. Dumbell samples were cut using Die C specified in ASTM Method D412 and tested for tensile and elongation at yield and Young's modulus using an Instron Tensile Tester Model TTC with a cross-head speed of 0.25 cm per minute.

(4) Water vapor transmission obtained at 37°C and 0% relative humidity using ASTM Method E96 Procedure D.

(5) Duplicate determinations made, one set using polymer A and the second using polymer B. See note (1).

Table 3.2

STUDY OF SOLVENTS FOR POLY-ε-CAPROLACTONE

No.	Solvent	Volume Ratio of Solvents in Mixture	Solubility Parameter (1) λ	λd	λa	Boiling Pt. °C	Solvent for PCL
1	Benzene	--	9.15	9.03	1.48	79	yes
2	Dloxane	--	9.74	8.55	4.65	101	yes
3	Methylene chloride	--	9.53	8.52	5.08	46	yes
4.	Tetrahydrofuran	--	9.52	9.25	2.28	78	yes
5.	Acetone	--	9.10	7.49	5.19	--	no
6.	Methyl Acetate	--	9.49	7.56	5.72	--	no
7.	Ethyl Acetate	--	9.10	7.44	5.19	--	no
8.	Methyl Ethyl Ketone	--	9.27	7.77	5.06	--	no
9.	Methanol	--	14.28	7.42	12.40	--	no
10.	Ethanol	--	12.92	7.73	10.45	--	no
11.	Ethyl Ether	--	7.62	7.05	2.88	--	no
12.	Acetone, Ethanol	9/1	10.1	7.62	6.5	--	Fair, not equal to number 15
13.	Methyl Ethyl Ketone Ethanol	82/18	9.92	7.74	6.04	--	no
14.	Methyl Ethyl Ketone Ethanol	75/25	10.18	7.75	6.41	--	no
15.	Acetone Methylene Chloride	4/1	9.29	7.65	5.18	--	Yes, gels at about 15°C
16.	Acetone Methylene Chloride	3/1	9.29	7.65	5.18	--	Better solvent than 15
17.	Acetone Ethanol	95/5	9.90	7.59	6.35	--	Fair not equal to number 15
18.	Acetone Ethanol	90/10	10.1	7.62	6.5	--	delete
19.	Methyl Ethyl Ketone Ethanol	82/18	9.92	7.74	6.04	--	delete
20.	Methyl Ethyl Ketone Ethenol	75/25	10.18	7.75	6.41	--	poor
21.	Ethyl Ether Ethanol	56/44	9.95	7.34	2.90	--	no
22.	Ethyl Acetone Ethanol	78/22	9.94	7.46	6.40	--	no
23.	Methyl Acetate Ethanol	9/1	10.17	7.60	6.24	--	Fair not equal to number 5
24.	Methyl Acetate Methanol	9/1	10.45	7.53	6.63	--	Fair not equal to number 5
25.	Methyl Acetate Methylene Chloride	4/1	9.58	7.75	5.60	--	Gels at a lower temperature than number 15, hence, best solution of mixtures tested

NOTES

(1) For solubility parameters for individual solvents see C. M. Hansen J. of Paint Tech 39, 104 (1967). Values for mixtures calculated by assuming such component contributes to the total in proportion to the volume fraction present.

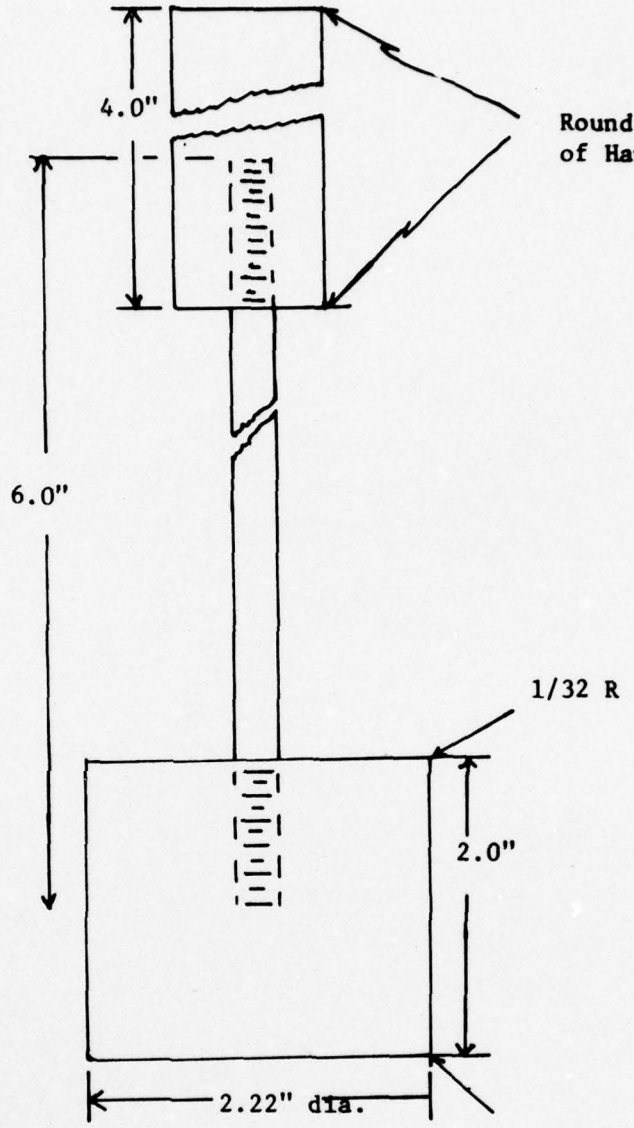
However, both acetone and methyl acetate are satisfactory solvents if mixed 4/1 by volume with methylene chloride. The 4/1 methyl acetate/methylene chloride is the better solvent of the two and is the solvent used in the plasticized PCL wipe-on coating being tested by Captain Burgoon. (See Table 3.2 for data.)

3.4 Measurement of Skin Contact Temperature (TC).

The Dynatech R/D Company manufactures a thermesthesiometer (Trade name Thermotouch) used for measuring the temperature which skin reaches when in contact with various surfaces. The instrument is constructed according to the specifications and procedure given in National Bureau of Standards Technical Note 816. The skin contact temperature, or TC value, varies with the nature of the surface coming in contact with the skin as well as with its temperature and contact time. For example, a metal surface feels much hotter and is more hazardous than a plastic or wood surface having the same temperature. One of these instruments was used to determine the TC value of an iron similar to the one used by Captain Burgoon to brand the pigs (see Figure 3.1). The iron was heated in both air and in water and was used both wet and dry to determine the dependence of TC on these variables.

The results given in Table 3.3 show the TC value to be the same whether the iron is heated to a given temperature in an oven or in a water bath and whether it is wet or dry. We were unable to test irons heated in an oil bath such as that used at NMRI as any oil on the iron would damage the probe on the Thermotouch instrument. However, if the oil is wiped off the iron carefully, the TC value would not be expected to be affected by this mode of heating. Comparison of the results presented in Table 3.3 with the data plotted in Figure 3.2 shows that with the iron at 67°C, at least an 8 second contact time is required to produce a third

Figure 3.1
Branding Iron



Materials:

1" dia. maple dowel 4" long size 0 dia. drill 1" deep in center of end 3/8-24 tap.

3/8" dia. drill rod 6" long 3/8-24 thread 1" from each end.

2.22 dia. stainless steel iron 2" long size 0 dia. drill in center of 1 end 1.0" deep 3/8-24 tap.

Table 3.3

Skin Contact Temperature (TC) Obtained from Branding Iron For Various Contact Times When the Iron is Heated In An Oven and In A Hot Water Bath[1]

Mode of Heating Branding Iron	Temperature of Branding Iron °C	Skin Contact Temperature, Tc in °C		
		2Sec. Exposure	4Sec. Exposure	8Sec. Exposure
Oven	67.2 ± 0.1	55.8 ± 0.5	58.3 ± 0.5	60.1 ± 0.4
Water Bath (Iron dried before testing	67.6 ± 0.3	55.3 ± 0.1	57.6 ± 0.5	60.4 ± 0.3[2]
Water Bath (Iron left wet)	67.5 ± 0.4	55.6	57.7	60.5

NOTES:

1. See Figure 3.1 for sketch of branding iron. Values are given ± the standard deviation. If no ± given after value only one determination was made. The iron temperatures were masured 9, 8, and 3 times respectively for each mode. The Tc values were obtained with the Thermotouch after calibration. All values except those with no ± were obtained from the mean of three readings except were indicated.

2. Average of two readings.

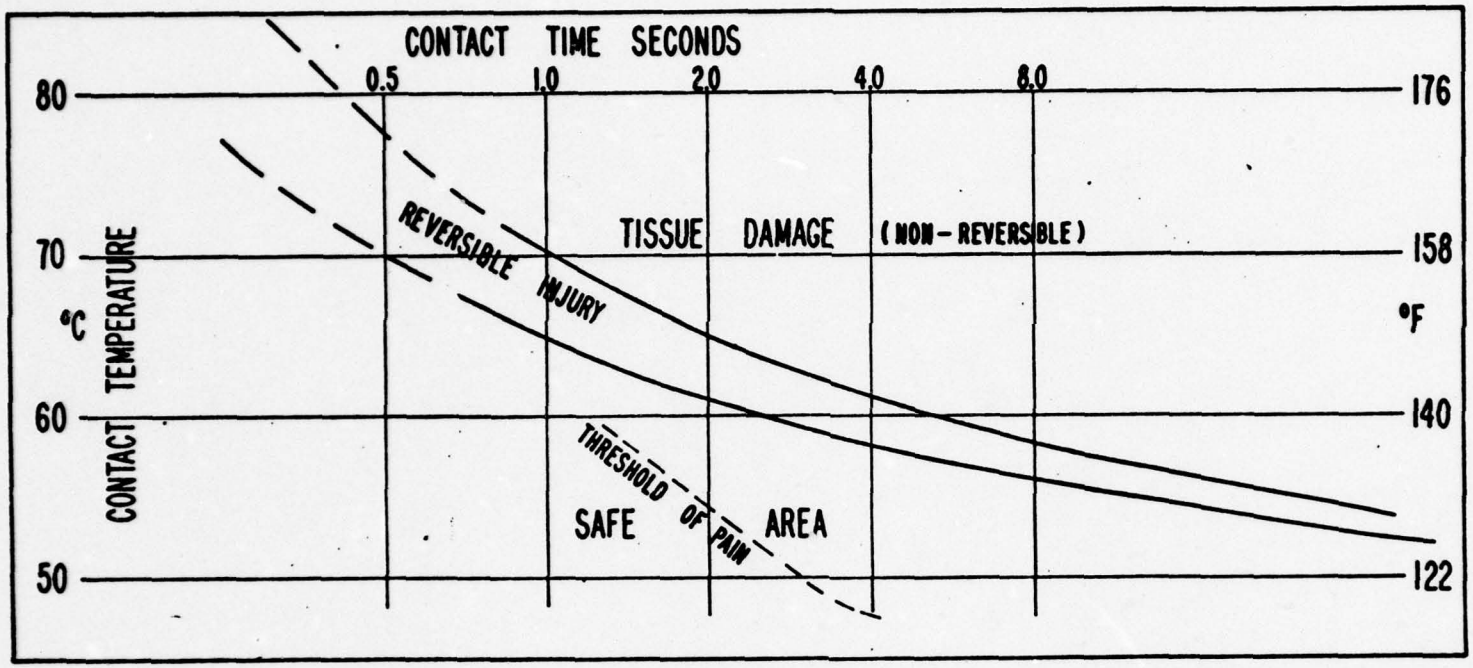


Fig. 3.2 Physiological Response Curve

degree burn on typical human skin. At NMRI (see Section 3.4) a 15 second contact time on the young pigs was observed to give a burn which is borderline between 2nd and 3rd degree when the iron is 65°C. Figure 3.2 is taken from the NBS Technical Note 816 referenced earlier.

3.5 Evaluation of PCL Wipe-On Burn Coverings by NMRI

Dynatech engineers visited Captain Burgoon D.V.M. on June 27, 1977 to observe the tests of our wipe-on coating on young pigs burned with a 5.59 cm (2.22") diameter branding iron heated to 65°C in an oil bath. Each pig, 10 to 12 weeks old, is shaved on both sides. The iron is applied in four places on each side with contact times of 10, 15, 25, and 45 seconds respectively. A freshly heated iron is used for each application. The burns on the left side of the pig serve as controls. Those on the right side are covered by brushing with one coat of wipe-on coating using a nylon paint brush. The burns were observed for healing and photographed weekly for a period of at least two months. The 10 second burn was 2nd degree and heals naturally. The 15 second burns were borderline between 3rd and 2nd. The 25 and 45 second burns were 3rd degree and heal only by formation of granulation tissue. A circle was tatooed around each burn to delineate the area. Differences in the area of the tatooed circle or between the treated and control burns during the healing process are indicative of scar tissue formation.

Formulation 26359 containing no plasticizer peeled off rather easily and was only marginally effective. Formulation 26387 containing plasticizer was more adherent and significantly effective in promoting both healing and reduced scar formation. The formulations submitted are as follows:

	26359 Submitted 01/26/77	26387 Submitted 05/23/77	26391 Submitted 07/1/77	30284 Submitted 09/14/77
Poly-ε-caprolactone	100g	100g	100g	100g
Triethyl Citrate	---	33g	33g	33g
Methylene Chloride	200ml	300ml	300ml	300ml
Acetone	800ml	---	---	---
Methyl Acetate	---	1200ml	1200ml	1200ml

3.6 Applicator and Package for Wipe-On Solutions.

The wipe-on solutions sent to Captain Burgoon were shipped in cone top cans with 1" (2.54 cm) diameter caps (Freund Can Co. catalogue numbers 1908 and 1914). Captain Burgoon stated that for field use a similar package with an integral brush would be more useful than an aerosol can. Such a commercially available container is a heavy duty brush top can, Freund Can Co. catalogue nos. D1, D2, and D4, having respective capacities of one quart, one pint, and one-half pint. A 1" (2.54 cm) bristle brush is supplied as an integral part of the caps of each can.

Captain Burgoon also stated that for hospital use an aerosol might be useful. An attempt was made to spray the wipe-on coating formulation tested by Captain Burgoon but they were too viscous to spray unless diluted 2 to 1 with methyl acetate. After dilution, the dryed sprayed film was consequently very thin compared to the one applied by brush. Toward the close of the contract a lower molecular weight PCL polymer (No. 26393, Table 4.1) was made to see if a thicker sprayed film could be obtained from a solution of suitable viscosity. Direct substitution of this low molecular weight polymer in the solution formula supplied to Captain Burgoon gave a film which was too weak to be useful. The work required to find the optimum molecular weight and plasticizer content for a sprayable wipe-on coating could not be completed because of contract funding limitations.

3.7 Absorption of PCL Through Traumatized Areas on Rats' Backs When Applied Topically As A Wipe-On Coating.

In this experiment, a solution of ^{14}C-labelled PCL was applied to burned areas on rats'backs. Forty-eight hours later the rats were sacrificed and samples of various tissues analyzed for radioacticity. Table 3.4 summarizes the results.

Note that no radioactivity was found in the blood, muscle, kidney or urine of any animal. Some activity was found in the dorsal skin of most animals. This skin was sampled from directly beneath the wipe-on covering. However, two animals out of eight had no significant activity in this skin area. It seems likely that not all of the wipe-on coating was removed prior to testing the skin and what is measured is residual wipe-on coating rather than absorbed PCL. Activity was also found in the feces of all rats except the controls and in the liver of all but one. The rats were not restrained prior to testing and since they often nibble at the wound area, they probably ingested some of the wipe-on covering.

In order to determine more accurately the origin of the fecal liver, and skin radioactivity, the experiment was repeated with the rats held in restraining cases. Results are presented in Table 3.5.

No activity was observed in the livers of any animal in this experiment. Furthermore, fecal activity was much less than previously observed indicating that although the cages do reduce the ability of the rats to nibble at the wound coverings, they were not completely effective and that a small amount of film was ingested. The reduction in skin activity compared to the values in Table 3.4 was due to exercise of greater care in removal of the film prior to sampling the skin directly beneath it. However, it was apparently not possible to remove the wipe-on coating entirely and some ^{14}C activity was still found in the immediately adjacent tissue.

Table 3.4

Absorption of PCL Wipe-On Through Traumatized Skin, First Experiment (1)

Group	No. Rats	Treatment	Thickness of PCL Coat	Absorbed 14.C Radioactivity, DPM/gram						
				Blood	Kidney	Muscle	Urine	Feces	Liver	Skin
I (2)	1	No burn	No coat	None	None	None	None	None	None	None
II	2	No burn	2 mil (3)	None	None	None	None	19830.2 2909.1 Mean 11400	787.7 99.4 Mean 440	220.9 2.0 Mean 100
III	2	Burned with 0.25 ml ethanol	2 mil	None	None	None	None	38811.2 4776.3 Mean 21800	626.2 60.5 Mean 340	2236.8 0 Mean 1100
IV	2	Burned with 0.50 ml ethanol	2 mil	None	None	None	None	1724.8 949.6 Mean 1300	49.4 0 Mean 20	329.7 293.5 Mean 300
V	2	Burned with	2 mil	None	None	None	None	14784.9 3709.2 Mean 9200	1145.4 107.9 Mean 630	3558.0 2315.4 Mean 2900

NOTES: (1) A sample of PCL wipe-on burn covering, 10% PCL by weight, was prepared containing ^{14}C labelled PCL with a specific activity of 2.788μCi/g. Fifty grams of the PCL (Sample 26329, Table 4.1) was dissolved in 400 ml of acetone and 100 ml CH_2Cl_2 to give a solution with a specific activity of 0.286μCi/gm.

