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DEVELOPMENT OF AN ULTRAFAST-CURING WOUND DRESSING

ANNUAL REPORT

Michael Szycher, Ph.D. and Jonathan L. Rolfe

March 15, 1985

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-83-C-3240

Thermedics Inc.
470 Wildwood Street
P.O. Box 2999
Woburn, Massachusetts 01888-1799

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We are developing a drug-dispensing field wound dressing. The wound dressing, which can be easily applied by an untrained person, contains a coagulant to stop bleeding, and an antibiotic to prevent bacterial infection.

The medicated wound dressing is made of an ultrafast-curing polyurethane oligomer which is designed to cure at room temperature and delivers drugs on a controlled, sustained and highly reproducible basis.

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SUMMARY

Thermedics Inc. is developing a second-generation, drug-dispensing wound dressing. The wound dressing, which can be applied by the wounded soldier himself, incorporates thrombin as a coagulant and gentamycin sulfate as a wide-spectrum antibiotic.

The new wound dressing is a trilaminate composite. The air side of the trilaminate is a fabric impregnated with an aliphatic, medical grade polyurethane elastomer; the middle laminate is a controlled release layer, containing the microencapsulated pharmacoactive agents, and the third laminate is a 1.0-mil-thick layer of acrylic-based, pressure-sensitive adhesive.

The middle layer is fabricated from a mixture of urethane and silicone oligomers, which are precompounded with pharmacoactive agents, and is subsequently solidified (cured) upon mere exposure to low-intensity UV radiation at room temperature. Solidification at room temperature is a vital consideration, because most drugs are rapidly inactivated upon mild heating. Once cured, the oligomer layer containing pharmacoactive agents becomes a controlled-release monolith, capable of dispensing drugs at a continuous and predictable rate.

FOREWORD

Future conflicts may have to be fought without the advantage of overwhelming American air supremacy. In the absence of air supremacy, it may not be possible to evacuate wounded American soldiers for proper medical treatment for at least several days. This situation implies that a wounded soldier would need to be treated in the field; the initial treatment would have to be performed by himself, a buddy, or by a paramedic.

Based on this scenario, we embarked on the development of a new field wound dressing. The new field wound dressing would need to be applied without the benefit of prior medical training, during combat, and under all imaginable climatic conditions. Furthermore, the new wound dressing needs to incorporate coagulants and extended-action therapeutic agents to provide immediate stabilization of the wound. Currently available hospital wound dressings do not meet these requirements.

Under research contract DAMD17-83-C-3240, Thermedics is developing a second-generation wound dressing which speeds wound healing, incorporates pharmacoactive substances, and can be easily applied by the wounded soldier himself. This new wound dressing is based on an ultrafast-curing liquid polyurethane oligomer. The oligomer can be easily precompounded with pharmacoactive agents and, subsequently, cured in less than seconds at room temperature by illumination with UV radiation. Following cure, the wound dressing delivers the pharmacoactive agents in a controlled, sustained-release basis.

This second-generation, medicated wound dressing, when properly developed and tested, may become an ideal vehicle for the initial wound stabilization of wounded soldiers. Our research is being aimed at the development of medicated wound dressing with the following characteristics:

- Oligomer cured at room temperature during manufacture; thus, even heat-sensitive drugs may be incorporated.
- The ready-to-use field wound dressing will be dispensed from waterproof kits carried in a standard-issue backpack.
- Field wound dressing may be applied under any conceivable climatic condition by nonmedical personnel.
- Dressing is highly compliant for physical comfort and is highly abrasion resistant, even when wet.
- Dressing is moisture permeable but does not permit penetration of water or bacteria.
- Dressing delivers medicaments on a controlled, predictable and sustained basis.

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I. MILITARY SIGNIFICANCE

Contingency plans for future conflicts place unique demands on the military which are not experienced in the civilian community. Contrary to the present treatment rendered to most casualties, it is most probable that soldiers wounded in future combat environments will face an entirely different situation. It will be common for evacuation of these patients to be delayed for 72 hours and possibly longer. During this critical post-wounding period, qualified medical personnel will not be immediately available to initiate therapy. It is during this crucial time that care will be self administered or at best be provided by minimally trained personnel.(1) It thus becomes critical that means be available to initiate therapeutic measures under these unusual circumstances.

Less than half the number of soldiers killed in battle die outright as a result of explosions or high-velocity missiles. The high morbidity and mortality associated with combat injuries is primarily attributable to post-wound medical complications, such as overwhelming infections and uncontrolled bleeding. Traditionally, wounds have been treated with dressings. Wound dressings are usually composed of sterile, absorbent cloth, pressure bandages, or a flat strip of elasticized, adhesive film, designed to cover and protect wounds.

The vast majority of maxillofacial wounds inflicted in combat are infected or become infected early on in their course of treatment.(2) Currently available wound dressings are primarily limited to gauze pressure bandages. These materials have minimal beneficial characteristics. They function as simple coverings that are not impervious to microorganisms, thereby providing little protection from infection. By being absorbent, they may tend to desiccate the wound thus delaying healing. The material absorbed into the dressing may provide an excellent substrate supporting microbial growth. These materials may provide a mild measure of hemorrhage control by the application of pressure. However, pressure must be maintained for long periods, thereby restricting body movement so important in combat.

It is our intent to provide a compliant, thin, easily applied medicated wound dressing, dispensed from water-impermeable packages. The medicated wound dressing would be applied to maxillofacial wounds to stop bleeding and prevent bacterial infection, thus providing immediate stabilization of wounds until more definitive medical attention becomes available to the soldier.

Under these circumstances, a wounded soldier can return to combat with the comforting knowledge that the wound dressing is delivering a precise, controlled, and reproducible amount of coagulant and antibiotic. Further, the highly compliant wound dressing will reduce abrasion pain and will not interfere with normal body movements.

II. RESEARCH OBJECTIVES

A. IDEAL REQUIREMENTS

The ideal second-generation medicated field wound dressing should:

- Be soft and elastic, closely mimicking the mechanical properties of natural, intact skin.
- Display adequate adhesion to intact skin, but be minimally adhering to clot, so it may be removed at will.
- Control water vapor and oxygen exchange, thus maintaining a moist environment for rapid healing.
- Gradually deliver broad-spectrum antimicrobial agents that are nontoxic to the injured tissue.
- Deliver a bolus of coagulant, to stop and control bleeding for prolonged periods.

These research objectives are aimed at the development of a field wound dressing that provides immediate wound stabilization. This wound stabilization is expected to be accomplished through: (a) reduction of abrasion trauma, (b) easy removal without precipitating another bleeding episode, (c) promotion of normal wound healing under moist, aseptic environment, (d) prevention of bacterial infection, and (e) efficient return to hemostasis by hemorrhage control.

Incorporation of pharmacoactive agents is a key feature of the new wound dressing. The microencapsulation of drugs into a polymeric matrix was made possible by the development of a room-temperature, ultrafast UV-curable liquid polyurethane oligomer. This is a crucial consideration, since most drugs are rapidly inactivated by mild heat. To insure full pharmacological activity, the drugs should not be subjected to heat. This requirement was met by incorporating the drugs into the liquid matrix of the uncured oligomer followed by a room-temperature, UV-cure of the dressing.

Once cured, the wound dressing, containing drugs, becomes a sustained-release formulation. The dressing, in turn, once in contact with the wound and bodily fluids, provides immediate, direct, and controlled doses of drugs, targeted to the wound site, thus minimizing problems inherent in systemic drug delivery.

Promotion of the normal wound healing mechanism is another feature of the new field wound dressing. The dressing is semi-occlusive; i.e., it allows O_2, CO_2 and water vapor to permeate in physiological amounts,

but it excludes bacteria. This feature is important because, under these conditions, the field dressing is capable of maintaining the wound moist, but aseptic. And, as explained in the following paragraphs, it is now apparent that moist, aseptic wounds heal faster.

B. HYPOTHESES

The above-mentioned research objectives are based on the hypothesis that an elastic, semiocclusive wound dressing, containing extended-action pharmacological agents will provide soldiers immediate wound stabilization. Our assumptions are that immediate wound stabilization will be accomplished through: (a) hemostasis, (b) control of infection, and (c) promotion of normal wound healing mechanisms.

We hypothesize that hemostasis will be rapidly reached through the incorporation of a coagulant such as thrombostat (lyophilized thrombin). Infection control (from pathogenic bacteria, opportunistic invaders), will be accomplished by incorporation of pharmacological agent(s), such as gentamycin sulfate. Finally, promotion of normal wound healing mechanisms will be accomplished by the use of an abrasion-resistant, field-curable, polymeric membrane, which is: (a) noninflammatory and nonantigenic to the wound, (b) as compliant as skin, (c) similar to skin in oxygen permeability, and (d) similar to skin in water vapor transmission characteristics, thus maintaining an aseptic, moist environment.

For centuries, the common understanding of wound healing remained relatively static. There was an awareness that an open wound was subject to the threat of infection. Optimal wound healing was thought to occur under a scab. Dressings were used as protection from bacterial invasion and infection. Dressing materials, traditionally composed of gauze, encouraged the drying of wounds to facilitate scab formation.

In the 1950s, observers realized that an unbroken blister healed more rapidly. Since the blister protects the wound surface with a layer of fluid, this realization led to a new understanding of wound healing.[3]

Healing of partial-thickness damage has three major steps:

1. Epithelial Proliferation
2. Epithelial Migration
3. Dermal Proliferation

Complete epithelialization (steps 1 and 2) represents an effectively closed wound. The epidermal migration necessary to accomplish this closure is now understood to occur only over moist and healthy tissue.

Research in the 1960s, and published articles of the early 1970s, showed that the optimum conditions for steps 1 and 2 above (epithelialization) occurred under a dressing that maintained a moist environment. The development of the polyurethane products (a temporary artificial skin) arose from the recognition of this wound healing principle. The materials were utilized in the attempt to provide a moist environment much like nature's blister.[4]

Prior to the studies on the potential effects of dressings on the repair process mentioned above, the medical community had thought that the surgical dressing mainly absorbed exudate, cushioned the wound site, and hid the site from the patient. That research illustrated that dressings can affect the response to the wound and even retard healing through dehydration or tissue damage during removal. It is now appreciated that dressings can serve to promote faster healing. They can optimize epithelialization, reduce pain (which is associated with wound dehydration), and minimize local inflammation. If impregnated with drugs, they can also deliver medication at a controlled rate.