Three groups of two rats each (140-160g) were anesthetized with Penthrane, their backs shaved and depilated with Nair, and burned with ethanol over an area of 11.4cm^2 (diameter of burned area = 3.6 cm).

Two other groups served as controls as indicated in the accompanying table. Forty-eight hours after burning the animals were sacrificed and samples of various tissues were analyzed for radioactivity. Tissue samples were oxidized in a Harvey Biological oxidizer and ^{14}C measured as $^{14}CO_2$ by liquid scintillation counting.

(2) Group 1 served as control for background DPM.

(3) Film easier to remove than in burned groups.

TABLE 3.5

ABSORPTION OF PCL WIPE-ON THROUGH
TRAUMATIZED SKIN, SECOND EXPERIMENT (1)

Absorbed ^{14}C-Radioactivity, DPM/g

Tissue	Group I	Group II	Group III
Blood	-----	----(3)	-----
Feces	-----	41.3	743.7
Kidney	-----	----	-----
Liver	-----	----	-----
Muscle	-----	----	-----
Skin	-----	111.2	166.4
Urine	-----	----(4)	-----

NOTES:

1. Group I - 2 control rats; unburned and uncovered
   Group II - 3 rats; unburned but covered with PCL wipe-on (2)
   Group III - 3 rats; burned and covered with PCL wipe-on (2)

   Group I controls were used to measure background for calculation of activities of Groups II and III. In order to minimize injestion of PCL covering all rats were placed in small wire mesh restraining cages for the 48 hours prior to sacrifice. This reduced their mobility but did not render them completely immobile; although no biting of the backs was observed, it is reasonable to assume that this did occur.

2. See Table 3.4 Note 1 for formulation of PCL solution used: PCL activity = 2.700 mCi/g; solution activity - 0.286 mCi/g.

3. One animal had minimal activity above background. The remaining two had none.

4. One animal showed 131.1 DPM/ml; the remaining two had none. This animal was not the one with activity in the blood.

One animal in Group II had some activity in its blood, minimally above background. Another in this group had 13.11 DPM/ml above background in the urine, again a small amount. As the first experiment showed no blood or urinary activity, we are confident that this represents contamination of the sample rather than a reproducible experimental result.

It appears that the PCL in the wipe-on coating is not absorbed into tissues through either normal or burn traumatized skin.

3.8 Proline Uptake by Traumatized Areas

The purpose of this experiment using rats was to determine if there was an enhanced uptake of tritiated proline by traumatized areas and if application of a wipe-on burn covering would show reduced trauma signified by reduced proline uptake. A similar experiment was reported in Section 3.5 of the Fourth Annual Report (Reference 11) on this project. In the latest experiments, changes in procedure were made to correct inadequacies in the previous experimental design as follows: The rats were sacrificed 24 hours after traumatization and treatment with labelled proline. The route of labelled proline administration was per os rather than i.p. Two groups of rats received a mild burn so that the degree of uptake of labelled proline by living and dead tissue (eschar) could be compared:

From the data which are summarized in Table 3.6, we conclude as follows:

1. Proline uptake by Groups II, III, and VI are almost the same and significantly greater than the controls. In these three cases, the trauma was sufficiently severe to kill the skin of that region.

2. Groups IV and V received milder trauma which did not kill the burned skin. In these cases significantly greater proline uptake was observed than for the other groups.

Table 3.6

PROLINE UPTAKE BY TRAUMATIZED RATS (1)

Group	Treatment	Comments	DPM/g	
I	No trauma (proline control)	proline control	10492.1 4426.5 4783.5 Mean (2)	6,600±3400
II	Burned with 0.50ml ethanol. Covered with 1 mil PCL (2)	Burned skin is dead.	88,636.4 61,167.8 67,133.7 Mean (2)	72,300±1440
III	Burned with 0.50 ml ethanol. No burn cover applied. (2)	Burned skin is dead.	61,655.5 80,138.1 65,753.4 Mean (2)	69,200±9700
IV	Burned with 0.25 ml ethanol Covered with 1 ml PCL. (2)	Skin not dead.	58,543.7 114,599.0 137,940.0 Mean (2)	103,700±40,8
V	Burned with 0.25 ml ethanol. No burn covering applied. (2)	Skin not dead.	85,396.8 138,891.8 89,741.0 Mean (2)	104,700±29,7
VI	Cut skin, separate from peritoneum, and reseal with wound clips.	Skin on cut area is dead.	76,354.1 64,417.5 71,142.9 Mean (2)	70,600±6000

NOTES

1. Groups of three rats each (140-160g) were anesthetized with Penthrane after which they were shaved, depilated with Nair cream, washed, and traumatized as indicated in the above table. In some cases PCL wipe-on burn covering was applied to burned areas, but this preparation contained no radioactivity. Immediately after traumatization each animal received 1.0 ml of 10 μCi/ml aqueous L-[14-^{3}H(N)]-proline *per os*. Twenty-four hours later animals were sacrificed and a sample of skin from the traumatized area was excised for combustion and liquid scintillation counting of $^{3}H_2O$.

2. 20 cm^2 template was used to confine alcohol and delineate burned area.

3. Apparently tritiated proline can be used successfully as a measure of collagen formation in traumatized areas. However, if dead eschar is formed, no proline is incorporated into this, so results on a DPM/gram basis do not reflect the high counts which would probably be obtained for newly formed living tissue.

4. Groups II and III showed similar uptake, as did Groups IV and V.

We conclude from the above that while the presence of tritiated proline is indicative of collagen formation in traumatized areas, any difference in the rate of new collagen formation between traumatized areas covered with the wipe-on coating and such areas when not covered is too small to be detected by this technique.

3.9 Measurement of Pervaporation by Resistance Hygometry

The Evapometer shown schematically in Figure 3.3 was set-up and calibration started by clamping the evapometer cup to a moisture dish. For more details see the notes to Table 3.7. The initial runs (see Table 3.7) gave widely different results for the moisture loss as calculated from humidity measurements when compared to the gravimetric weight loss. Note that when air is pulled through the apparatus by a vacuum pump the calculated moisture loss is higher than the gravimetric weight loss and the opposite occurs when the air is pushed through the apparatus. We calibrated the humidity sensors against a wet and dry bulb psychrometer (Fisher Scientific Cat. No. 11-662-100) and obtained good checks at both low and high humidities with the sensor calibration data supplied by the maker of the sensors. When we learned that the NMRI had developed a satisfactory instrument, work on this apparatus was discontinued.

Figure 3.3

SCHEMATIC OF EVAPOMETER CALIBRATION SET-UP

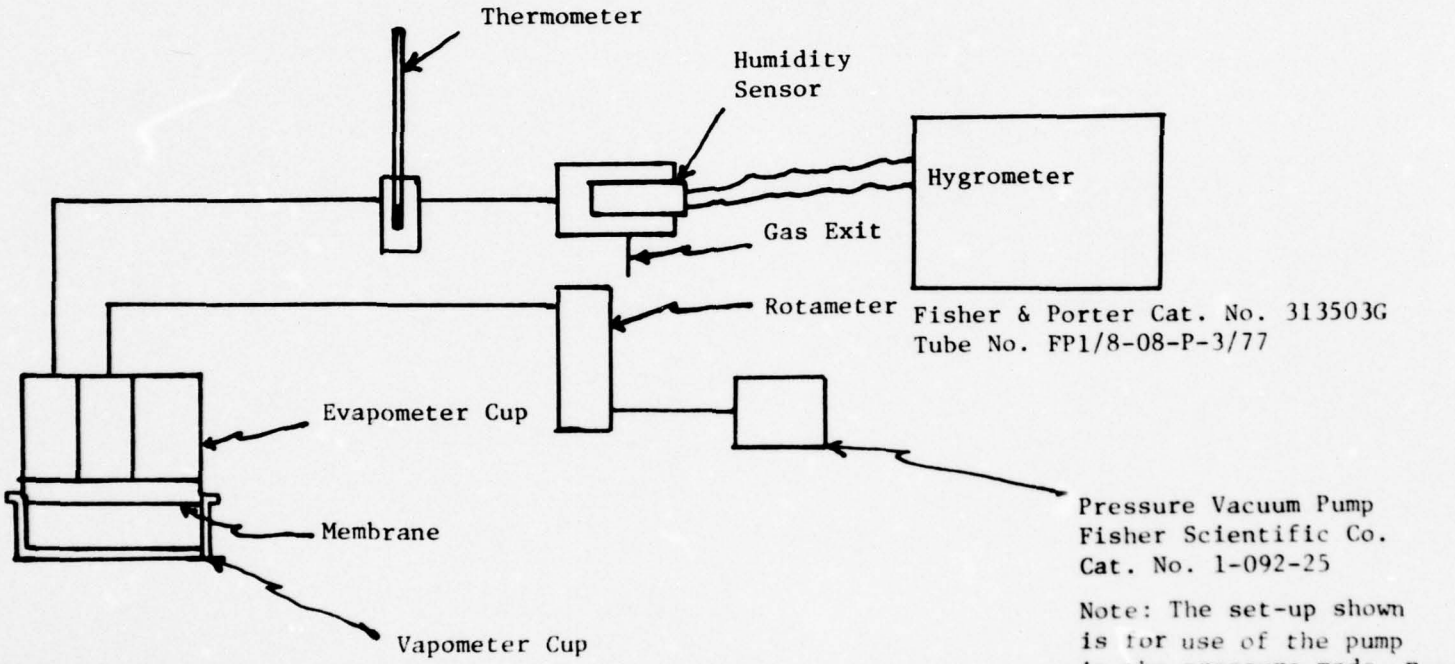


Table 3.7

COMPARISON OF WATER LOSS MEASURED BY RESISTANCE HYGROMETRY AND GRAVIMETRICALLY USING EVAPOMETER CUP PLACED OVER A MOISUTRE CUP COVERED BY VARIOUS FILMS[1]

Run No.	Film	Sensor Temp °C	% Relative Humidity Over Empty Disk	% Relative Humidity Over Disk Containing Water and Covered by Film	Length of Run Min.	Water Loss Grams Calculated	Water Loss Grams Gravimetric	Col.7-Col.8 Grams	% Difference
30212	Filter Paper(2)	271	37.4	64.2	41	0.217	0.093	+0.124	+133
30217	"	27.6	37.5	71.5	21	0.141	0.077	+0.064	+83
30226	PCL(3)	27	47.2	53	33	0.038	0.010	+0.028	+276
30230	"	27	47.2	53.2	41	0.052	0.017	+0.024	+207
30236	Plasti-cized PCL(4)	26	46.5	59.75	55	0.138	0.045	+0.093	+206
30242	"	28	46.6	58.75	45	0.115	0.049	+0.066	+134
30251	PCL(3)	25	41.9	49.2	22	0.0013	0.013	-0.0117	-90
30274	Filter Paper(2)	25	56	63	18	0.0009	0.0019	-0.0010	-53
30277	"	25	66.3	67.8	8	0.0003	0.0257	-0.0254	-99

NOTES:

1. The evapometer cup shown in Plate 3.5 of the Annual Report was clamped over a vapometer cup 1.3 cm deep and 6.35 cm in diameter illustrated in figure 4.1 of the 1st Annual Report. For blank runs the cup was empty. The cup was then partially filled with water and the film indicated clamped in position. The cup was weighed before and after each run to determine the water loss in grams. The difference in weight is the gravimetric water loss in grams.

   During the run ambient air was passed through the evapometer at a rate of 0.78/min over the top of the vapometer cup and past a hygrometer sensor. The temperature of cup and sensor were monitored during the run. The cup temperature was between 25 and 27°C for all runs and varied less than 0.5° during any run. The hygrosensors L4-4815 to L4-4822 (American Instrument Company) each cover a narrow humidity range so that eight sensors are needed to cover from 5 to 100% relative humidity. A model L15-3050 Universal Indicator (American Instrument Co.) is used to show the sensor output. The % relative humidity is determined from calibration curves supplied with each sensor. The water loss is calculated as follows:

   Water loss g = (Flow Rate ℓ/mm)(Flow Time min.) (gH_2O/ℓ sample - gH_2O/ℓ blank) x 10^{-3}.

   The g H_2O/ℓ for saturated air is obtained from page 1424 of Lange's Handbook of Chemistry, 9th Edition. Handbook Publishers, Inc., Sandusky, Ohio, 1949.

2. Whatman #41.

3. Film of PCL polymer No. 26341 (152000 MW, see Table 4.1) obtained by spreading out a 10% solution in THF using a film caster set at 0.64 mm evaporating the solvent and evaluating for 24 hrs. at room temperature.

4. Film of PCL polymer No. 26341 containing 33 g of triethyl citrate per 100 grams of PCL made as in Note 3.

3.10 Summary of Accomplishments Pertaining to Wipe-On Coatings During the 5th Year of the Project Vs. Proposed Objectives Listed in Section 2.

Of the tasks listed in Section 2 pertaining to the Immediate Post-Burn Wipe-On Treatment System, the work proposed for the year covered by this report has been completed with the exception of Task 4, The Study of Sterilization Procedures in Anticipation of Clinical Trials. Sterilization procedures were not evaluated as the particular wipe-on formulation to be used awaits a report of the results of the tests by Captain Burgoon. It is, of course, unlikely that viable pathogens can live in the solvent combination used for the wipe-on coating, therefore, the PCL solutions are probably self-sterilizing but testing should be conducted to establish this as a fact.

A summary of the important accomplishments vis-a-vis the proposed tasks is as follows:

- Close liaison with the pig testing at NMRI by Captain Burgoon has been maintained and samples of wipe-on coating have been supplied when needed. Section 3.5.
- Attempts to calibrate our resistance hygrometry apparatus for measuring pervaporation was discontinued when the NMRI apparatus was reported to function satisfactorily. Section 3.9.
- ^{14}C labelled proline was found to be useful as a measure of wound healing but to be insufficiently sensitive by the techniques used to show any difference between the rate of healing of burns covered by the wipe-on coating and those not so covered. Section 3.8.
- Sources for a practical container for the wipe-on solution with an integral applicator are given in Section 3.6.

3.11 Recommendations

If the final report of the tests on pigs at NMRI is favorable additional work should be done on the wipe-on covering to determine whether any sterilization treatment is required. Also the solution should be reformulated as necessary so that a PCL coating can be applied by aerosol for hospital use.

Section 4

SYNTHETIC GRAFT

The characteristics desirable for synthetic graft have been enumerated in early reports and included a surface, which when placed onto a wound resulting from removal of burn eschar, promotes the adherance of the graft to the wound (see especially References 4, 6, and 8). Velours, non-woven fiber mats, and foams are examples of materials having such a surface. A second component of the covering is a membrane which controls evaporative water loss from the wound. Engineers at Dynatech have proposed that both the adhering surface and the membrane be prepared from the same polymer, poly-ε-caprolactone (PCL). Suitable films have been made with PCL polymers having intrinsic viscosities in benzene at 37°C or over.

The procedures for preparing the polymer, spinning the fiber and knitting the fabric are given in the *Fourth Annual Report*, Reference 11. Table 4.1 gives details about polymerization of recent lots of PCL some of which were used for spinning yarn. Included in this table is data for polymer no. 26393, a low molecular weight material made for the wipe-on coating described in Section 3.

Although problems were encountered while melt spinning the polymer no. 26397 (Table 4.1), one pound of useful 120-140 denier fiber was made. This fiber called Lot 1 was warp knitted and brushed to form a looped velour under the direction of Professor Thomas Edman of the Philadelphia College of Textiles and Science. Five pile depths were prepared and sent to Dynatech where they were laminated to PCL films.

4.1 In Vivo Evaluation of Fabric Film Laminates Made from Fabric Woven From PCL

Thirty-two PCL fabric PCL film laminates cut to approximately 5 cm x 7.6 cm were placed on full thickness excision wounds on the backs of

Table 4.1

SUMMARY OF ε-CAPROLACTONE POLYMERIZATIONS[1]

Batch No.	Amount of ε-Caprolactone g	Catalyst % W/W	Amount Benzene g	Time (Hrs.)	Molecular Weight M_w	Intrinsic Viscosity in Benzene at 37°C [n]
22397[2]	5537g (5160 mls)	.23[3] (93 mls)	5448g (6190 mls)	20	118,000	1.44
22397-1[4]					97,000	1.22[4]
26902[5]	5537g (5160 mls)	.31[3] (125 mls)	5448g (6190 mls)	24	76,000	1.00
26902-1[6]					56,000	.774[7]
26318[7]	537g (500 mls)	.23[8] (9 mls)	528g (600 mls)	24	152,000	1.76
26321[9]	537g (500 mls)	.31[8] (12 mls)	634g (720 mls)	24	105,000	1.30
26341[10]	4569g (4250 mls)	.13[8] (45 mls)	5368g (6100 mls)	24	152,000	1.73
26393	430g (400 mls)	.46[8] (45 mls)	507g (576 mls)	24	21,900	0.36

NOTES

(1) See Appendix 4.1 for general procedure.