Optimal wound healing occurs when the dressing material strikes a balance between dehydration and maceration (which results from accumulation of excess exudate). In addition to stimulating pain, dehydration leads to desiccation and cell death, undermining epithelial movement and wound closure. Prevention of dehydration can minimize eschar formation and inflammatory response. Maceration, which is stimulated by excess fluids and debris, is often accompanied by bacterial proliferation; it also has its own attendant negative effects on wound healing.

We have carefully studied the desired balance between dehydration and maceration. We have thus selected an optimal balance between the moist healing environment (to counter dehydration), and vapor permeability (to counter maceration). A key element in our wound dressing development has been our selection of the most appropriate combination of vapor permeable polyurethane and acrylic, pressure-sensitive adhesive to produce a "second generation" wound dressing.

Therefore, another of our research goals is currently directed toward producing a "second generation" wound dressing capable of producing an aseptic microenvironment under the wound which is most conducive to rapid healing.

III. WORK TO DATE

Our wound dressing is a trilaminate composite, shown in Figure III-1. The air side of the trilaminate is a polyurethane-impregnated fabric. The middle laminate is a controlled-release layer containing the microencapsulated pharmacoactive agents; and the third laminate is a 1.0-mil-thick layer of acrylic-based, pressure-sensitive adhesive. The entire trilaminate composite is attached to release paper; prior to use, the soldier removes the release paper, and the wound dressing is applied to the wound. The dressing is held onto intact skin by means of the pressure-sensitive adhesive.

The fabric was specifically selected for its ability to stretch like skin. Intact, healthy skin is anisotropic; that is, it stretches more in one direction than in another. The fabric mimics this property and, as a result, the new wound dressing is very comfortable once applied, because it "gives" like skin. In addition, incorporation of the fabric into the dressing imparts drapability previously unattainable by commercially available thin-film wound dressings, since it does not wrinkle when the bandage is removed from the release paper.

However, the most important technical breakthrough of the new wound dressing is our development of non-toxic, tissue-compatible oligomers which cure under UV radiation. Curing by UV radiation is a breakthrough in medical-grade polymer technology, since it allows ultrafast curing (solidification) of biocompatible materials in a matter of seconds at room temperature.

Utilization of UV-curing oligomers permits the production of ingenious drug-dispensing wound dressings. The liquid oligomer may be compounded with pharmacoactive agents, yet it will solidify upon mere exposure to low-intensity UV radiation at room temperature. Solidification at room temperature is a vital consideration, because most drugs are rapidly inactivated upon mild heating. Once cured, the oligomer containing pharmacoactive agents becomes a controlled-release monolith, capable of dispensing drugs at a continuous and predictable rate.

In our technology, we utilize a mixture of two oligomers: (1) a vinyl-terminated polyurethane, and (2) a vinyl-terminated silicone. The synthesis and compounding of these unique materials is fully described in the paragraphs that follow.

A. SYNTHESIS OF VINYL-TERMINATED POLYURETHANE OLIGOMERS

The polyurethane oligomer comprises a diisocyanate, a macroglycol, and an acrylyl chain terminator which provides the necessary vinyl end

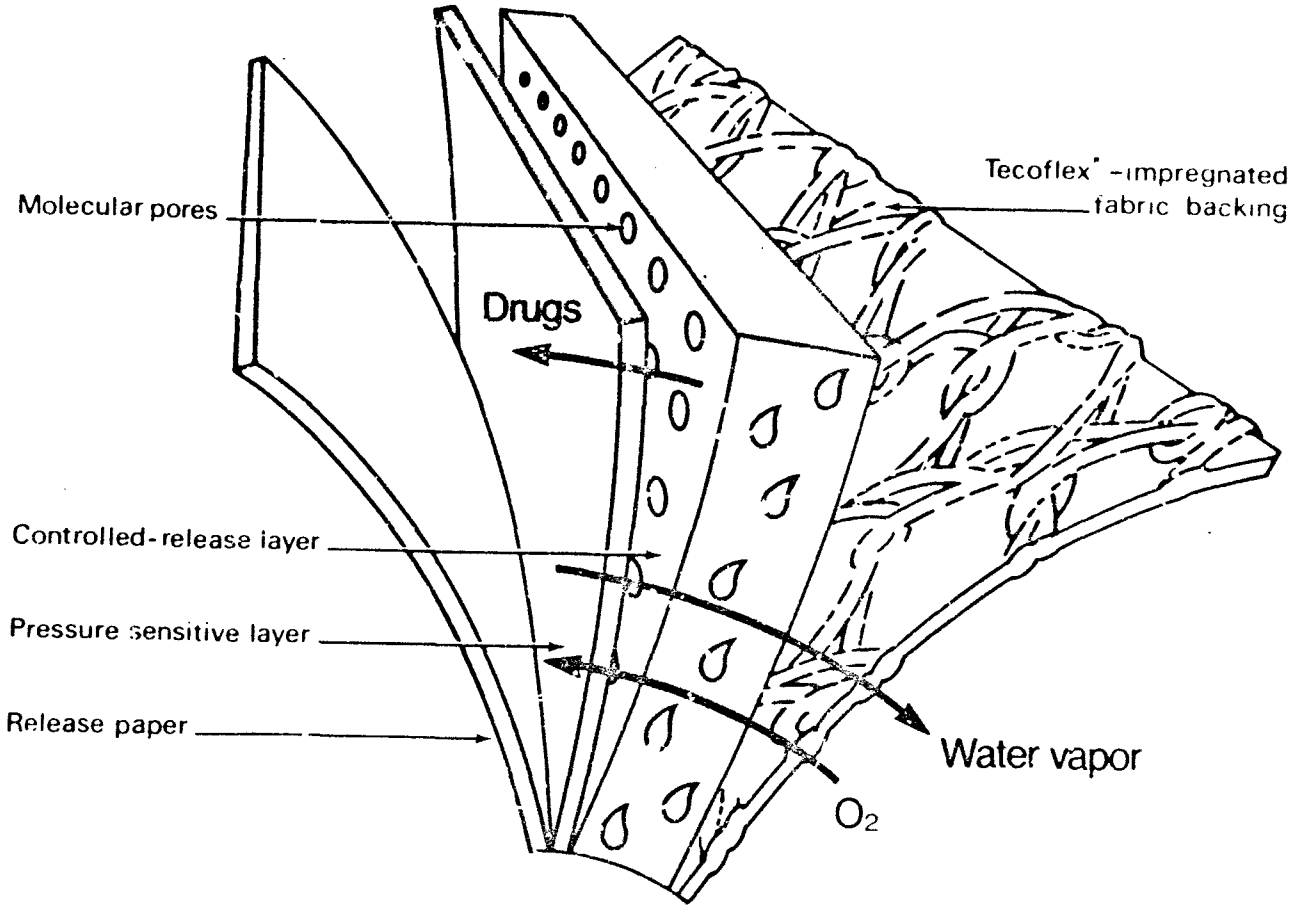

Figure III-1 **The Thermedics wound dressing, containing thrombin and gentamycin sulfate in the middle, controlled-release area**

groups. Incorporation of a photoinitiator into this oligomer, and subsequent UV bombardment, results in a flexible, elastomeric and highly abrasion-resistant cured film. This film is expected to result in a superior field wound dressing, or a "super Band-Aid," when extended-action therapeutic agents are compounded into the oligomer.

Specifically, we have produced UV-curable polyurethane films, with high mechanical properties, such as 1500 psi ultimate tensile strength, 300 percent ultimate elongation, and excellent abrasion resistance by reacting 25.4 percent by weight of isophorone diisocyanate with 57.2 percent of 1000 Dalton polypropylene glycol (PPG). This isocyanate-terminated prepolymer is chain extended with 13.3 percent by weight of hydroxyethyl acrylate. The final product, designated as an oligomer (shown in Figure III-2) was then further compounded with 3.8 percent by weight of diacetoxyacetobenzophenone (the photoinitiator). The photoinitiator is activated under UV illumination to produce two free radicals, as shown in Figure III-3. Polymer curing proceeds at room temperature when the free radicals generated by the photoinitiator react with the vinyl end groups, resulting in additional polymerization.

The above constituents were emulsified and cast unto 250-μm-thick films and exposed for 60 seconds to UV radiation from a commercially available UV source to produce the above-mentioned mechanical properties.

During the first year, we synthesized a variety of urethane oligomers to maximize those properties most desirable in a field wound dressing, such as tensile strength and hardness. In our trials, we need only vary the molecular weight of the PPG to reduce the experimental matrix.

In varying the molecular weight of the PPG, we were guided by well-known principles in polymer chemistry. These principles state that as the molecular weight of the PPG decreases, the tensile strength and hardness decrease concomitantly. Inversely, as the molecular weight of the PPG increases, the tensile strength and hardness increase, thus allowing us to tailor the properties of the finished, cured film.

B. SYNTHESIS OF VINYL-TERMINATED SILICONE OLIGOMERS

The second step in our development program was the synthesis of vinyl-terminated silicone oligomers. These high-molecular-weight silicone oligomers are important in the development of a suitable field wound dressing for two important reasons. First, the higher the silicone content,