(2) Several minutes after the addition of the catalyst, the temperature of the batch increased rapidly due to the heat of reaction. The heating mantles were turned off at this point. The batch became very viscous and hot enough to boil the benzene. The volume increase due to the bubbles of benzene vapor caused a portion of the material to overflow the 22 liter kettle. This batch was sent to SRI on 1/30/76 for spinning into Lot 1 of PCL fiber.

(3) Diethyl zinc (DEZ) in benzene 15% by weight, density 0.91 (est.).

(4) Approx. 1969 g of PCL lot 22397 was returned to Dynatech from SRI for filtration to remove foreign matter and reprecipitation. 1800 grms of the filtered PCL was sent back to SRI on 7/21/76 for spinning into Lot 2 of PCL fiber. This was labelled 22397-1. Note that [n] dropped to 1.22 from 1.44 as a result of the reprocessing.

(5) The polymerization reaction had not occurred 45 minutes following the injection of 95 mls of DEZ. 30 mls additional of DEZ from a new bottle was injected. Several minutes after the second injection the temperature of the system increased rapidly. Foaming and expansion began because of the vaporization of the benzene. The volume increase caused a portion of the material to overflow out of the 22ℓ kettle.

(6) Due to the appearance of foreign particles in the precipitated polymer, the PCL was filtered and reprecipitated. The batch was then called 26902-1. This material was sent to SRI on 10/14/76 for spinning into Lot 3 of PCL fiber. Note that the [n] dropped to .774 from 1.00 as a result of the reprecipitation.

(7) Redistilled benzene was used in making this polymer. Approx. 10 minutes after the addition of the catalyst, the reaction temperature slowly began to rise. The mixture turned a slight yellow color. Approx. 20 minutes following the injection of catalyst, the mixture became more viscous with no further color change. At this point the reaction temperature substantially increased to a high point of 92°C and a pronounced yellow color developed. After 1 hr. the expansion of the mixture due to vaporization of the benzene ceased. There was no material overflow.

(8) 14.4% DEZ in Toluene.

(9) Redistilled benzene was used in making this polymer. There was no noticable reaction 1 hour after the addition of 9 mls of DEZ catalyst. The only noticeable change was the development of a slight yellow color. 3 additional mls of DEZ were then added. Several minutes later, the reaction proceeded rapidly with noticeable expansion due to vaporization of the benzene and an increase in temperature to 84°C. Unlike previous batches, this polymerized mixture was sufficiently fluid to permit the benzene vapor bubbles to collapse when the temperature of the mixture dropped back to 60°C.

(10) Redistilled benzene was used in making this polymer. A rise in temperature and thickening of the mixture began almost immediately following the addition of 45 mls of catalyst. The heating mantle was turned off but the temperature and viscosity continued to increase rapidly and the thermocouple broke at a reading of 70°C. Foaming and expansion began due to benzene vaporization. The volume increase caused a portion of the material to overflow out of the 22 liter kettle. However, the mixture soon cooled below the boiling point of benzene causing the foam to collapse so the overflow which was collected on release paper could be returned to the flask.

200-250 gram Wistar rats (Charles River Breeding Laboratories) and held in place using 9 mm stainless steel wound clips. Details of the grafting procedure are given in Appendix 4.2. The grafting was carried out by J. F. Howes, Ph.D. at SISA, Inc., Cambridge, Mass. Three days after grafting the strength of the interfacial bond that had developed between the wound and the covering was measured at Dynatech using an Instron Model TT-c Tensile Tester. Prior to testing the adhesion, the stainless steel wound clips were removed and the edges of the covering cut with scissors to produce an even width strip about 4 cm wide. The covering was removed at a rate of 7.5 cm/min. (jaw separation 15 cm/min.) in a posterior to anterior direction. The direction of the laminates and the results are summarized in Table 4.2.

There were two important findings:

- The degree of adhesion increased with the amount of nap in the fabric. However, the amount of nap is critical with a very light nap appearing to be optimum. With heavier naps, the fabric adhered so strongly that a considerable amount of the new tissue formed beneath the covering was torn from the back of the rat when the graft was removed three days after application.

- The PCL fabric-PCL film laminates were thicker than the grafts used previously and were somewhat too stiff to conform to the compound curves required to conform to the back of an active rat without forming creases or puckers along the two edges of the graft. These creases permitted access of air, occasional pockets of slight infection, and non-adherence.

The grafts were dry to the touch and other than the defects noted were well tolerated by most of the rats. No unusual inflammation was noted other than the occasional slight pockets noted above.

Table 4.2

ADHESION TO FULL THICKNESS EXCISION WOUNDS OF CUT PLUSH PCL FABRIC PCL-FILM LAMINATES (26310-26311 SERIES)[1]

Laminate Number	Fabricate Number	Fabric Laminate Thickness mm	PCL Film Thickness mm	Comments		Adhesion After 3 days[2] N/m	Comments[3]
11	IV-22 unfinished	6 to 8	0.3 to 0.4	No nap		49	
12	"	"	"	"		42	
13	"	"	"	"		--	Rat died
					Average:	46	
1	IV-22	7 to 9	0.3 to 0.4	Very little nap		42	
2	"	"	"	"		42	
3	"	"	"	"		44	
4	"	"	"	"		58	
5	"	"	"	"		63	
6	"	"	"	"		61	
7	"	"	"	"		23	No adherence one side
					Average:	47	
8	IV-22 double	8 to 10	0.3 to 0.4	Light nap		51	
9	"	"	"	"		91	
10	"	"	"	"		33	Poor adherence one side
					Average:	58	
14	III-18	10 to 14	0.3 to 0.4	Medium nap	Poor laminate adhesion one side	--	Rat died
15	"	"	"	"		84	Rat tissue failure
16	"	"	"	"		95	" " "
17	"	"	"	"		70	" " "
					Average:	83	
30	V-14	10 to 14	0.4 to 0.5	DuPont sanding	Areas with no nap	47	Rat tissue failure
31	"	"	"	"		89	" " "
32	"	"	"	"		98	" " "
33	"	14 to 16	"			196	Rat tissue failure
34	"	"	"			67	Rat nearly dead, rat tissue failure
					Average:	113	
18	V-10	13 to 14	0.3 to 0.4	Medium heavy nap	Poor lamination one side	105	Rat tissue failure
19	"	14 to 15	"	"	Poor lamination some film missing	98	" " "
20	"	"	"	"		61	" " "
21	"	"	"	"		72	Rat tissue failure
22	"	"	0.4 to 0.5	"		103	" " "
					Average:	84	
23	V-22	14 to 15	0.4 to 0.4	Heavy nap		154	Rat tissue failure
24	"	14 to 17	0.3 to 0.4	"		89	" " "
25	"	15 to 17	"	"		11	Film stiff, rigid with little adherence
26	"	14 to 17	0.3 to 0.4	"		116	Rat tissue failure
27	"	15 to 17	0.4 to 0.5	"		75	" " "
28	"	14 to 17	0.3 to 0.4	"		109	" " "
29	"	"	0.3 to 0.4	Poor lamination one corner		--	Rat died
					Average:	92	

NOTES: (1) The laminates were placed on full thickness excision wounds on the backs of rats and removed using an Instron Tensile Tester after 3 days. Details of the lamination procedure are given in Appendix 4.3.

(2) Obtained by measuring area under the stress strain curve and dividing by the length of the curve in the strain direction times the average sample width.

(3) In addition to the comments in the table it should be noted that there were about 3 creases on the wound covering and concommitant poor adhesion along each side of the covering. These result in dips in the stress strain curve and sugnificant lowering of the average adhesion.

Table 4.3a

ADHESION TO FULL THICKNESS EXCISION WOUNDS OF PCL FABRIC - PCL FILM LAMINATES (1)

Rat No.	Laminate No.	Fabric No.(2)	PCL Film Thickness μ	Adhesion N/m after(3) 1 day	3 days	6 days	Comments
1	26379A	26347-1	38	75			Stiff fibers in one small area of fabric.
2	26379B	"	48	70			
3	26379C	"	48		109		Tissue failure.
4	26379D	"	38		111		Tissue failure.
5	26379E	"	38			78	Good conformance - lot of blood in new tissue. No tissue failure.
6	26379F	"	38			54	Little or no vascularization in new tissue. Good conformance. Two small pockets - no infection visible.
		Average	41	73	110	66	
7	26384A	26347-2A	25	54			Tissue failure.
8	"	"	"	124			Tissue failure.
9	"	"	"	50			
10	"	"	"	43			Tissue failure.
11	"	"	"	14 (5)			Fabric dry - little adhesion.
12	"	"	"		64		Tissue failure.
13	"	"	"		43		Fabric conformed well to rat's back.
14	"	"	"		18(5)		Fabric conforming to rat's back. One small pocket near edge.
15	"	"	"		54		Fabric conforming. One small pocket.
16	"	"	"		59		Like 15 except some tissue failure near shoulder of rat.
17	"	"	"			rat died	
18	"	"	"			59	One small infected pocket. Some tissue failure.
19	"	"	"			45	New tissue not vasculated. Part of new tissue carried away on burn covering part. No tissue tearing below surface layer
20	"	"	"			63	New tissue well vasculated. No tissue failure.
21	"	"	"			64	
		Average	25	68	55	58	

NOTES

(1) See Table 4.3b for concluding data as well as for explanation of notes.

Table 4.3b

ADHESION TO FULL THICKNESS EXCISION WOUNDS OF

PCL FABRIC - PCL FILM LAMINATES[1]

Rat No.	Laminate No.	Fabric No.[2]	PCL Film Thickness μ	Adhesion N/m after[3] 1 day	3 days	6 days	Comments
22	26384B-1	36347-2B	25	50			Poor bond one side.
23	-2	"	"	34			Poor bond one side.
24	-3	"	"	23			
25	-4	"	"	41			Small unbonded area.
26	-5	"	"	45			Small unbonded area.
27	-6	"	"		45		Some tissue failure one side. Rest strips well
28	-7	"	"		21		Good fit. Strips well at sides. Some tissue failure over rat's spine.
29	-8	"	"		36		Good fit. Strips well.
30	-9	"	"		84		One wrinkle. Considerable tissue failure.
31	-10	"	"		88		One small pocket. Some tissue failure.
32	-11	"	"			50	Covering strips cleanly from tissue
33	-12	"	"			64	One large pocket. No apparent infection.
34	-13	"	"			54	Well vasculated new tissue. Burn covering strips clean.
35	-14	"	"			43	Same as 34.
36	-15	"	"			45	Some weakly adherent areas with little new tissue beneath.
		Average	25	39	65	51	
37	26384C-1	36347-2A[4]	"	47			Tissue failure.
38	-2	"	"	25			Small unbonded area.
39	-3	"	"	25			
40	-4	"	"		43		Tissue failure.
41	-5	"	"		27		Good fit. Strips well.
42	-6	"	"		21		Good fit. Strips well.
43	-7	"	"			39	Well vasculated new tissue.
44	-8	"	"			52	Some tissue failure. One small pocket - infected.
		Average	25	32	30	46	

NOTES

(1) Films of PCL were cast from a solution using a Bradley Blade set to give the desire dry film thickness onto a sheet of plate glass treated with Frekote 33 (Frekote, Inc.) polished with a paper towel wet with THF. The solution contained 100 parts by wt. of PCL batch 26341 Table 4.1 (mol. wt. 152,000) plus 33 parts by wt. of triethyl citrate (Citroflex 2 Chas. Pfizer & Co., Inc.) dissolved in 888 parts by wt. of THF. 4 minutes after casting, the fabric was pressed against the tacky films. After 2 hours, the laminate was removed and evacuated overnight at room temperature to remove the residual THF. After measuring the film thickness, the laminates were trimmed to 5 x 8 cm and the corners rounded to a radius of ~ 2.5 cm. The samples were applied to full excision wounds on the backs of rats (approx. wt. 150 g) using 12 evenly-spaced stainless steel wound clips. At the time indicate, the animals were injected i.p. with a lethal dose of pentobarbitol, the wound clips were removed, the fabric detached from the skin, trimmed to a width of 4 cm, the rat mounted on a harness and the fabric pulled from the rat using an Instron Tensile Tester at a rate of 1.2 cm/min (jaw separation rate 2.4 cm/min) in a posterior-anterior direction.

(2) Description of fabrics: 26347-1 - PCL brushed velour with Dacron backing similar to fabric IV22 (see Table 4.2 and page 37 of Reference 11). 26347-A - PCL cut plush with pile cut to 1.6 mm. Dacron backing (see page 37 of Reference 11). 26347-2B - same as above except pile 0.8 mm high.

(3) Average adhesion in lbs/in obtained by measuring the area under stress strain curve plotted by the x,y, recorder of the Instron Tensile Tester and dividing by the product of the length of the curve in the strain direction and the average sample width in inches. To convert the results from lbs/in to N/m, they were multiplied by 175.

(4) Fabric samples cut on bias.

(5) Not included in average.

4.2 Comparison of PCL Looped Velour Fabric Film Laminate and A PCL Cut Plush Fabric Film Laminate.

After reprecipitation to remove impurities which had caused the difficulties mentioned earlier in spinning PCL fiber Lot 1, about 1.4 lbs. of PCL fiber were produced from the polymer now designated 22397-1 (see Table 4.1). This fiber designated as Lot 2 was knit into two fabrics under the supervision of Professor Edman. One of the fabrics was a looped velour similar to fabric IV-22 described in Table 4.2 of the Fourth Annual Report, Reference 11, and the second a cut plush fabric with an open weave. The latter was designed to conform well when spread over a complex shape such as a rat's back or a person's knee or elbow. It was expected that the cut plush would be easier to remove from the healing tissue than the looped velour evaluated previously since the pile of a cut plush is formed by individual fibers rather than loops.

Laminates were prepared by bonding 25 μ thick films of PCL plasticized with 33 PHR of triethylcitrate to the back of the fabrics. The four laminates evaluated were as follows:

1. Laminate using looped velour similar to fabric IV-22 (See Table 4.2).
2. Laminate using cut plush with a pile height of 3.2 mm (1/8").
3. Ditto with a pile height of 1.6 mm (1/16").
4. Same as 3 except sample cut on the bias.

The detailed results of the tests on the laminates when applied to full excision wounds on rats' backs and the test procedure are given in Tables 4.3a and 4.3b. We found that the cut plush fabric laminates conformed better to the rat's back than the looped velour laminates and

that there was slightly less damage to the underlying tissue when the pile of the cut plush was 0.8 mm high rather than 1.6 mm. Applying laminates cut on the bias was of further help in permitting the graft to conform to the complex curves of the rat's back. Use of plasticized PCL in place of the unplasticized PCL used in earlier tests also was helpful.

It should be noted from the data obtained that the average laminate adhesion to the rat's back was about the same on day 1 as on days 3 and 6. However, we noted that failure of the new tissue was pronounced when the fabric was removed on days 1 and 3, but by day 6 tissue failure was minimal. Apparently, it takes several days for the new tissue growing into the PCL fabric to become strong enough to withstand having the fabric stripped from the wound without damage.

Samples of the tissue from the underlying wound were taken from the backs of rats 19 and 20 and preserved in formalin so that they could be examined under the microscope to determine if there was any difference,other than the amount of blood,between the whitish non-vasculated tissue obtained from the back of rat 19 and the red, bloodly, well-vasculated tissued obtained from the back of rat 20. The microscopic examination showed that both samples are typical healthy granulation tissue with no significant difference between them.

4.3 Procurement of Additional Fabric

Part of a lot of 3.4 lbs. of PCL fiber spun from PCL 26902-1 (Table 4.1) and called Lot 3 was knit under Professor Edman's supervision into additional fabric. The characteristics of the fabric desired was specified to be as follows:

Type	-	Cut plush
Plush height	-	0.8 mm
Plush density	-	Up to 50% more fibers/in^2 than in the previous cut plush fabric. See Table 4.3b Note (2).
Flexibility and backing density	-	equal to or more flexible and less dense than the previous cut plush, op. cit. cit.
Backing fiber	-	56 denier Dacron same as in previous cut plush op. cit.

Note that the PCL fiber had been sized with a solution containing 10% Drakeol 36 mineral oil (Penreco, Inc.). The average denier and tenacity is 173 and 1.6 g/d respectively. The elongation at break is 80%. The twist is about 0.3 tpi.

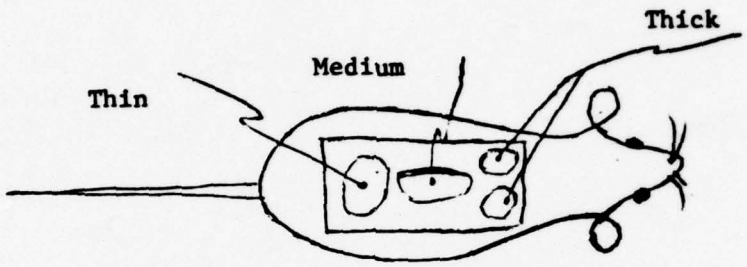
Although some fabric was knitted, the fabric was so loosely woven that shearing the plush to the desired height could not be done mechanically. Also, instead of having more pile fibers per square inch than previously, as specified, this fabric had fewer. This fabric, therefore, was not tested on rats and although additional fiber is available, there was insufficient time remaining before the termination of the project to permit knitting and testing more fabric. If this program should be reactivated, it is recommended that additional PCL fabric having the desired characteristics be procured and tested after lamination to plasticized PCL film.