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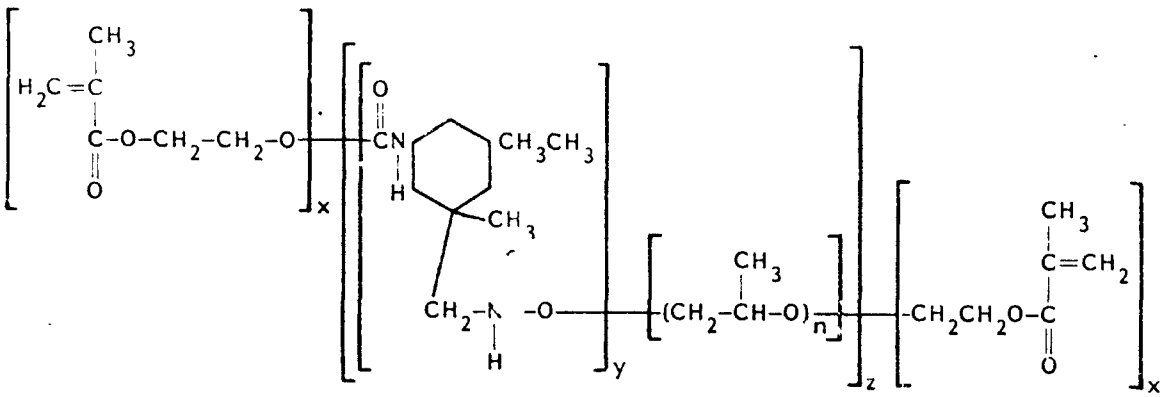

Figure III-2. Acrylic-Terminated Polyurethane Oligomer

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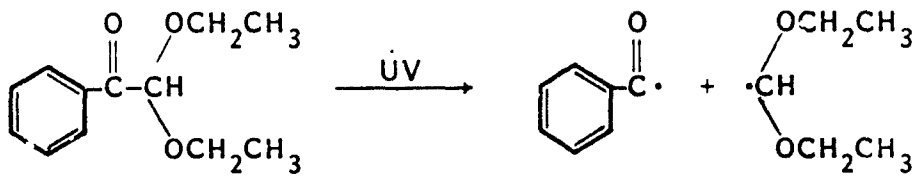


BENZOPHENONE INITIATOR

Figure III-3. UV-Induced Free Radical Formation

the lower the adhesion of the dressing to the wound. Second, silicone oligomers can be synthesized in very high molecular weight (high viscosities), thereby providing convenient thixotropic properties to the uncured dressing.

The synthesis of vinyl-terminated silicone elastomers (specifically vinyl-capped alklyl siloxane copolymers) was undertaken in our laboratories according to a proprietary series of steps. Our approach consisted of copolymerizing stoichiometric mixtures of octamethylcyclotetrasiloxane and tetramethylvinylcyclosiloxane. The initial polymerization takes place under the influence of a catalyst (KOH), which is subsequently neutralized by the formation of potassium acetate (KAC). Following the removal of H_2O by a vacuum process, the silicone fluid is copolymerized with tetramethylvinylcyclosiloxane to form a vinyl-terminated silicone oligomer.

The copolymerization begins with the anionic, ring opening polymerization of octamethylcyclotetrasiloxane (D_4), the cyclic tetramer of PolydiMethylsiloxane (PDMS). This reaction is shown in Figure III-4.

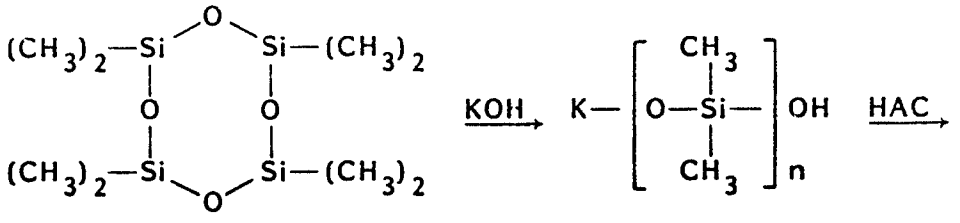
The initial product of the ring opening polymerization is an equilibrium mixture of cyclic and linear PDMS, with a mean molecular weight determined by the amount of alkali metal catalyst employed. Neutralization, repeated washings, and thorough vacuum stripping at elevated temperatures yield a pure silanol-terminated PDMS fluid, with fluid viscosities increasing with increasing M. For instance, at $n = M_W = 3600$, methyl-terminated PDMS has a viscosity of 60 centistokes; at $n = 1400$ $(M_W) = 10,000$ the kinematic viscosity is 10,000 centistokes.

The PDMS was next made to copolymerize with tetramethylvinylcyclosiloxane to produce a high-viscosity, vinyl-terminated silicone oligomer (>6,000,000 cP). The overall initial formula for the synthesis of a silicone oligomer proceeds as follows:

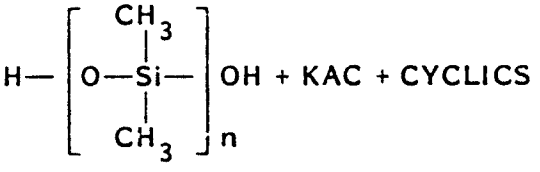
Octamethylcyclotetrasiloxane	100 moles
Tetramethylvinylcyclotetrasiloxane	0.3 moles
Analytical-Grade Potassium Hydroxide (Reacted at 145°C for 5 hours)	0.001% by weight

The vinyl-terminated silicone oligomer can be cured into a soft, pliable elastomer by exposure to UV bombardment via free radical addition polymerization, according to the reaction shown in Figure III-5.

Using this procedure, we have successfully UV cured vinyl-terminated silicone oligomers, which have proven to be biocompatible in preliminary animal experiments. Typical physical properties of the fully cured silicone elastomers are summarized in Table III-1.



Octamethylcyclotetrasiloxane (D_4) Silanolate Polymer



Silanol-Terminated Polymer, Raw

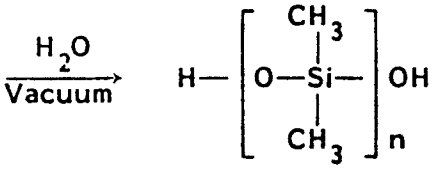


Figure III-4. Pure, Silanol-Terminated Di Methyl Siloxane Silicone Fluid Via Ring Opening of Octamethylcyclotetrasiloxane

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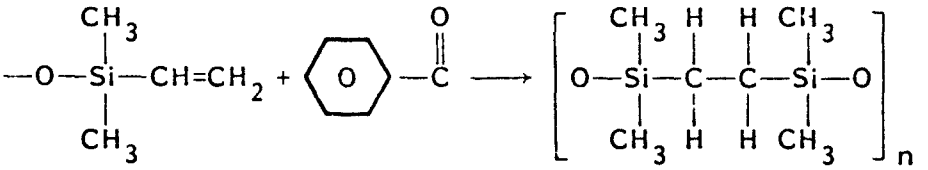

Figure III-5. Free Radical Polymerization of a Vinyl-Terminated Silicone Gum

TABLE III-1

TYPICAL PROPERTIES OF AN ELASTOMERIC SILICONE POLYMER

Hardness (Shore A)	60
Tensile Strength (psi)	1000
Elongation (%)	300
Tear Strength (pli)	175

C. COMPOUNDING

The urethane and silicone oligomers are intimately mixed in a heated two-roll mill. The gentle shearing action of the rotating rolls results in a thorough dispersion of the two liquids.

Once adequate dispersion of the two oligomers has been achieved, thrombin and gentamycin sulfate are slowly added to the rolling bank. The mill is then used to disperse the pharmacoactive agents in a highly controlled fashion; mixing, dispersion and microencapsulation of the drug powder are attained in approximately 20 minutes. After the 20 minutes have elapsed, a microencapsulated powder (average particle size = 0.71 μm) is obtained.

At this time all fluorescent lights (which emit weak UV radiation) are shut off. In a darkened laboratory, with only lights from red bulbs (similar to those used in photographic darkrooms), the photoinitiator is added to the oligomer/drug mixture. An additional period of 10 minutes of mixing in the mill is required for complete solution. At the end of this operation, the uncured oligomer/drug/photoinitiator mixture is a thixotropic mixture, ready for curing.

The mixture is next applied in the form of a 250-μm-thick membrane onto the TECOFLEX®-saturated fabric. The oligomer layer is cured by illumination from UV-curing lamps, emitting a radiation spectrum covering the range from 320 to 440 nm. The curing is performed in continuous ovens, in a nitrogen atmosphere to protect the uncured membrane from oxygen, moisture, or other airborne contaminants.

D. PRESSURE-SENSITIVE ADHESIVE

To apply the wound dressing, and to keep it in place for the desired time period, a pressure-sensitive adhesive must be used. Delivery of pharmacoactive agents by a medicated wound dressing utilizing a pressure-sensitive adhesive to maintain effective wound contact demands the marriage of three unrelated disciplines: pharmaceutical technology, polymer technology, and pressure-sensitive-adhesive technology.

In our development of the field wound dressing, we have been guided by a number of key principles. These principles are encompassed in pharmaceutical, polymer, and adhesive technologies, and will be discussed in the following order: (1) adhesion to skin, (2) cohesive strength, (3) anchorage of adhesives, (4) skin irritation, (5) drug-oligomer-adhesive interaction, and (6) shelf stability.

1. Adhesion to Skin

Skin adhesion is a fundamental property required to hold any device in place. However, adhesive properties should be such that the dressing can be removed after the required residence time in an unremarkable manner. Skin adhesion should be balanced between: (a) the adhesion level required for secure holding regardless of patient movement, perspiration level or bathing, and (b) ease of removal when dosage is complete.

The most desirable adhesive system will also show uniform adhesion to skin vs time with only moderate adhesion buildup or loss. Also, the range of values observed should be statistically reproducible and as small as possible.

Adhesion level to the patient dosage site with a wound dressing should only be enough to effectively keep the device in place for the necessary dosage period. Higher levels of skin adhesion should be avoided where possible, since high skin adhesion levels increase the incidence of excoriation during removal. Higher than necessary levels of skin adhesion also increased the probability of skin sensitization and irritation with repeated use on the same site.

In our medicated wound dressing, we have chosen an acrylic-based, pressure-sensitive adhesive that builds adhesive to the skin site rapidly, plateaus, and thereafter maintains uniform adhesion for up to seven days. Upon removal, we have observed a minimum of adhesive residue left on the skin site, and removal has been unremarkable.

2. Cohesive Strength

This is the ability of the adhesive to stay together and to stay in place under load, i.e., resist shear. Good cohesive strength is also vital for clean removal from the skin with minimum residue. It is a manifestation of the visco-elastic properties of a particular system.