4.4 Tissue Growth Into PCL Fabric-PCL Film Laminate Burn Coverings As Measured by Uptake of Tritiated Proline.

The purpose of this experiment was to determine from the uptake of tritiated proline the rate at which tissue from the traumatized area grows beneath and into the burn covering. Using the data obtained,

we planned to select the time, amount and specific activity of the proline injection required for future autoradiography experiments.

The samples were taken by carefully excising the fabric with the underlying adhering tissue intact. The thickness of tissue adhering to the fabric varied depending upon the section of the rat's back in contact with the fabric. The following diagram illustrates this.



The raw data is summarized in Table 4.4. In Table 4.5 the data has been averaged according to tissue distribution. There seems to be no significant variation in the samples taken from the rats given all the proline in one injection and sampled 24 hours later and those given two injections at 24 hour intervals and sampled 48 hours after the first injection. Since only two rats were used for each group, large variations between individuals may mask trends.

The experiments show clearly, however, that there is enough tritium in the tissue of all groups for future autoradiography experiments. We therefore conclude that one injection i.p. of 5μCi/g will be given and that samples will be taken for autoradiography 24 hours later.

Twenty-four hours after the last injection, the fabric was removed with the underlying tissue intact. This new tissue was not evenly distributed but ranged from very thin to thick. Therefore, three samples of known weight and area were taken from each burn covering for tritium

Table 4.4

Uptake of Tritiated Proline in Tissue Beneath PCL Fabric-PCL Film Burn Coverings.

Group	Sample	Tissue Distribution	DPM/Gram	DPM/cm^2
I	26347-2B-1	Thin	5,222,504	509,557
	-2	Medium	1,997,578	260,557
	-3	Thick	2,209,448	437,016
	-2D-1	Thin	1,284,596	61,363
	-2	Medium	2,095,147	185,570
	-3	Thick	2,595,290	418,259
II	26347-2I-1	Thin	5,618,613	402,082
	-2	Medium	1,529,459	317,727
	-3	Thick	550,460	99,083
	-2E-1	Thin	3,367,150	309,375
	-2	Medium	5,137,096	1,720,927
	-3	Thick	689,165	205,291
III	26347-2L-1	Thin	2,458,559	546,773
	-2	Medium	2,071,287	496,270
	-3	Thick	2,072,084	1,092,679
	26347-2S-1	Thin	2,743,363	363,630
	-2	Medium	2,816,087	713,049
	-3	Thick	2,823,769	897,331

Table 4.5

Up-Take of Tritiated Proline in Tissue Beneath PCL Fabric-PCL Film Laminate Burn Coverings.

Summary of Data from Table 4.4

Group	Treatment	Tissue Distribution	Tritium Recovery: DPMx10^{-3}/gram of fabric plus Underlying Tissue	Tritium Recovery: DPMx10^{-3}/cm^2 of fabric plus plus underlying tissue
I	one 5μCi/g dose Tissue sampled 24hrs later	Thin	3254 ± 1969	285 ± 224
		Medium	2046 ± 49	223 ± 38
		Thick	2402 ± 193	428 ± 9
		Mean (1)	2567 ± 1369	312 ± 172
II	Two 2.5μ Ci/g doses at 24hr intervals-Tissue sampled 48hrs after 1st.	Thin	4493 ± 1126	356 ± 46
		Medium	3333 ± 1804	1019 ± 702
		Thick	620 ± 69	152 ± 53
		Mean (1)	2815 ± 2230	509 ± 603
III	Two 1.25μ Ci/g doses as in group II	Thin	2601 ± 142	455 ± 92
		Medium	2444 ± 372	605 ± 108
		Thick	2448 ± 376	995 ± 98
		Mean (1)	2498 ± 356	685 ± 272

Notes: (1) Mean of all values from Table 4.4 ± standard deviation.

analysis. These three were representative of tissue distribution, one thin to almost bare, one with a medium tissue layer, one with a thick tissue layer. Each sample was oxidized in a Harvey Biological Oxidizer, the tritiated water collected and measured by liquid scintillation counting. Table 4.4 presents results as DPM/gram as well as DPM/cm^2 for each rat.

4.5 Summary of Accomplishments Pertaining to PCL Fabric-PCL Film Laminate During the 5th Year of the Project vs. the Proposed Objectives Listed in Section 2.

Tests on a loosely woven cut plush PCL fabric laminated to a plasticized film of PCL show the combination to have good conformability to complex anatomical contours, especially wehn applied with the fabric cut on the bias. Also the cut plush is easier to remove than a looped velour from the new tissue when tested several days after application to full excision wounds. At this time tearing of the newly grown tissue is minimized.

Preliminary experiments determined that one injection i.p. of 5μCi/g of tritiated proline should be sufficient to show tissue ingrowth into the PCL fabric PCL-film laminate 24 hours later by autoradiography. These autoradiography experiments were planned for the new fabric being knit by Professor Edman. As the material obtained was not suitable for testing and time remaining before termination of the project did not permit obtaining more fabric, neither autoradiography experiment nor the sterilization studies planned were carried out.

4.6 Recommendations

Procurement of additional PCL cut plush as specified earlier is recommended. This fabric should then be laminated to a film of plasticized PCL and tested on rats. Studies of tritiated proline uptake in

the healing wound by radioautography should be used to elucidate completely the potential of PCL fabric-PCL film laminates for burn healing. This technique could give important information on the kinetics of tissue regeneration and the optimal time for changing dressings. In addition, this combination of histology and radioautography will provide a more sophisticated technique for comparing different synthetic polymer fabric-film laminates than the measurement of the force required to remove the covering from the wound.

Synthetic fiber film laminates appear to have significant advantages over human cadaver and porcine skin with respect to infection and the incidence of rejection. Further investigation of these laminates is certainly in the best interests of the Navy and of the general public.

Appendix 4.1

POLYMERIZATION OF 6-HEXANOLACTONE (ε-CAPROLACTONE)
TO POLY-ε-CAPROLACTONE

To obtain high molecular weight polymer suitable for fiber and film making, pure 6-hexanolactone is required as the reactant. As received from Eastman Chemical Co., 6-hexanolactone is slightly yellow; therefore it is purified by vacuum distillation (15 mm Hg, 118°C) to a water-white liquid before use.

To a three-neck flask equipped with agitator, Dean-Stark trap, and condenser charge equal weights of distilled 6-hexanolactone (sp.g. 1.073) and benzene (sp.g. 0.88). Under nitrogen purge, heat to 60°C and hold at that temperature for one hour after the initiation of overflow from the Dean-Stark trap. Then add the catalyst. (Within 10 minutes a temperature rise accompanied by an increase in the viscosity will be observed.) Maintain at 60°C for the time specified. Cool. Dissolve polymer in benzene. Collect the polymer by precipitation in hexane. Dry polymer under vacuum at 45-50°C.

Determine the approximate intrinsic viscosity [n] in benzene. (Average of inherent and reduced viscosity of 0.2 g/dl in benzene at 37°C.)

(Reference 15)

$$M_w = \left(\frac{[n]}{9.94 \times 10^{-5}}\right)^{0.82}$$

Appendix 4.2

DESCRIPTION OF THE BURNED RAT MODEL,
EXCISION AND GRAFTING PROCEDURES

Poly-ε-caprolactone fabric-film laminates obtained from Dynatech R/D Company were evaluated for adherence to full thickness excision wounds as follows. Male Wistar rats weighing between 200 and 250 grams were anesthetized by an intraperitoneal injection of sodium pentobarbital (40 mg/kg), and shaved with a #40 blade electric clipper. Twenty percent of the rat's skin was excised from the dorsal surface, and one of the laminates measuring approximately 5cm x 7.7cm, was placed on the open wound. No attempt was made to prepare the wound prior to application of the covering which was clipped in place with 9 mm wound clips. Post excision and grafting, each rat was kept in an individual cage and given food and water ad libitum. Room temperature and humidity were kept constant.

Appendix 4.3

PREPARATION OF PCL FABRIC-PCL FILM LAMINATES

10 grams of PCL polymer 22397 (see Table 4.1), intrinsic viscosity 1.15, was dissolved in 100 mls of tetrahydrofuran (THF) and filtered through a 25 Teflon Millipore filter. A glass plate was sprayed with Frekote 33 (Frekote, Inc.), wiped thoroughly and polished with a clean paper towel. A film of the PCL polymer solution was then cast onto the plate using a Boston Bradley Blade set at 0.64 mm (25 mils) and allowed to dry for 4 mins. $\pm$ 0.1 min. The non-napped side of the PCL fabric was then gently pressed against the film. The laminate was then peeled from the plate and the residual THF allowed to evaporate from the laminate.

Section 5

REFERENCES

5.1 Index of Technical Reports on Contract No. N00014-73-C-0201.

Reference No.

1 Progress Report No. 1, Period 2/1/73 inception to 3/23/73.
Dynatech Report No. 1084.

2 Progress Report No. 2, Period 3/24/73 to 5/31/73.
Dynatech Report No. 1095.

3 Progress Report No. 3, Period 6/1/73 to 8/11/73.
Dynatech Report No. 1110.

4 Annual Report, Period 2/1/73 to 1/31/74.
Dynatech Report No. 1154.

5 Progress Report No. 4, Period 2/1/74 to 11/1/74.
Dynatech Report No. 1246.

6 Second Annual Report, Period 2/1/74 to 12/31/74.
Dynatech Report No. 1253.

7 Progress Report, Period 1/1/75 to 6/1/75.
Dynatech Report No. 1300.

8 Third Annual Report, Period 6/1/75 to 12/31/75.
Dynatech Report No. 1363.

9 Progress Report, Period 1/1/76 to 7/16/76.
Dynatech Report No. 1464.

Reference No.

10 Interim Report Dated 8/16/76.
Dynatech Report No. 1506.

11 Fourth Annual Report, Period 1/1/76 to 12/31/76.
Dynatech Report No. 1571.

12 Progress Report, Period 1/1/77 to 6/30/77.
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5.2 Index of Publications

Reference No.

13 Development of a Synthetic Burn Covering by Schwope, A.D., D.L. Wise, K.W. Sell, W.A. Skornick, and D.P. Dressler, Trans. Am. Sol. Artif. Int. Organs, 20A, 103 (1974).

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5.3 Literature Citations

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APPENDIX A

Copies of Patent Disclosures Made As Required
By Contract N00014-73-C-0201

Appendix A

CONTENTS

	Page
Disclosures submitted October 30, 1973 covering a PCL wipe-on burn covering and structured laminates of PCL film with nylon velour, collagen, porous PCL and PCL fabrics.	50
Copies of executed NAVSO forms 5870/43 and 5870/18 with covering letter dated June 13, 1974.	56
Letter of December 23, 1974 giving additional information pertaining to the disclosure submitted October 30, 1973.	72
Disclosures submitted with letter dated August 11, 1977 covering use of plasticized PCL film laminates. Two disclosures dated August 15, 1977.	76
U.S. Patent 3,935,308 dated January 27, 1976 covering a PCL wipe-on covering for interim treatment of extensive burn injuries.	82

Progress through Research

DYNATECH R/D COMPANY
A DIVISION OF DYNATECH CORPORATION
99 ERIE STREET, CAMBRIDGE, MASS., 02139

617-868-8050

October 30, 1973

Department of the Navy
Office of Naval Research
Arlington, Virginia 22217

Attention: A.F. Kwitnieski, Patent Counsel

Subject: Invention reporting under Contract N00014-73-C-0201

Gentlemen:

In response to your letter of August 28, we have prepared the attached disclosures describing a laminate burn covering and a spray-on burn covering, based upon the use of poly-ϵ-caprolactone films. These two disclosures cover all inventions which were first conceived and reduced to practice under the subject contract. To the best of our knowledge the disclosures include all reportable items, and no further work is being done which might generate additional reportable information under this contract.

By separate letter, and as required by the contract terms, these disclosures are being submitted also directly to the Administrative Contracting Officer. It is Dynatech's intention at this time to request greater rights than the license reserved under paragraph (b) of clause 57, in order to pursue possible commercial applications in the event that the Government chooses not to apply for or prosecute a patent application on its own behalf. In such an event Dynatech would request that it be given title rights.

Very truly yours,

F. Robert Johnson

F. Robert Johnson, Manager
Government Marketing Department

FRJ/mfk
Enclosures
cc: Dr. A.B. Callahan, Code 444

NAVSO 5510/15 (REV. 6-73)
S/N

DEPARTMENT OF THE NAVY
OFFICE OF NAVAL RESEARCH
ARLINGTON, VA. 22217

INSTRUCTIONS. A Navy employee or an employee of a Navy contractor should use this form when submitting an invention disclosure to the Department of the Navy. Original and two copies should be printed or typed and forwarded to the Navy Patent representative in the area or directly to the Office of Naval Research at the above address. If space on form is inadequate, enter "see attached page", identify item by number and use plain paper as needed. When completely executed, this form becomes an important legal document useful in proving priority of invention.

FOR USE BY NAVY PATENT ACTIVITY	
PATENT ACTIVITY (Name)	NAVY CASE NO.
DATE DISCLOSURE RECEIVED	LOCAL CASE NO

PART I - RECORD OF INVENTION

1. INVENTOR(S)	ADDRESS	POSITION TITLE	EMPLOYER (Activity & Code No., or Company & address)
Donald L. Wise, PhD Arthur D. Schwope	99 Erie Street Cambridge, Ma.	Mgr., Bioengineering Staff Engineer	Dynatech R/D Co.
Kenneth W. Sell, M.D.	Naval Medical Research Inst. Bethesda, Md.	Director, Clinical Medical Sciences Dept.	U.S. Navy

2. DESCRIPTIVE TITLE OF INVENTION (Disclose details of invention in Part II on reverse)

The application of a thin film of poly-ϵ-caprolactone to a flash burn in order to control evaporative water loss at a normal level.

RECOMMENDED SECURITY CLASSIFICATION OF INVENTION DISCLOSURE

3. CONCEPTION, INITIAL RECORDS AND RESULTS OF FIRST MODEL

a. EARLIEST DATE AND PLACE INVENTION WAS CONCEIVED (Identify persons and records to support date and place)

June 11, 1973, meeting at the Office of Naval Research - meeting attended by Dr. K. Sell and Dr. A. Callahan of ONR and Dr. D. Wise and A. D. Schwope of Dynatech R/D Co.

b. DATE AND PRESENT LOCATION OF FIRST SKETCH, DRAWING OR PHOTO AND FIRST WRITTEN DESCRIPTION (Such as notebook entries, etc.)

1) Progress Report #2 on Contract #N00014-73-C-0201 - June 8, 1973.
2) Dynatech R/D Co., Cambridge, Mass., Lab Notebook #14601 - June 27, 1973.

c. DATE AND PLACE OF COMPLETION OF FIRST OPERATING MODEL OR FULL SIZE DEVICE AND ITS PRESENT LOCATION

Dynatech R/D Co., Cambridge, Mass. - June 27, 1973

d. DATE AND PLACE OF FIRST TEST OR OPERATION AND THE RESULTS (Give name and address of witnesses, and present location of records)

During the weeks of July 23rd and 30th, a solution of poly-ϵ-caprolactone in a solvent was applied directly to a flash burn on the back of a laboratory rat. For the ten day test period, the thin (0.003 inch) film of poly-ϵ-caprolactone adhered to the burn and controlled the evaporative water loss at normal levels. The tests were performed in the laboratory of D. P. Dressler, M. D., at the Youville Hospital in Cambridge, Mass. Present for the test were Donald L. Wise, PhD, Donald P. Dressler, M. D., William Skornik, and Arthur D. Schwope.

4. OTHER RECORDS (Notebook entries, descriptions, reports, drawings, etc.)

IDENTIFICATION	DATE OF DOCUMENT	PRESENT LOCATION

5. OTHER INDIVIDUALS TO WHOM INVENTION WAS DISCLOSED

NAME	ACTIVITY OR COMPANY INDIVIDUAL REPRESENTS	DATE DISCLOSED	TYPE (Oral or written disclosure)
Arthur B. Callahan, MD	Biological and Medical Science Div., Office of Naval Research	Aug. 17, 1973	Oral & Written

6. DATE AND PLACE OF OTHER TESTS OR OPERATIONS, AND THE RESULTS (Give name and address of witnesses and identify present location of records)

None.

7. IDENTIFY ANY PAST, PRESENT OR CONTEMPLATED USE OR PUBLICATION OF THE INVENTION

It is intended that direct application of poly-ϵ-caprolactone from a solution to a burn be used in an emergency to control evaporative fluids loss from the body until the victim is transported to a burn treatment center.