Cohesive strength or lack thereof is a function of the molecular weight and molecular weight distribution. Addition of relatively low molecular weight tackifying agents to compounded adhesives affects the molecular weight distribution. Adhesive processing during coating can also directly influence final molecular weight distribution.

Positive tests for good cohesive strength in vivo are the unit staying in place on the patient (not sliding) and unremarkable removal with no visible adhesive residue left on the skin.

In our wound dressing, we selected a pressure-sensitive adhesive which displayed sufficient cohesive (or internal) strength to remain in place, yet it peeled from the skin cleanly. Cohesive strength was not adversely affected by either ethylene oxide or gamma radiation sterilization, and was unaffected by temperatures between +95°F and -20°F.

3. Anchorage of Adhesive

The pressure-sensitive adhesive, which is designed to hold a medicated wound dressing to a soldiers' skin, must on the obverse side stay adhered to the dressing. Keeping the adhesive firmly attached to the dressing is referred to as adhesive mass anchorage.

Adhesive mass anchorage is most easily tested in a direct manner. The tests are essentially qualitative - you either have it or you don't. An effective test that can be done without instrumentation is to simply fold the adhesive film composite pressure-sensitive side upon itself and press together to insure good contact. Then peel one end back on itself creating a 180 degree peel test.

Acceptable mass anchorage is also demonstrated by lack of adhesive transfer from one surface to the other. Still another sign of good mass anchorage is a uniform adhesive appearance after adhesive separation by the above tests. Unacceptable mass anchorage is gross transfer or delamination of adhesive from its support film or layer.

Mass adhesive anchorage is critical to device performance. Firstly, loss of mass anchorage may cause the device to fall off (in the worst case). Secondly, poor mass anchorage with attendant separation of device layers can cause dosage interruption, and/or dose dumping. In our medicated wound dressing, all components (saturated fabric, oligomer layer and pressure-sensitive adhesive) were carefully chosen for compatibility with the foreseen field service demands.

4. Skin Irritation

It is an unnatural condition for the skin to be covered with an adherent wound dressing, and to keep potential skin irritation, we have considered the following parameters:

- Skin Irritation Potential (Rubber, Silicone, or Acrylic)
- Length of Time Worn
- Drug Adhesive Interaction
- Adhesive Permeability/Porosity

In terms of skin irritation potential, rubber-band adhesives have shown the greatest potential; silicones were excellent, but changed tackiness after gamma sterilization; acrylics offered the best combination of properties.

Acrylics were shown to remain stable in contact with human skin for about seven days and no drug/adhesive interaction was observed. Acrylics were also the most permeable/porous adhesives tested; this is important, since the more permeable/porous an adhesive is, the more it allows skin to breathe or respire resulting in less tendency toward skin irritation.

This is particularly important in a field wound dressing that may not be replaced for several days. Under these conditions, large patches of skin will be continually covered by an adhesive dressing, which may lead to skin maceration. The selected acrylic adhesive has demonstrated the lowest tendency toward skin maceration, since it is highly porous.

5. Drug/Adhesive Interactions

The possibility of drug/adhesive interaction is an important consideration as it may change:

- Drug Potency as a Function of Time
- Device Wear Characteristics
- Skin Adhesion
- Skin Irritation

Drug/adhesive interaction can affect skin adhesion. This can manifest itself as a softening of the adhesive mass making it too tacky with loss of cohesive strength. It may also cause irritation due to high skin adhesion. Excessively high drug levels can also work in the opposite direction and dry up the mass with resultant loss of tack or quick-stick.

We are cognizant of skin irritation phenomena which can result from unforeseen drug/adhesive interactions. To date, our tests have shown that drugs maintain their integrity and pharmacological activity when incorporated into our medicated wound dressing system.

6. Shelf Stability

The best designed system is of little value if its performance is lacking when it is finally used. Substandard shelf stability may be manifested by incorrect dose delivery or deterioration of pressure sensitive.

The choice of a pressure-sensitive adhesive polymer system will play a major role in shelf stability of the adhesive component of the delivery device. While there are probably exceptions, it has generally been demonstrated that synthetic rubber/natural rubber resin adhesives deteriorate most quickly with time. Acrylic polymer pressure sensitives show exceptional aging properties, and have thus become our choice for use in the manufacture of medicated field wound dressing.

IV. PROGRAM STATUS

The following paragraphs summarize the status of each program task.

A. TASK 1 - DEVELOPMENT OF VINYL-TERMINATED URETHANE OLIGOMER

Both acrylate and methacrylate versions of the urethane oligomer were prepared with polypropylene gylcols of 1000 mol wt and 2000 mol wt, respectively. Candidate oligomers were selected on the basis of optimal rheology of the uncured material, rapidity and ease of cure, as well as cured physical properties.

Oligomers prepared from 2000 mol wt glycol were excessively viscous at room temperature, making them unsuitable for further consideration. Oligomers prepared from 1000 mol wt glycol displayed good viscosity and adequate tear strength and shelf stability.

Oligomers prepared with methacrylate termination cured more slowly (30 seconds) than those prepared from acrylate termination (20 seconds). Since the cure time is still rapid for either system, the use of hydroxy ethyl methacrylate was selected on the basis of experience and demonstrated low toxicity.