8. CLOSELY RELATED PATENTS, PATENT APPLICATIONS AND PUBLICATIONS

PATENT OR APPLICATION NO. AND DATE	TITLE OF PUBLICATION, ARTICLE	PUBLICATION NAME (Vol., No., etc.)
	"Water Loss in the Burned Patient" Surg. Forum 13 (1962).	

(Over)

describe the invention fully and completely, using the outline given below. Sketches, prints, photos and other data which should be attached to this disclosure. For additional, more space as needed to complete the disclosure.

1. GENERAL PURPOSE. State in general terms the purpose and objects of the invention.

2. BACKGROUND. Describe the old methods, materials or apparatus used to perform the objects of the invention and give their limitations and disadvantages.

3. DESCRIPTION AND OPERATION. Describe clearly and completely the construction of the invention and give a detailed description of its operation and use. In the description, use reference characters to refer to components in attached illustrations.

4. ADVANTAGES AND NEW FEATURES. State the advantages of the invention over the old methods described in paragraph #2 above, and the features believed to be new.

5. ALTERNATIVES. Indicate any alternative methods, materials or constructions of the invention.

6. CONTRIBUTIONS BY INVENTORS. If this is a joint invention, indicate what contribution was made by each inventor.

7. EXECUTION OF DISCLOSURE. The end of the disclosure should be signed and dated by the inventor(s), in addition to any signatures in Part I. The disclosure should then be read and understood by two technically qualified witnesses. Under inventor(s) signatures, enter the statement: "Disclosed to and understood by me on (date)." The two witnesses should sign under this statement.

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1. Purpose

The purpose of this invention is to control the evaporative water loss from severe flash burns during the immediate post burn period. This is accomplished by application of a solution of the polymer, poly-ϵ-caprolactone, by swab or by spray from an aerosol container. The solvent evaporates after application, leaving a thin, flexible film which successfully controls the insensible water loss from the burned area.

2. Background

Shock is a major cause of death in the immediate period following a severe flash burn over large portions of the body. A primary cause of shock is the excessive loss of body fluids and protein.

Presently there are many creams, greases, sprays and homemade concoctions designed to soothe and protect the wound immediately following a flash burn. These first-aid treatments are applied directly to the burn and remain there until the victim can be treated with more sophisticated methods.

(Gump and Kinney, Surg. Clin. N. Amer., 50 (6) Dec., 1970, and Rozin, et al, Ann, N.Y. Acad. Sci., 150 Aug. 14, 1968).

3. Description and Operation

The invention is a solution of poly-ϵ-caprolactone which can be applied directly to a flash burn by swab or spray. *Poly-ϵ-caprolactone* (mol. wt. 2,000 - 300,000) is a biodegradable, solid polymer which is soluble in liquids such as acetone and tetrahydrofuran. When the polymer-solvent solution is spread over a surface (e.g., a burn wound), the solvent evaporates, leaving a thin, flexible film (0.001 to 0.01 inches thick) of the polymer. This film replaces the destroyed natural keratin moisture barrier, and controls the water transpired from the burned area to normal levels. Once the victim reaches a burn treatment center, the film can be removed and traditional burn treatment begun.

4. Advantages and New Features

Poly-ϵ-caprolactone in solution is inexpensive, has a long shelf life, and is easy to apply. More importantly, the film is the only tissue compatible first-aid treatment (known to the inventors) which is designed to control the rate of water loss from a burned area while protecting the wound from contamination from the outside environment.

6. Contributions by Inventors

The invention is the direct result of idea put forth by Dr. K. Sell at the Office of Naval Research and the materials development and engineering capabilities of Dynatech R/D Co. (specifically Donald L. Wise and Arthur D. Schwope).

7. Execution of Disclosure

INVENTOR(S):

Donald L. Wise — Date: October 30, 1973

Arthur D. Schwope — Date: October 30, 1973

_____ — Date

_____ — Date

Disclosed to and understood by me on October 30, 1973 (date).

WITNESSES:

Ralph L. Wentworth

John B. Gregory

NAVSO 5870/1* (REV. 1-73)
S/N

OFFICE OF NAVAL RESEARCH
ARLINGTON, VA 22217

INSTRUCTIONS. A Navy employee or an employee of a Navy contractor should use this form when submitting an invention disclosure to the Department of the Navy. Original and two copies should be printed or typed and forwarded to the Navy Patent representative in the area or directly to the Office of Naval Research at the above address. Where space on form is inadequate, enter "see attached page", identify item by number and use plain pages as needed. When completely executed, this form becomes an important legal document useful in proving priority of invention.

FOR USE BY NAVY PATENT ACTIVITY

Patent Activity (Name)	Navy Case No.
Date Disclosure Received	Local Case No.

PART I - RECORD OF INVENTION

1. INVENTOR(S)	ADDRESS	POSITION TITLE	EMPLOYER (Activity & Code No. or Company & address)
Donald L. Wise, PhD Arthur D. Schwope	99 Erie Street Cambridge, Mass.	Mgr., Bioengineering Staff Engineer	Dynatech R/D Co.
Kenneth W. Sell, M.D.	Naval Medical Research Inst. Bethesda, Md.	Director, Clinical Medical Sciences Dept.	U.S. Navy

2. DESCRIPTIVE TITLE OF INVENTION (Enclose details of invention in Part II on reverse)

A flexible, biocompatible synthetic sheet material to cover burns during therapy. The functions required are obtained in a composite structure formed by laminating poly-ϵ-caprolactone sheets or sheets of this polymer and another.

RECOMMENDED SECURITY CLASSIFICATION ON INVENTION DISCLOSURE

3. CONCEPTION - INITIAL DISCLOSURE AND EFFORTS TO FIRST MODEL

a. EARLIEST DATE AND PLACE INVENTION WAS CONCEIVED (Identify persons and records to support date and place)

June 11, 1973, meeting at the Office of Naval Research - meeting attended by K. Sell, M.D., and A. Callahan, M.D., of ONR and D. Wise, PhD, and A.D. Schwope of Dynatech R/D Co.

b. DATE AND PRESENT LOCATION OF FIRST SKETCH, DRAWING OR PHOTO AND FIRST WRITTEN DESCRIPTION (Such as notebook entries, etc.)

1) Progress Report #2 on Contract #N00014-73-C-0201 - June 8, 1973.
2) Dynatech R/D Co., Cambridge, Mass., Lab Notebook #14601 - June 27, 1973.

c. DATE AND PLACE OF COMPLETION OF FIRST OPERATING MODEL OR FULL SIZE DEVICE AND ITS PRESENT LOCATION

Dynatech R/D Co., Cambridge, Mass. - June 27, 1973.

d. DATE AND PLACE OF FIRST TEST OR OPERATION AND THE RESULTS (Give name and address of witnesses, and present location of records)

During the weeks of July 23rd and 30th, 1973, structured laminates of poly-ϵ-caprolactone film with either nylon velour, collagen, or porous poly-ϵ-caprolactone - the invention - were applied to fully excised sections of rats' backs in the laboratory of Dr. D.P. Dressler, M.D., at the Youville Hospital in Cambridge, Mass. The laminates adhered to the wound, remained flexible and controlled evaporative water loss from the animal for the test period. Present for the tests were Donald L. Wise, PhD, Donald P. Dressler, M.D., William Skornik, and Arthur D. Schwope.

4. OTHER RECORDS (Notebook entries, descriptions, reports, drawings, etc.)

IDENTIFICATION	DATE OF DOCUMENT	PRESENT LOCATION

5. OTHER INDIVIDUALS TO WHOM INVENTION WAS DISCLOSED

NAME	ACTIVITY OR COMPANY INDIVIDUAL REPRESENTS	DATE DISCLOSED	TYPE (Oral or written disclosure)
Arthur B. Callahan, MD	Biological and Medical Science Div., Office of Naval Research	Aug. 17, 1973	Oral & Written

6. DATE AND PLACE OF OTHER TESTS OR OPERATIONS, AND THE RESULTS (List name and address of witnesses and identify present location of records)

None

7. IDENTIFY ANY PAST, PRESENT OR CONTEMPLATED USE OR PUBLICATION OF THE INVENTION

It is intended that laminates of poly-ϵ-caprolactone with collagen and various synthetic (including poly-ϵ-caprolactone itself) velours, foams, and flocculated fabrics be used as a synthetic skin for the treatment of wounds in which areas of the skin have been damaged or destroyed by fire and/or chemical burns.

8. CLOSELY RELATED PATENTS, PATENT APPLICATIONS AND PUBLICATIONS

Title of Published Article / Publication Name and Date

"Viable Prosthetic Interface" J. Biomed. Mater. Res. Symp., vol 1, 1971.
"Velour Fabrics Applied to Medicine" J. Biomed. Mater. Res., vol 1, 1967.
"Eval. of artificial skin models presentation of 3 clinical cases" Trans. Am. Soc. Artif. Int. Organs vol 16,
"Water Loss in the Burned Patient" Surg. Forum 13 (1962)
"Adherence of Prosthetic Skin" J. Biomed. Mater. Res., vol 2 (1968)
"Eval. of Synthetic Fabrics as Artif. Skin grafts to Experi. burn wounds" J. Biomed. Mater. Res. vol 3 (19

(over)

... the ... invention fully and ... details using the outline given ... Sections, points, charts and other illustrations should be attached ... this outline to ... additional pages as needed to complete the disclosure.

1. GENERAL PURPOSE. State in general terms the purpose and objects of the invention.

2. BACKGROUND. Describe the old methods, materials or apparatus used to perform the objects of the invention and give their limitations and disadvantages.

3. DESCRIPTION AND OPERATION. Describe clearly and completely the construction of the invention and give a detailed description of its operation and use. In the description use reference characters to refer to components in attached illustrations.

4. ADVANTAGES AND NEW FEATURES. State the advantages of the invention over the old methods described in paragraph #2 above, and the features believed to be new.

5. ALTERNATIVES. Indicate any alternative methods, materials or constructions of the invention.

6. CONTRIBUTIONS BY INVENTORS. If this is a joint invention, indicate what contribution was made by each inventor.

7. EXECUTION OF DISCLOSURE. The end of the disclosure should be dated and signed by the inventor(s). - In addition to any signatures in Part I. The disclosure should then be read and understood by two technically qualified witnesses. Below inventor(s) signatures, enter the statement: "Disclosed to and understood by me on (date)." The two witnesses should sign under this statement.

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1. Purpose

The invention is a flexible laminate of a thin synthetic, biodegradable, polymeric film to a structured material such as collagen or synthetic velour, velvet, flocked cloth or foams to be used as artificial skin during the treatment and healing of burns. The covering is placed structured-side toward the wound (i.e., the film-side out).

The purpose of the covering is to control moisture loss from the burn, help prevent burn sepsis, and prepare the burn area for autograft acceptance. The purpose of the thin film is to control the rate of evaporative water loss from the victim. The purpose of the structured under-layer is to promote the growth of a shallow fibrin network into which neutrophils and macrophages readily enter to entrap and kill bacteria.

2. Background

A burn covering has two functions: 1) to prevent excessive loss of body fluids and proteins due to uncontrolled evaporative water loss from the burned area. This water loss can be of the order of ten times greater than the normal rate of evaporation through the skin. For a victim with severe burns over a large portion of his body, the total loss is substantial and can lead to shock and death during the immediate (0-5 days) postburn period. 2) to promote the formation of a viable interface between ...ound and the covering. A viable interface is defined as a living, growing fibrin network and is de...rable for two reasons. One, neutrophils and macrophages readily enter the network and kill bacteria. This action helps not only to prevent burn wound sepsis - a major cause of limb loss or death - but also to remove exudate which is typically found in a wound. And two, once the fibrin network is developed, the damaged area will more readily accept an autograft - the ultimate goal of burn therapy. A viable interface is indicated by adherence of the covering to the wound. The covering must be flexible in order to conform to the contours of the body so adherence is complete.

Presently human-donor and porcine skin are the most successful and widely used burn coverings. Both promote the formation of a viable interface and control the evaporative water loss from the burn area. Coverings composed of those skins must be removed or are rejected by the body every 3 to 5 days. New skins are then applied. (Zaroff, et al, "Surgery" 59: 308, 1966). Collagen film has also been tested as an artificial skin (Pappas and Hyatt, Surgical Forum 10, 1960).

Laminates of synthetic, non-biodegradable materials are available. Silastic film laminated with nylon velour has been applied to animals during experimental studies. (Hall. et al, J. Biomed. Mater. Res. 1, 179-96, 1967). The ideal combination of physical properties desirable in a burn covering were ascertained. They are an ultimate elongation at yield of greater than 10%, a Young's modulus less than 50,000 psi at a pull rate of 0.1 inch/min and an absolute water vapor transmission rate between 1 and 3 mg/hr. cm^2. From the materials selection program which followed, poly-ϵ-caprolactone was selected and animal tests performed.

3. Description and Operation

The burn covering proposed for patent is a lamination of biodegradable, synthetic poly-ϵ-caprolactone film with a material having a suitable physical structure, such as natural collagen and velours, velvets foams and flocked fabrics of synthetic biocompatible materials including poly-ϵ-caprolactone, itself. As explained above, the upper film layer controls the water vapor loss from the wound area and the lower structured layer promotes fibrin growth. The upper layer is a flexible film 0.001 to 0.01 inch in thickness composed of poly-ϵ-caprolactone (mol. wt. 2,000-300,000). The lower structured layer is flexible and from 0.005 (collagen) to 0.25 (velours and foams) inches in thickness. The covering is applied structured side down to the cleaned wound area.

4. Advantages and New Features

Three general classifications of burn coverings are presently available. They are: 1) natural skins, non-biodegradable synthetic laminates, and 3) biodegradable synthetic coverings. With poly-ϵ-caprolactone the desirable characteristics of each classification are combined to form an economical and practical synthetic burn covering.

As mentioned above skins are presently the most successful burn coverings. However, skin is a delicate and very scarce (therefore expensive) material which has a short shelf life. In addition, the skin must be removed and new skin applied every 3 to 5 days. Laminates made with poly-ϵ-caprolactone are inexpensive and easily handled coverings with the conformability, water evaporation control capability and structural qualities of skin. Collagen films alone provide successful burn

cont'd...

Continuation of RECORD AND DISCLOSURE OF INVENTION form NAVSO 5870/35 (Rev. 6-73).

Part II. Disclosure of Invention

Section 4. Advantages and New Features (cont'd)

coverings for 2 to 3 days, but then dry out. However, lamination of a poly-ϵ-caprolactone film to the outside of a collagen film prevents drying out and successfully controls insensible water loss.

The poly-ϵ-caprolactone laminates are more conformable than the silastic-nylon velour covering and have not exhibited the failure of the lamination bond as has been observed with The Epigard covering. The advantage of the poly-ϵ-caprolactone over polyglycolic acid (PGA), another biocompatible polymer, is that the former is significantly more conformable than PGA. This is of major importance to initial application and the ultimate formation of a viable interface between the wound and the covering.

In terms of ease and simplicity of production and behavior on the wound, a covering made solely of poly-ϵ-caprolactone is most desirable. It is composed of an upper film layer and a lower velour or foam layer of the polymer. In addition to being totally biodegradable and biocompatible, lamination problems are eliminated.

Section 6. Contributions by Inventors

The invention is the direct result of an idea put forth by Dr. K. Sell at The Office of Naval Research and the materials development and engineering capabilities of Dynatech R/D Co. (specifically Donald L. Wise, PhD and Arthur D. Schwope).

Section 7. Execution of Disclosure

INVENTOR(S):

Donald L. Wise — October 30, 1973 (Date)

Arthur D. Schwope — October 30, 1973 (Date)

_____ (Date)

Disclosed to and understood by me on October 30, 1973 (date).

WITNESSES:

Ralph L. Wentworth

John B. Gregory

Progress through Research

DYNATECH R/D COMPANY
A DIVISION OF DYNATECH CORPORATION
99 ERIE STREET, CAMBRIDGE, MASS., 02139

617-868-8050

June 13, 1974

Patent Counsel (Code 109)
Naval Coastal Systems Laboratory
Panama City, Florida 32401

Dear Mr. Doty:

Enclosed are three signed and sealed NAVSO 5870/43 forms and four signed NAVSO 5870/18 forms.

Dr. Donald L. Wise and I have read the patent application and have the following comments:

1. Page 4, lines 15-22: "Those burn wound coverings..."

Viable human skin and procine do require special storage facilities. However, freeze-dried skin is available which, once it is bottled under vacuum, has a long shelf life. The major draw backs of skin are its scarcity and expense. Also skilled personnel are required for procurement of natural skins.

Most gels and foams do not require special storage facilities; rather it is the impracticallity of gel and foam application in "various remote, isolated and limited facilities areas" that limit their use.

2. The thickness range of the film should be extended from 0.001-0.01 inch to 0.0005-0.01 inch.

3. Page 7, lines 16, 17

Tetrahydrofuran <u>is not</u> a "substantially non-irritating" solvent. However, acetone (E.F. Cox, U.S. Patent 3,021,309, page 8, lines 25-30) or mixtures with or of Freons 11 and 12 are much less toxic and more preferred solvents. The best solvent has not been determined.

4. "Tetrahydrofuran" is misspelled throughout the application.

5. "Particularly" is misspelled on page 2, line 14.

These are our comments and change recommendations for the applications. Questions should be directed to Dr. Wise or myself.

Sincerely,

Arthur D. Schwope

A.D. Schwope
Staff Engineer

ADS/klh
Enclosure

DYNATECH

Navy Case No. 57,354
Harvey A. David, Patent Adviser
Naval Coastal Systems Laboratory
Panama City, Florida 32401
Telephone: 904-234-4331

DEPARTMENT OF THE NAVY

APPLICATION FOR LETTERS PATENT

TO ALL WHOM IT MAY CONCERN:

BE IT KNOWN THAT DONALD L. WISE, ARTHUR D. SCHWOPE, and KENNETH W. SELL, citizens of the United States of America, and residents of have invented certain new and useful improvements in WOUND COVERING AND METHOD OF APPLICATION of which the following is a specification:

Navy Case No. 57,354

ABSTRACT OF THE DISCLOSURE

A preparation and a method are described for emergency, interim treatment of extensive burn injuries, e.g., flash burns, to external portions of a person. A solution of the polymer poly-ε-caproloctone in a volatile solvent, such as acetone or tetrahydrofuron, is applied to the burn area by spraying or swabbing, so that upon evaporation of the solvent a film of the polymer is left to serve as a barrier to insensible water loss.

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STATEMENT OF GOVERNMENT INTEREST

The invention described herein may be manufactured and used by or for the Government of the United States of America for Governmental purposes without the payment of any royalties thereon or therefor.

FIELD OF THE INVENTION

This invention relates to the treatment of burn wounds, and more particularloy to a method and means for providing such treatment as a "first aid" expedient, and at times as part of more sophisticated supportive treatment.

Shock is a major cause of death in the immediate period following a severe burn, such as a flash burn, over large portions

of the body. A primary cause of shock has been recognized as the excessive loss of body fluids and protein through the burned areas. This loss occurs primarily through evaporation, and the process is not visible or otherwise readily detectable to the subject or observer. The loss is therefore termed insensible, although the results thereof are dramatically apparent in the shock process.

Many, if not most, burn accidents occur under circumstances that make it impossible for the victim to receive immediate supportive treatment in a hospital. Such is the case, for example, with disasters, accidents, or conflicts occurring in remote areas, at sea, or under other adverse conditions. Accordingly, there has long been a need for suitable, adequate, readily available, and easily applied burn treatment that can be administered by relatively unskilled persons at the scene of injury.

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DISCUSSION OF THE PRIOR ART

In the past there have been used various creams, greases, sprays, and homemade concoctions designed to sooth and protect the wound, immediately following a burn, as a first-aid treatment. In general, these have been ineffective in stopping insensible fluid and protein loss through the burn site and have been messy

and difficult to apply. The latter factors are, of course, deterrents to effective use by unskilled persons in a first-aid situation.

In addition, there have existed various coverings for burns and similar wounds requiring covering of a substantial area for extended periods of time during the skin regeneration and healing process. These have included skin grafts where the skin was obtained either from another person or animal, or from another area of the injured party. Also, there have been provided various sheets, foils, and webs or fabrics made from various synthetic plastic materials, animal collagen, and the like. Examples of the latter are described in U. S. Patent No. 3,491,760 to Bernhard Braun et al. Use of burn wound coverings in the form of fibrillar products comprsing polyglycolic acid are alluded to in U. S. Patent No. 3,739,773 to Edard E. Schmitt et al. Those burn wound coverings, and particularly those comprising foams, gells or foils of collagen, or other moist, conformable dressing, require special storage techniques and facilities that render them quite impractical to have available for immediate use as a first-aid supply in various remote, isolated, and limited facility places where flash burns and other extensive injuries to the skin may occur.

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SUMMARY OF THE INVENTION

The present invention aims to overcome some or many of the disadvantages and shortcomings of the prior art, with respect to emergency or first-aid burn dressings or treatment, through the utilization of our discovery that a thin plastic film of poly-ε-caprolactone formed directly on the surface of a burn wound will adhere thereto and will control insensible fluid loss by evaporation so as to occur at a substantially normal rate, and that such a film can be effectively formed by applying a solution of poly-ε-caprolactone in a suitable solvent, such as acetone or tetrahydrofuran.

With the foregoing in mind, it is a principal object of the invention to provide an improved wound covering which is suitable for first-aid use on burns, is sufficiently compatible with human tissue and fluids to adhere to a burn wound for a useful period of time, and is notably effective in maintaining fluid balance in a subject.

Another object of the invention is to provide a burn wound treatment materials which can be stored for prolonged periods of time in a convenient and readily usable form, without any requirement for special storage facilities or conditions.

Still another object is the provision of burn treatment material of the foregoing character and comprising poly-ε-caprolactone in a solvent or vehicle that will rapidly evaporate

DEPARTMENT OF THE NAVY

after application to a wound surface to leave a thin, covering film of the poly-ε-caprolactone adhering to the wound.

As another object, the invention contemplates the packaging of the poly-ε-caprolactone and its solvent in a container having means for ejecting the contents thereof in the form of a spray or aerosol onto an affected area to be treated, such as a flash burn.

Yet another object of the invention is to provide a method of burn treatment including the steps of forming a solution of poly-ε-caprolactone in a volatile solvent, applying a layer of the solution over a surface to be treated, and allowing the solvent to evaporate so as to form a film of poly-ε caprolactone having a thickness in a predetermined range.

The poly-ε-caprolactone, with which the discovery of this invention is concerned, is a biodegradable solid polymer having a molecular weight in the range of 2,000 to 300,000, and which polymer is soluble in liquid solvents, specifically acetone and tetrahydrofuran. U. S. Patent No. 3,021,309 to E. F. Cox et al describes the polymer poly-ε-caprolactone and its generation. The chemical derivation of the polymer per se is not considered to be part of this invention, poly-ε-caprolactones having been known in the chemical arts for many years now, as is evident from that patent. Moreover, as also pointed out by that patent,

the polymer concerned is soluble in acetone, and is capable of being formed into films.

What is considered to be a notable advancement in the medical art is our discovery that a solution of poly-ε-caprolactone in a volatile solvent can be applied directly to a burn wound surface, and that the solvent will evaporate to leave a thin, flexible film or skin of poly-ε-caprolactone that will adhere to the wound surface and will effectively control the evaporative water loss from a severe burn during the immediate post burn period and until more conventional supportive burn treatment can be undertaken.

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DESCRIPTION OF THE PREFERRED EMBODIMENT

In carrying out the invention it is preferred that the solution of poly-ε-caprolactone be prepared with a solvent that is volatile and substantially non-irritating to a subject when applied thereto. Accordingly, in an exemplary embodiment the solvent may comprise liquid tetrahydrofuron, and the prepared solution may be placed in a suitable container for prolonged storage in contemplation of possible future emergency use.

In some instances, it may be desirable to utilize a container that has spraying capability, such as the conventional aerosol spray can. A suitable propellant, such as that sold under

the name Freon, may be included in a pressurized state in the container to facilitate spraying of the solution. Alternatively, the solution may be stored in a container without spraying capability, with the intention of applying the solution to a burn by means of a swab.

When an injury occurs that removes or destroys the normal water retaining capabilities of a subject's keratinaceous tissue, for example in the case of a severe abrasion, flash burn, or the like, the poly-ε-caprolactone and solvent solution is applied, either by spraying or swabbing, as a coating over the entire injured area. As the solvent evaporates a thin flexible film of the polymer is left adhered to the wound surface. This film, which is preferably in the thickness range of 0.001 inch to 0.01 inch in thickness, replaces the destroyed natural keratin moisture barrier. Once the victim reaches a burn treatment center, the film can be removed and traditional burn treatment begun.

Obviously, other embodiments and modifications of the subject invention will readily come to the mind of one skilled in the art having the benefit of the teachings presented in the foregoing description. It is, therefore, to be understood that this invention is not to be limited thereto and that said modifications and embodiments are intended to be included

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within the scope of the appended claims.

CLAIMS

What is claimed is:

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Navy Case No. 57,354

Claim 1

A preparation for treatment of burn wounds, said preparation comprising:

a solution of the polymer poly-ε-caprolactone in a volatile solvent;

said solution being free of irritating effects when applied to a burn surface of a person; and

said solution being adapted to form a thin, flexible film of said polymer on said surface upon evaporation of said solvent.

Claim 2

A preparation for treatment of burn wounds, as defined in claim 1, and wherein:

said solvent comprises acetone.

Claim 3

A preparation for treatment of burn wounds, as defined in claim 1, and wherein:

said solvent comprises tetrahydrofuron.

Claim 4

A preparation for treatment of burn wounds, as defined in claim 1, and wherein:

said solution is adapted to form said film, with said film having a thickness in the range of 0.001 inch to 0.01 inch.

Claim 5

A preparation for treatment of burn wounds, as defined in claim 4, and wherein:

said solvent comprises acetone.

Claim 6

A preparation for treatment of burn wounds, as defined in claim 4, and wherein:

said solvent comprises tetrahydrofuran.

Claim 7

A method of treating an extensive burn injury to a person, comprising the steps of:

coating the injured area with a solution of poly-ε-caprolacton in a volatile solvent;

allowing said solvent to evaporate, so as to leave a flexible, thin film of said poly-ε-caprolactone as a barrier to insensible water loss through said injured area.

Claim 8

A method of treating an extensive burn injury to a person as defined in claim 7, and wherein:

said step of coating comprises spraying of said solution onto said injured area.

Claim 9

A method of treating an extensive burn injury to a person, as defined in claim 7, and wherein:

said step of coating comprises swabbing said solution onto said injured area.

Claim 10

A method of treating an extensive burn injury to an external portion of a person, comprising the steps of:

spraying a layer of a solution of poly-ε-caprolactone in a volatile solvent comprising liquid tetrahydrofuran onto said external portion;

allowing said solvent to evaporate so as to leave a thin, flexible film of said poly-ε-caprolactone, having a thickness of 0.001 inch to 0.01 inch, adhering to said portion so as to form a barrier to insensible water loss therethrough.

NAVSO 5870/43 (3-70)
S/N 0104-909 0225

ASSIGNMENT

TITLE
WOUND COVERING AND METHOD OF APPLICATION

INVENTOR(S) (Name)	CONTRACTOR	
Donald L. Wise Arthur D. Schwope	Dynatech R/D Company	
	CONTRACT NO. N00014-73-C-0201	GOVERNMENT AGENCY U. S. Navy
	CONTRACTOR INVENTION DOCKET NO.	AGENCY DOCKET NO. Navy Case No. 57,354
	DATE EXECUTED	SERIAL NO. / FILING DATE

The undersigned Inventor(s), in recognition of ~~XXX~~(their) obligation as employee(s) of the Contractor to assign inventions to the Contractor, and pursuant to the obligations of the Contractor to th Government under the above contract, hereby ~~XXXXXX~~ (assign) to the United States of America, subject t a nonexclusive and royalty-free license which is hereby reserved to the Contractor, all right, title an interest in and to each invention disclosed and claimed in the above U.S. patent application.

The license reserved to the Contractor shall extend to all existing and future associated and affiliated companies, if any, within the corporate structure of which the Contractor is a part and shall be assignable to the successor of that part of the Contractor's business to which such invention pertains.

The Inventor(s) further ~~XXXXX~~ (agree) to assist the Contractor, and the Government, upon request, by furnishing any available information and documents, and by performing all acts and doing all things which may be reasonably necessary to make this assignment effective.

The Contractor joins in and agrees to the foregoing assignment, and except for the above reservation of a license relinquishes and assigns all right, title and interest in and to such invention, and further agrees to furnish to the United States of America, upon request, any available information and documents necessary for the prosecution of the above-identified application for patent (including prosecution and settlement of interferences), and any substitution, division, continuation-in-part, or continuation of such patent application and any application for reissue of any patent resulting from such patent application.

June 13, 1974 — DATE — Donald L. Wise — INVENTOR (Seal)

13 June 1974 — DATE — Arthur D. Schwope — INVENTOR (Seal)

DATE — INVENTOR (Seal)

DATE — INVENTOR (Seal)

SIGNED THIS 13th DAY OF June, 1974

ATTEST
Donna M Matis
My Commission Expires January 13, 1978
(Seal)

CONTRACTOR

BY

DECLARATION, POWER OF ATTORNEY, AND PETITION

---

xxx (We), DONALD L. WISE, ARTHUR D. SCHWOPE, and KENNETH W. SELL

declare that we are citizens of the United States of America

residing at _____;

that we have read the foregoing specification and claims and we verily believe we are the original, first and joint inventors of the invention or discovery in WOUND COVERING AND METHOD OF APPLICATION

described and claimed therein; that we do not know and do not believe that this invention was ever known or used before our invention or discovery thereof, or patented or described in any printed publication in any country before our invention or discovery thereof, or more than one year prior to this application, or in public use or on sale in the United States for more than one year prior to this application; that this invention or discovery has not been patented in any country foreign to the United States on an application filed by us or our legal representatives or assigns more than twelve months before this application; and that no application for patent on this invention or discovery has been filed by us or our representatives or assigns in any country foreign to the United States;

And we hereby appoint Richard S. Sciascia, Registry No. 17,547; Don D. Doty, Registry No. 19,314; and Harvey A. David, Registry No. 18,937; or either of them of the Office of Naval Research, Department of the Navy, Washington, D. C., 20360, our attorneys _____ with full power to prosecute this application and to transact all business in the Patent Office connected therewith;

The undersigned petitioners declare further that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon;

And we hereby certify that the Government of the United States of America, represented by the Secretary of the Navy, has an Assignment of the invention set forth in this application and has the irrevocable right to prosecute this application;

Wherefore, we pray that Letters Patent be granted to us for this invention or discovery described and claimed in the foregoing specification and claims, and we hereby subscribe our names to the foregoing specification and claims, declaration, power of attorney, and this petition.

Date June 13, 1974 Inventor's Signature Donald L. Wise — First name Donald — Middle initial L — Last name Wise

Post Office Address 195 [illegible] St [illegible] Mass 02172

Date 13 June 1974 Inventor's Signature Arthur D. Schwope — First name Arthur — Middle initial D. — Last name Schwope

Post Office Address 11 Burnham St Watertown Mass. 02172

Date _____ Inventor's Signature _____ First name _____ Middle initial _____ Last name _____

Post Office Address _____

Date _____ Inventor's Signature _____ First name _____ Middle initial _____ Last name _____

Post Office Address _____

This form may be executed only when attached to complete application as the last page thereof.

Progress through Research

DYNATECH R/D COMPANY
A DIVISION OF DYNATECH CORPORATION
99 ERIE STREET, CAMBRIDGE, MASS., 02139

617-868-8050

December 23, 1974

Department of the Navy
Office of Naval Research
Arlington, Virginia 22217

Attention: A. F. Kwitnieski, Patent Counsel

Subject: Invention Reporting Under Contract N00014-73-C-0201

Dear Sir:

On October 30, 1973 Dynatech R/D Co. submitted two patent disclosures to your attention. The disclosures resulted from our contract work for the Office of Naval Research to develop a synthetic polymer burn covering as a substitute for cadaver and other natural skins in the treatment of major burns. A laminate covering and an immediate post-burn, spray-on covering, both based upon the use of poly-ε-caprolactone, were described. Poly-ε-caprolactone has been selected as the material from which the synthetic covering will be fabricated because thin films are pliable and have moisture vapor transpiration properties similar to that of skin.

The laminate covering is composed of a thin poly-ε-caprolactone (PCL) film which controls insensible water loss and a substrate material (velour, foam or collagen) which provides a structure onto and into which tissue growth is promoted. Tissue growth - evidenced by adherence of the covering to the wound - is of major importance to the acceptance of autograft as the treatment progresses.

Since the time of the above referenced disclosures, in vivo and in vitro experimentation have refined the laminate burn covering. It is the purpose of this letter to disclose two new advances in our substrate preparation process, the development of a freeze-dried poly-ε-caprolactone foam and the development of a freeze-dried collagen foam/PCL laminate. In both cases, freeze-drying is used to obtain porous substrates which result in more "skin-like" burn coverings when laminated to PCL films. The descriptions of the processes follow.

Freeze-dried Poly-ε-caprolactone Foam

As mentioned above, adherence of the covering to the wound is essential to the successful treatment of the burn. Flat films do not adhere. Therefore we have developed a freeze-drying process to prepare a porous foam of PCL which is laminated to a thin film of PCL resulting in a totally synthetic covering of one material. This avoids the oftentimes objectionable and impractical task of bonding dissimilar materials. Adhesive degradation has been a major factor in the failures of other laminate, synthetic burn coverings.

The freeze-drying process is as follows:

1) Prepare 50 milliliters of 0.013 gm PCL/ml benzene solution.
2) Charge the solution to a 500 milliliter straight-walled flask.
3) Position the flask so the wall is parallel to the floor.
4) Rotate the flask until the wall is uniformly coated with the solution.
5) Freeze the solution by lowering the flask into an ice-acetone bath. Continue rotating for 30 minutes.
6) Reduce internal flask pressure to < 5 mm. in order sublime and remove the solvent.
7) Continue rotating and evacuating the flask for two hours.
8) Raise the flask from the ice bath; equilibrate to room temperature; and remove the foam from the flask.