B. TASK 2 - DEVELOPMENT OF VINYL-TERMINATED SILICONE OLIGOMER

The oligomer is based on a low-viscosity silicone fluid (20 cs) which is chain terminated with an acrylic chain extender.

The silicone oligomer was prepared and, as expected, trial formulations incorporating the silicone oligomer exhibited marked lowering of adhesion. We have found that we can increase or decrease the level of adhesion with the silicone, so a very diversified range of formulations can be readily prepared.

C. TASK 3 - DEVELOPMENT AND TESTING OF OPTIMAL PHOTOINITIATOR SYSTEM

Candidate urethane oligomers synthesized from isophorone diisocyanate, 1000 mol wt glycol and hydroxy ethyl methacrylate were used to study several different photoinitiators.

Formulations containing different photoinitiators in amounts varying from 2 to 6 percent by weight were prepared, and cured for 30 seconds with a phosphor-enhanced, portable, low-pressure mercury lamp. Cured specimens were evaluated visually, physically, and chemically; thoroughness

of cure was determined by immersion in acetone to ascertain degree of swelling (crosslinking).

Several photoinitiators were evaluated including 2,2, di-sec butoxy acetophenone, 2-hydroxy 2-methyl 1-phenyl propanone, 2,2 diethoxyacetophenone, benzophenone and benzophenone tetra carboxylic dianhydride. From these photoinitiators, 2,2 diethoxyacetophenone (DEAP) gave the best results; cures were fast, were reproducible, and physical properties of the cured films confirmed a high degree of reaction completeness. These factors, combined with indications that DEAP has low toxicity, make this our preferred photoinitiator.

Dr. J. Vincent, USAIDR, tested the in vitro compatibility of the photocured composition, containing our preferred photoinitiator. The photocurable composition was tested in both its cured and its uncured condition with excellent results. Dr. Vincent reports no adverse reaction or evidence of cytotoxicity when the composition was exposed to cultured Vero cells for 72 hours at all concentrations of the photoinitiator. These conclusive results encouraged us to proceed with our preferred photoinitiator for all subsequent trials.

D. TASK 4 - OPTIMIZATION OF RHEOLOGY

Two rheologically related problems were addressed and solved, in this task: First, the uncured oligomer tended to migrate from the dressing package during storage, particularly if continuous pressure was applied. Second, some uncured oligomer was lost when the dressing was removed from the backing paper.

Testing showed that both problems could be solved simultaneously by the simple addition of 10% Cab-O-Sil N70 as a thickening agent, and about 10% of TECOFLEX EG-60D as a non-Newtonian thixotropic agent, a biomedical-grade polyurethane elastomer synthesized and manufactured by Thermedics.

Significant progress was achieved on both problems by immobilizing the uncured oligomer in a gel of TECOFLEX thickened by 10 parts per hundred of resin (phr) of Cab-O-Sil. This composition allowed the fabrication of a rheologically stabilized wound dressing, with virtually unchanged cure properties, since neither Cab-O-Sil nor TECOFLEX significantly absorb UV radiation.

E. TASK 5 - SELECTION OF MOST PROMISING COMPOSITION

Six specimens each of six different formulations, both cured and uncured, were submitted to Dr. J. Vincent, USAIDR, on December 15, 1983, for evaluation and comment. All specimens were based on 2.0

equivalents of isophorone diisocyanate, 1.0 equivalent of 1000 mol wt poly propylene glycol and 1.0 equivalent of hydroxy ethyl methacrylate containing 10% by weight of Cab-O-Sil M-70.

The following specimens of both cured and uncured wound dressings were submitted.

Formula No.	Description
1	2% DEAP
2	4% DEAP
3	6% DEAP
4	4% DEAP 5% thixotropic agent (TECOFLEX EG-60D)
5	4% DEAP 10% thixotropic agent
6	4% DEAP 15% thixotropic agent

We had recommended that the specimens be cured under readily available UV sun lamps, or high-pressure mercury lamps, with a spectral output between 250 and 450 mm; under these conditions, the uncured dressing should fully polymerize in approximately 30 seconds. Conversely, the uncured dressing could also be fully polymerized when exposed to direct sunlight for approximately 5 minutes.

F. TASK 6 - CHEMICAL AND PHYSICAL TESTING

The uncured dressings have been chemically characterized by gel permeation chromatography (GPC) and by IR spectroscopy. Physical properties of formulation No. 5 (Task 5) were as follows:

Ultimate Tensile Strength	1235 psi
Ultimate Elongation	415%

Oligomer synthesis was closely monitored by IR absorption spectrophotometry by recording isocyanate depletion during reaction. No unusual problems were encountered, and this task is completed.

In addition, on December 8, 1983, Thermedics acquired (at no cost to USAIDR) a Waters GPC-II microprocessor-based high-performance liquid chromatograph. This new instrument will allow us to initiate surveillance of incoming raw materials such as poly propylene glycol as well as the molecular weight distribution of the finished oligomers. This instrument will also furnish a strong technology base for anticipated incorporation of pharmacoactive agents into the oligomeric matrix in year two.

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