The resulting foam will be 45 to 50 mils thick with pores ranging from 0.001 to 0.03 inch in diameter. Foams of other thicknesses and pore sizes can be made by changing the amount and concentration of the solution charged to the flask.

The burn covering is then made by solvent welding the foam to a thin film of poly-ε-caprolactone. Such a laminate has been evaluated in vivo using the burnt rat model. The results are favorable and further testing is in progress. The foam laminate concept was disclosed on October 30, 1973 and was first evaluated in vivo in September, 1974, by Dr. D. P. Dressler of the Harvard Medical School.

Freeze-dried Collagen Foam/PCL Laminate

The October 30, 1973, disclosure also included laminates of poly-ε-caprolactone with collagen. The collagen available at that time had been dried and pressed into a flat film. In vivo evaluation showed that the collagen/PCL laminates fabricated with that collagen successfully controlled insensible water loss from the excised wound; however, these laminates did not exhibit the early adherence required of a burn covering. Also the laminate did not have the high degree of conformability that is required for a material to readily conform to body contours and movements. Therefore work was initiated to prepare a more pliable and three-dimensionally structured (i.e., porous) form of collagen for use as the substrate material which can be laminated to the PCL film.

Since the objective of this project is to develop a synthetic burn covering which approximates human skin in end results, we have used freeze-dried cadaver skin as base line material. This skin is prepared by freezing excised skin and reducing the pressure to sublimate the water from the skin. The resulting rather hard and non-conformable material is bottled under vacuum. Immediately prior to use; the bottle is opened under physiological saline solution. The solution rushes into the bottle and completely saturates the previously dried skin making it highly conformable. The skin is then applied directly to the excised burn wound.

Following this example we have freeze-dried a moist, cadaver-like form of collagen. This dried, stable, porous material (2" x 10") is then pressed onto a tacky, cast film of poly-ε-caprolactone. (The film is made tacky with benzene solvent.) The solvent is removed; and a laminate of porous, freeze-dried collagen and PCL remains. Similar to the cadaver skin, the laminate is bottled under vacuum and prior to use, the bottle is opened under aqueous solution. The resulting moistened, collagen/PCL laminate is very conformable. Upon wetting delamination has not been observed. The covering is applied with the collagen side towards the excision.

On April 2, 1974 U.S. Pat 3,800,792 - "Laminated Collagen Film Dressing"- was granted to McKnight et al. The discussion of prior art and background contained therein is directly applicable to the work at Dynatech R/D Co. The patent describes a laminate composed of a collagen foam film and a synthetic polymer layer to control insensible water loss.

The advantage of the dressing which we have developed over that described in U.S. Pat 3,800,792 is the higher degree of conformability which is a result of the lower total laminate thickness (8 mils vs. 18 mils) and the skin-like behavior of the remoistened PCL/collagen laminate. The high degree of conformability which has been attained is expected to increase the degree of early adherence between the covering and the wound.

This information about two refinements of the previously disclosed laminate wound covering is provided in fulfillment of the Patent Rights (title) clause, General Provision Clause No. 57 of the contract. We feel both improvements are significant and warrant patent application.

Sincerely,

Arthur D. Schwope

Arthur D. Schwope
Principal Engineer

ADS:vw

DYNATECH R/D COMPANY TEL. 617-868-8050
99 ERIE STREET • CAMBRIDGE, MA 02139 • USA

DYNATECH

August 11, 1977
ONR-2

Defense Logistics Agency
Defense Contract Administration Services
Management Area, Boston
666 Summer Street
Boston, Massachusetts 02210

Attention: Edwin H. Chadwick

Subject: Disclosure of Inventions Required by Contract N00014-73-C-0201

Gentlemen:

On October 30, 1973, Dynatech R/D Co. submitted two patent disclosures to A.F. Kwietnieski Patent Council for the Department of the Navy. The disclosures covered patentable items developed during work for the Office of Naval Research on the subject contract covering the development of a synthetic polymer burn covering as a substitute for cadaver and other natural skins in the treatment of major burns. A laminate covering and an immediate post-burn, spray-on covering, both based upon the use of poly-ε-caprolactone, were described. Poly-ε-caprolactone (PCL) has been selected as the material from which the synthetic covering will be fabricated because thin films are pliable and have moisture vapor transpiration properties similar to that of skin.

The laminate covering is composed of a thin poly-ε-caprolactone film which controls insensible water loss and a substrate material (fabric, foam, or collagen) which provides a structure onto and into which tissue can grow. Tissue growth unto the coating - evidenced by adherence of the covering to the wound - is of major importance to the acceptance of autograft as the treatment progresses.

On December 23, 1974, two refinements on the laminate burn covering were disclosed to A. F. Kwietnieski. These were the preparation of a freeze dried poly-ε-caprolactone (PCL) foam and a freeze dried PCL foam/PCL film laminate.

Since that time refinements have been made in both the laminate covering and in the immediate post-burn spray-on or wipe-on covering which was in the discovery that addition of a biocompatible plasticizer increases flexibility and adhesion of the PCL film.

Copies of the Record and Disclosure of these inventions on NASO Form 5870/35 (Rev. 6-73) are enclosed. These disclosures complete the requirements of Paragraph (c) of the Patents Rights Clause in contract N00014-73-C-0201.

Very truly yours,

Donald Lee Wise

D.L. Wise, Ph.D.
Manager, Biochemical Engineering

DLW:lmv

Enclosures

Copies to: Capt. K.W. Sell, M.D.
Commander J. Bond
A.B. Callahan, Ph.D.

INSTRUCTIONS. A Navy employee or an employee of a Navy contractor should use this form when submitting an invention disclosure to the Department of the Navy. Original and two copies should be printed or typed and forwarded to the Navy Patent representative in the area or directly to the Office of Naval Research at the above address. Where space on form is inadequate, enter "see attached page", identify item by number and use plain pages as needed. When completely executed, this form becomes an important legal document useful in proving priority of invention.

FOR USE BY NAVY PATENT ACTIVITY	
PATENT ACTIVITY (Name)	NAVY CASE NO.
DATE DISCLOSURE RECEIVED	LOCAL CASE NO.

PART I. RECORD OF INVENTION

1. INVENTOR(S)	ADDRESS	POSITION TITLE	EMPLOYER (Activity & Code No., or Company & address)
John B. Gregory	19 Concord Road Wayland, Mass.	Engineering Director	Dynatech R/D Co. 99 Erie Street Cambridge, Mass.

2. DESCRIPTIVE TITLE OF INVENTION (Disclose details of invention in Part II as required) A flexible biocompatible synthetic sheet material for covering burns during therapy. The functions required are obtained by a composite structure formed by laminating a plasticized poly- -caprolactone (PCL) film to a fabric knit from PCL fiber with or without admixture with other biocompatible fibers.

RECOMMENDED SECURITY CLASSIFICATION ON INVENTION DISCLOSURE

3. CONCEPTION, INITIAL RECORDS AND RESULTS OF FIRST MODEL

a. EARLIEST DATE AND PLACE INVENTION WAS CONCEIVED (Identify persons and records to support date and place)

On March 1, 1977, John B. Gregory conceived of adding plasticizer to the PCL film to improve the flexibility and conformability of the PCL film PCL fabric laminate and gave detailed instructions to Jane L. Knowles to prepare such laminates.

b. DATE AND PRESENT LOCATION OF FIRST SKETCH, DRAWING OR PHOTO AND FIRST WRITTEN DESCRIPTION (Such as notebook entries, etc.) The first models made with plasticized PCL film were laminated at the Dynatech R/D Co. 99 Erie St., Cambridge, MA, on March 3, 1977. See Dynatech Notebook pages 26376 and 26379.

c. DATE AND PLACE OF COMPLETION OF FIRST OPERATING MODEL OR FULL SIZE DEVICE AND ITS PRESENT LOCATION

March 3, 1977 Dynatech R/D Company.

d. DATE AND PLACE OF FIRST TEST OR OPERATION AND THE RESULTS (Give name and address of witnesses, and present location of records)

The laminates were applied to full excision wounds on the backs of rats at SISA, Inc. 767-B Concord Ave. Cambridge, Mass. during the period March 29th to April 4, 1977 as specified by Dynatech Engineers in Dynatech Purchase Order No. 15634 dated 3/24/77 and under the supervision of John F. Howes, Ph.D. of SISA, Inc. The adhesion of the laminates to the wound was determined at the Dynatech R/D Company 1, 3, and 6 days after application using an Instron Tensile Tester.

4. OTHER RECORDS (Notebook entries, descriptions, reports, drawings, etc.)

IDENTIFICATION	DATE OF DOCUMENT	PRESENT LOCATION
The record of these tests is in the Progress Report on Contract N00014-73-C-0201 dated July 18, 1977 for the period January 1, 1977 to June 30, 1977 Dynatech Report Number 1631.		

5. OTHER INDIVIDUALS TO WHOM INVENTION WAS DISCLOSED

NAME	ACTIVITY OR COMPANY INDIVIDUAL REPRESENTS	DATE DISCLOSED	TYPE (Oral or written disclosure)
Arthur B. Callahan MD	Biological and Medical Science Div	July 21, 1977	
Kenneth W. Sell MD	Office of Naval Research		
Commander James Bond			

6. DATE AND PLACE OF OTHER TESTS OR OPERATIONS, AND THE RESULTS (List name and address of witnesses and identify present location of records)

None

7. IDENTIFY ANY PAST, PRESENT OR CONTEMPLATED USE OR PUBLICATION OF THE INVENTION It is intended that laminates of poly-ε-caprolactone (PCL) with fabrics knit or woven from PCL fiber with or without admixture with other biocompatible fibers be used as a synthetic skin for the treatment of wounds in which areas of the skin have been damaged by fire and/or chemical burns.

8. CLOSELY RELATED PATENTS, PATENT APPLICATIONS AND PUBLICATIONS

PATENT OR APPLICATION NO. AND DATE	TITLE OF PUBLISHED ARTICLE	PUBLICATION NAME AND DATE

NAVSO 5870/35 (REV. 6-73) - Reverse

PART II. DISCLOSURE OF INVENTION

Describe the invention fully and completely, using the outline given below. Sketches, prints, photos and other illustrations should be attached to this disclosure. Use additional plain pages as needed to complete the disclosure.

1. GENERAL PURPOSE. State in general terms the purpose and objects of the invention.

2. BACKGROUND. Describe the old methods, materials or apparatus used to perform the objects of the invention and give their limitations and disadvantages.

3. DESCRIPTION AND OPERATION. Describe clearly and completely the construction of the invention and give a detailed description of its operation and use. In the description, use reference characters to refer to components in attached illustrations.

4. ADVANTAGES AND NEW FEATURES. State the advantages of the invention over the old methods described in paragraph #2 above, and the features believed to be new.

5. ALTERNATIVES. Indicate any alternative methods, materials or constructions of the invention.

6. CONTRIBUTIONS BY INVENTORS. If this is a joint invention, indicate what contribution was made by each inventor.

7. EXECUTION OF DISCLOSURE. The end of the disclosure should be signed and dated by the inventor(s), - in addition to any signatures in Part I. The disclosure should then be read and understood by two technically qualified witnesses. Under inventor(s) signatures, enter the statement: "Disclosed to and understood by me on (date)." The two witnesses should sign under this statement.

1. Purpose

The invention is a flexible laminate of a thin synthetic, biodegradable, polymeric film to a structured material such as collagen for synthetic velour, velvet, flocked cloth or foams to be used as artificial skin during the treatment and healing of burns. The covering is placed structure side toward the wound (i.e., the film-side out).

The purpose of the covering is to control moisture loss from the burn, help prevent burn sepsis, and prepare the burn area for autograft accepta The purpose of the thin film is to control the rate of evaporative water loss from the victim. The purpose of the structured under-layer is to p mote the growth of a shallow fibrin network into which neutrophils and macrophages readily enter to entrap and kill bacteria.

2. Background

A burn covering has two functions: 1) to prevent excessive loss of body fluids and proteins due to uncontrolled evaporative water loss from the burned area. This water loss can be of the order of ten times greater than the normal rate of evaporation through the skin. For a victim with t burns over a large portion of his body, the total loss is substantial and can lead to shock and death during the immediate (0-5 days) postburn pe 2) to promote the formation of a viable interface between the wound and covering. A viable interface is defined as a living, growing fibrin net and is desirable for two reasons. One, neutrophils and macrophages readily enter the network and kill bacteria. This action helps not only to p burn wound sepsis - a major cause of limb loss or death - but also to remove exudate which is typically found in a wound. And two, once the fibr network is developed, the damaged area will more readily accept an autograft - the ultimate goal of burn therapy. A viable interface is indicate adherence of the covering to the wound. The covering must be flexible in order to conform to the contours of the body so adherence is complete.

Presently human-donor and porcine skin are the most successful and widely used burn coverings. Both promote the formation of a viable interface control the evaporative water loss from the burn area. Coverings composed of those skins must be removed or are rejected by the body every 3 to days. New skins are then applied. (Zaroff, et al, "Surgery" 59:368, 1966). Collagen film has also been tested as an artificial skin (Pappas an Hyatt, Surgical Forum 10, 1960).

Laminates of synthetic, non-biodegradable materials are available. Silastic film laminated with nylon velour has been applied to animals during experimental studies. (Hall, et al, J. Biomed. Mater. Res. 1, 179-96, 1967). The ideal combination of physical properties desirable in a burn covering were ascertained. They are an ultimate elongation at yield of greater than 10%, a Young's modulus less than 50,000 psi at pull rate of 0.1 inch/min and an absolute water vapor transmission rate between 1 and 3 mg/hr cm^2. From the materials selection program which followed, poly-e-caprolactone was selected and animal tests performed.

3. Description and Operation

The burn covering proposed for patent is a lamination of biodegradable, synthetic poly-e-caprolactone film with a material having a suitable phys structure, such as natural collagen and velours, velvets foams and flocked fabrics of synthetic biocompatible materials including poly-e-caprolac itself. As explained above, the upper film layer controls the water vapor loss from the wound area and the lower structured layer promotes fibri growth. The upper layer is a flexible film 0.001 to 0.01 inch in thickness composed of poly-e-caprolactone (mol. wt. 2,000 - 300,000). The lowe structured layer is flexible and from 0.003 (collagen) to 0.25 (velours and foams) inches in thickness. The covering is applied structured side down to the cleaned wound area.

4. Advantages and New Features

Three general classifications of burn coverings are presently available. They are: 1) natural skins, 2) non-biodegradable synthetic laminates, and 3) biodegradable synthetic coverings. With poly-e-caprolactone the desirable characteristics of each classification are combined to form an economical and practical synthetic burn covering.

As mentioned above skins are presently the most successful burn coverings. However, skin is a delicate and very scarce (therefore expensive) ma which has a short shelf life. In addition, the skin must be removed and new skin applied every 3 to 5 days. Laminates made with poly-e-caprolac are inexpensive and easily handled coverings with the conformability, water evaporation control capability and structural qualities of skin. Co films alone provide successful burn coverings for 2 to 3 days, but then dry out. However, lamination of a poly-e-caprolactone film to the outsi a collagen film prevents drying out and successfully controls insensible water loss.

The poly-e-caprolactone laminates are more conformable than the silastic-nylon velour (Epigard) covering and have not exhibited the failure of t lamination bond as has been observed with the Epigard covering. The advantage of the poly-e-caprolactone over polyglycolic acid (PGA), another biocompatible polymer, is that the former is significantly more conformable than PGA. This is of major importance in the initial application an the ultimate formation of a viable interface between the wound and the covering.

In the improved laminate which is the subject of this disclosure, a biocompatible plasticizer which is also a plasticizer for poly-e-caprolactone is incorporated. Examples of biocompatible plasticizers are triacetin and triethylcitrate. These are respectively the triacetic acid ester of glycerol and the triester of ethyl alcohol and citric acid. The materials which are the hydrolysis products of these esters are ingredients co found in living organisms and all are considered to be biocompatible. The addition of plasticizer makes the laminate more conformable without l ing the water permeability of the structure beyond the desired range. The prefered fabric for the laminate is a loosely knit PCL fabric with or out admixture of other biocompatible fibers and with a cut-plush nap. The structure formed by a cut-plush nap is easier to remove from the wound without tearing the newly formed tissue beneath the burn covering than the looped-velour used previously.

In terms of ease and simplicity of production and behavior on the wound, a covering made solely of poly-e-caprolactone is most desirable. It is composed of an upper film layer and a lower velour or foam layer of the polymer. In addition to being totally biodegradable and biocompatible, lamination problems are eliminated.

Inventor

John B. Gregory August 15 1977
Date

Disclosed to and understood by me on _____ (date)

Witnesses

Donald Ritchie Wiebe August 15 1977

Ralph Lindenwetter August 15, 1977

INSTRUCTIONS. A Navy employee or an employee of a Navy contractor should use this form when submitting an invention disclosure to the Department of the Navy. Original and two copies should be printed or typed and forwarded to the Navy Patent representative in the area or directly to the Office of Naval Research at the above address. Where space on form is inadequate, enter "see attached page", identify item by number and use plain pages as needed. When completely executed, this form becomes an important legal document useful in proving priority of invention.

FOR USE BY NAVY PATENT ACTIVITY	
PATENT ACTIVITY (Name)	NAVY CASE NO.
DATE DISCLOSURE RECEIVED	LOCAL CASE NO.

PART I. RECORD OF INVENTION

1. INVENTOR(S)	ADDRESS	POSITION TITLE	EMPLOYER (Activity & Code No., or Company & address)
John B. Gregory	19 Concord Road Wayland, MA 01728	Engineering Director	Dynatech R/D Company 99 Erie Street Cambridge, MA 02139

2. DESCRIPTIVE TITLE OF INVENTION (Disclose details of invention in Part II on reverse)

Modification of a solution of poly ε caprolactone (PCL) used as a burn covering by incorporating a platicizer for the PCL.

RECOMMENDED SECURITY CLASSIFICATION ON INVENTION DISCLOSURE

3. CONCEPTION - INITIAL RECORDS AND RESULTS OF FIRST MODEL

a. EARLIEST DATE AND PLACE INVENTION WAS CONCEIVED (Identify persons and records to support date and place)

On November 3, 1976 John B. Gregory coceived of the use of plasticized PCL fiber and instruc Jane L. Knowles to prepare solutions of poly ε caprolactone containing plasticizer. The sol utions were prepared on November 5, 1977 at the Dynatech R/D Company, 99 Erie Street, Cambridge, MA. See Notebook page 26326.

b. DATE AND PRESENT LOCATION OF FIRST SKETCH, DRAWING OR PHOTO AND EARLIEST WRITTEN DESCRIPTION (Such as notebook entry, etc.)

Fourth Annual Report on Contract N00014-73-C-0201, dated 1/31/77. This is Dynatech Report No. 1521, Progress Report on Contract N00014-73-C-0201 dated July 18, 1977. (Dynatech Report No. 1631).

c. DATE AND PLACE OF COMPLETION OF FIRST OPERATING MODEL OR FULL SIZE DEVICE AND ITS PRESENT LOCATION

Dynatech R/D Comp y, November 5, 1976.

d. DATE AND PLACE OF FIRST TEST OR OPERATION AND THE RESULTS (Give name and address of witnesses, and present location of records)

On May 23, 1977, one quart of plasticized PCL wipe-on coating was sent to Captain Charles Burgoon, D.V.M. at the Naval Medical Research Institute (NMRI), National Naval Medical Center, Bet esda, MD. On June, 27, 1977, John B. Gregory and Donald L. Wise, Ph.D. of the Dynatech R/D Compan observed the tests at NMRI.

4. OTHER RECORDS (Notebook entries, descriptions, reports, drawings, etc.)

IDENTIFICATION	DATE OF DOCUMENT	PRESENT LOCATION
The following notebook pages cover the trials to date of various plasticizers and proportions of plasticizer to PCL: 26320, 26323, 4, 5, 6, 26366, 7, 8, 9, 26370, 1, 2, 3, 4, 5, 6, between November 5, 1976 and March 3, 1977.		

5. OTHER INDIVIDUALS TO WHOM INVENTION WAS DISCLOSED

NAME	ACTIVITY OR COMPANY INDIVIDUAL REPRESENTS	DATE DISCLOSED	TYPE (Oral or written disclosure)
Arthur B. Callahan, M.D.	Biological and		Oral
Kenneth W. Sell, M.D.	Medical Science Division	July 21, '77	and
Commander James Bond	Office of Naval Research		Written

6. DATE AND PLACE OF OTHER TESTS OR OPERATIONS, AND THE RESULTS (Give name and address of witnesses and identify present location of records)

none

7. IDENTIFY ANY PAST, PRESENT OR CONTEMPLATED USE OR PUBLICATION OF THE INVENTION

It is intended that direct application of a solution of plasticized PCL to a burn be used in an emergency to control evaporative fluids loss from the body and promote healing until the time the victim can be transported to a burn treatment center.

8. CLOSELY RELATED PATENTS, PATENT APPLICATIONS AND PUBLICATIONS

PATENT OR APPLICATION NO. AND DATE	TITLE OF PUBLISHED ARTICLE	PUBLICATION NAME AND DATE

(over)

Describe the invention fully and completely, using the outline given below. Sketches, prints, photos and other illustrations should be attached to this disclosure. Use additional plain pages as needed to complete the disclosure.

1. GENERAL PURPOSE. State in general terms the purpose and objects of the invention.

2. BACKGROUND. Describe the old methods, materials or apparatus used to perform the objects of the invention and give their limitations and disadvantages.

3. DESCRIPTION AND OPERATION. Describe clearly and completely the construction of the invention and give a detailed description of its operation and use. In the description, use reference characters to refer to components in attached illustrations.

4. ADVANTAGES AND NEW FEATURES. State the advantages of the invention over the old methods described in paragraph #2 above, and the features believed to be new.

5. ALTERNATIVES. Indicate any alternative methods, materials or constructions of the invention.

6. CONTRIBUTIONS BY INVENTORS. If this is a joint invention, indicate what contribution was made by each inventor.

7. EXECUTION OF DISCLOSURE. The end of the disclosure should be signed and dated by the inventor(s), in addition to any signatures in Part I. The disclosure should then be read and understood by two technically qualified witnesses. Under inventor(s) signatures, enter the statement: "Disclosed to and understood by me on (date)." The two witnesses should sign under this statement.

1. Purpose

The purpose of this invention is to control the evaporative water loss from severe flash burns during the immediate post burn period. This is accomplished by application of a solution of the polymer, poly-ε-caprolactone, (PCL) by swab or by spray from an aerosol container. The solvent evaporates after application, leaving a thin, flexible film which successfully controls the insensible water loss from the burned area.

2. Background

Shock is a major cause of death in the immediate period following a severe flash burn over large portions of the body. A primary cause of shock is the excessive loss of body fluids and protein.

Presently, there are many creams, greases, sprays and homemade concoctions designed to soothe and protect the wound immediately following a flash burn. These first-aid treatments are applied directly to the burn and remain there until the victim can be treated with more sophisticated methods.

(Gump and Kinney, Surg. Clin. N. Amer., 50 (6) Dec., 1970, and Rozin, et al, Ann, N.Y. Acad. Sci., 150 Aug. 14, 1968).

3. Description and Operation

The invention is a solution of PCL which can be applied directly to a flash burn by swab or by spray. PCL (mol. wt. 2,000 - 300,000) is a biodegradable polymer which is soluble in liquids such as acetone and tetrahydrofuran. When the polymer-solvent solution is spread over a surface (e.g. a burn wound), the solvent evaporates, leaving a thin, flexible film (0.001 to 0.01 inches thick) of the polymer. This film replaces the destroyed natural keratin moisture barrier, and controls the water transpired from the burned area to normal levels. Once the victim reaches a burn treatment center, the film can be removed and traditional burn treatment begun.

Both a plasticized PCL solution and non plasticized PCL solution were sent to Captain Burgoon for evaluation. The formulae were as follows:

	Non plasticized	Plasticized
Poly ε caprolactone	100 g	100 g
Triethyl citrate	none	33 g
Methyl acetate	300 ml	1200 ml
Methylene chloride	200 ml	300 ml

The wipe-on coating was applied to third degree burns obtained by pressing a 2.22 inch diameter iron heated to 65 C against the shaven flank of the pig at various times varying from 10 to 45 seconds and then brushing the burned area with the wipe-on coating. Some pigs were treated with the non plasticized PCL coating and some with the plasticized PCL coating. The other side of each pig was burned in the same manner but was not coated with a wipe-on solution. The solution with no plasticizer peeled from the burned area within a few days and was only marginally effective. The solution containing plasticizer adhered well and burns coated with this solution healed better than those that were not coated. The improved healing was particularly significant when the burn was borderline between 2nd and 3rd degree.

4. Advantages and New Features

PCL in solution is inexpensive, has a long shelf life, and is easy to apply. More importantly, the film is the only tissue compatible first-aid treatment (known to the inventors) which is designed to control the rate of water loss from a burned area while protecting the wound from contamination from the outside environment. Solutions of other polymers sold as wound dressings which Dynatech Engineers have tested have been so impermeable to the passage of water vapor that fluid seepage from the wound collects beneath the film providing a locus for infection. Both the plasticized and non plasticized PCL films while controlling water loss to near that of normal skin do allow some water to pass so pockets of fluid are not likely to collect.

INVENTOR OF IMPROVEMENT TO ORIGINAL INVENTION

John B Burgoon — August 15, 1977
DATE

DISCLOSED AND UNDERSTOOD BY ME ON _____
DATE

Donald Lee Wise August 15, 1977

Ralph L. Wentworth August 15, 1977

United States Patent [19]

Wise et al.

[11] **3,935,308**

[45] **Jan. 27, 1976**

[54] **WOUND COVERING AND METHOD OF APPLICATION**

[75] Inventors: **Donald L. Wise, Belmont; Arthur D. Schwope, Watertown, both of Mass.; Kenneth W. Sell, Rockville, Md.**

[73] Assignee: **The United States of America as represented by the Secretary of the Navy, Washington, D.C.**

[22] Filed: **Aug. 8, 1974**

[21] Appl. No: **495,705**

[52] U.S. Cl. 424/78; 424/45, 424/DIG. 13

[51] Int. Cl.[2] A61K 31/74

[58] Field of Search 424/DIG. 13, 45, 78

[56] **References Cited**

UNITED STATES PATENTS

3,044,873	7/1962	Gallicano et al.	424/DIG. 13
3,021,309	2/1962	Cox et al.	260/78.3
3,577,516	5/1971	Gould et al.	424/45

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Chemical Abstracts, Vol. vol 71, (1969), 123181.

Primary Examiner—Frederick E. Waddell
Attorney, Agent, or Firm—Richard S. Sciascia; Don D. Doty; Harvey A. David

[57] **ABSTRACT**

A preparation and a method are described for emergency, interim treatment of extensive burn injuries, e.g., flash burns, to external portions of a person. A solution of the polymer poly-ε-caprolactone in a volatile solvent, such as acetone or tetrahydrofuran, is applied to the burn area by spraying or swabbing, so that upon evaporation of the solvent a film of the polymer is left to serve as a barrier to insensible water loss.

1 Claim, No Drawings

3,935,308

WOUND COVERING AND METHOD OF APPLICATION

STATEMENT OF GOVERNMENT INTEREST

The invention described herein may be manufactured and used by or for the Government of the United States of America for Governmental purposes without the payment of any royalties thereon or therefor.

FIELD OF THE INVENTION

This invention relates to the treatment of burn wounds, and more particularly to a method and means for providing such treatment as a "first aid" expedient, and at times as part of more sophisticated supportive treatment.

Shock is a major cause of death in the immediate period following a severe burn, such as a flash burn, over large portions of the body. A primary cause of shock has been recognized as the excessive loss of body fluids and protein through the burned areas. This loss occurs primarily through evaporation, and the process is not visible or otherwise readily detectable to the subject or observer. The loss is therefore termed insensible, although the results thereof are dramatically apparent in the shock process.

Many, if not most, burn accidents occur under circumstances that make it impossible for the victim to receive immediate supportive treatment in a hospital. Such is the case, for example, with disasters, accidents, or conflicts occurring in remote areas, at sea, or under other adverse conditions. Accordingly, there has long been a need for suitable, adequate, readily available, and easily applied burn treatment that can be administered by relatively unskilled persons at the scene of injury.

DISCUSSION OF THE PRIOR ART

In the past there have been used various creams, greases, sprays, and homemade concoctions designed to sooth and protect the wound, immediately following a burn, as a first-aid treatment. In general, these have been ineffective in stopping insensible fluid and protein loss through the burn site and have been messy and difficult to apply. The latter factors are, of course, deterrents to effective use by unskilled persons in a first-aid situation.

In addition, there have existed various coverings for burns and similar wounds requiring covering of a substantial area for extended periods of time during the skin regeneration and healing process. These have included skin grafts where the skin was obtained either from another person or animal, or from another area of the injured party. Also, there have been provided various sheets, foils, and webs or fabrics made from various synthetic plastic materials, animal collagen, and the like. Examples of the latter are described in U.S. Pat. No. 3,491,760 to Bernhard Braun et al. Use of burn wound coverings in the form of fibrillar products comprising polyglycolic acid are alluded to in U.S. Pat. No. 3,739,773 to Edard E. Schmitt et al. Those burn wound coverings, and particularly those comprising foams, gells or foils of collagen, or other moist, conformable dressing, require special storage techniques and facilities that render them quite impractical to have available for immediate use as a first aid supply in various [illegible] and limited facility places where flash

burns and other extensive injuries to the skin may occur.

SUMMARY OF THE INVENTION

The present invention aims to overcome some or many of the disadvantages and shortcomings of the prior art, with respect to emergency or first-aid burn dressings or treatment, through the utilization of our discovery that a thin plastic film of poly-ε-caprolactone formed directly on the surface of a burn wound will adhere thereto and will control insensible fluid loss by evaporation so as to occur at a substantially normal rate, and that such a film can be effectively formed by applying a solution of poly-ε-caprolactone in a suitable solvent, such as acetone or tetrahydrofuran.

With the foregoing in mind, it is a principal object of the invention to provide an improved wound covering which is suitable for first-aid use on burns, is sufficiently compatible with human tissue and fluids to adhere to a burn wound for a useful period of time, and is notably effective in maintaining fluid balance in a subject.

Another object of the invention is to provide a burn wound treatment materials which can be stored for prolonged periods of time in a convenient and readily usable form, without any requirement for special storage facilities or conditions.

Still another object is the provision of burn treatment material of the foregoing character and comprising poly-ε-caprolactone in a solvent or vehicle that will rapidly evaporate after application to a wound surface to leave a thin, covering film of the poly-ε-caprolactone adhering to the wound.

As another object, the invention contemplates the packaging of the poly-ε-caprolactone and its solvent in a container having means for ejecting the contents thereof in the form of a spray or aerosol onto an affected area to be treated, such as a flash burn.

Yet another object of the invention is to provide a method of burn treatment including the steps of forming a solution of poly-ε-caprolactone in a volatile solvent, applying a layer of the solution over a surface to be treated, and allowing the solvent to evaporate so as to form a film of poly-ε-caprolactone having a thickness in a predetermined range.

The poly-ε-caprolactone, with which the discovery of this invention is concerned, is a biodegradable solid polymer having a molecular weight in the range of 2,000 to 300,000, and which polymer is soluble in liquid solvents, specifically acetone and tetrahydrofuran. U.S. Pat. No. 3,021,309 to E. F. Cox et al describes the polymer poly-ε-caprolactone and its generation. The chemical derivation of the polymer per se is not considered to be part of this invention, poly-ε-caprolactones having been known in the chemical arts for many years now, as is evident from that patent. Moreover, as also pointed out by that patent, the polymer concerned is soluble in acetone, and is capable of being formed into films.

What is considered to be a notable advancement in the medical art is our discovery that a solution of poly-ε-caprolactone in a volatile solvent can be applied directly to a burn wound surface, and that the solvent will evaporate to leave a thin, flexible film or skin of poly-ε-caprolactone that will adhere to the wound surface and will effectively control the evaporative water loss from a severe burn during the immediate post burn period

and until more conventional supportive burn treatment can be undertaken.

DESCRIPTION OF THE PREFERRED EMBODIMENT

In carrying out the invention it is preferred that the solution of poly-ε-caprolactone be prepared with a solvent that is volatile and substantially non-irritating to a subject when applied thereto. Accordingly, in an exemplary embodiment the solvent may comprise the liquid acetone, and the prepared solution may be placed in a suitable container for prolonged storage in contemplation of possible future emergency use.

In some instances, it may be desirable to utilize a container that has spraying capability, such as the conventional aerosol spray can. A suitable propellant, such as that sold under the name Freon, may be included in a pressurized state in the container to facilitate spraying of the solution. Alternatively, the solution may be stored in a container without spraying capability, with the intention of applying the solution to a burn by means of a swab.

When an injury occurs that removes or destroys the normal water retaining capabilities of a subject's keratinaceous tissue, for example in the case of a severe abrasion, flash burn, or the like, the poly-ε-caprolactone and solvent solution is applied, either by spraying or swabbing, as a coating over the entire injured area. As the solvent evaporates a thin flexible film of the polymer is left adhered to the wound surface. This film, which is preferably in the thickness range of about 0.0005 inch to 0.01 inch in thickness, replaces the destroyed natural keratin moisture barrier. Once the victim reaches a burn treatment center, the film can be removed and traditional burn treatment begun.

Obviously, other embodiments and modifications of the subject invention will readily come to the mind of one skilled in the art having the benefit of the teachings presented in the foregoing description. It is, therefore, to be understood that this invention is not to be limited thereto and that said modifications and embodiments are intended to be included within the scope of the appended claims.

What is claimed is:

1. A method of treating an extensive burn injury to an external portion of a person, comprising the steps of:

spraying a layer of a solution of poly-ε-caprolactone, having a molecular weight in the range of 2,000 to 300,000, in a volatile solvent comprising liquid tetrahydrofuran onto said external portion;

allowing said solvent to evaporate so as to leave a thin, flexible film of said poly-ε-caprolactone, having a thickness of about 0.0005 inch to 0.01 inch, adhering to said portion so as to form a barrier to body fluid loss therethrough.

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