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Development of Bioelastic Material for Aspects of Wound Repair

Contract No. N00014-90-C-0265

TRIANNUAL PROGRESS REPORT FOR SECOND TRIMESTER OF YEAR 3

(January through April, 1993)

Bioelastics Research Ltd
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A. PURPOSE OF THE CONTRACT:

Broad Goal: The synthesis and characterization of bioelastic materials designed for specific applications of wound healing.

Specific Goals: For materials with possible use as wound coverings, control of the temperature of transition by changes in hydrophobicity will be examined. In addition, the rate of water passage through the matrix will be determined. The research approach is the stepwise coordination of the synthesis and characterization of the materials. The first application phase was concerned primarily with synthesis of the basic polypentapeptide poly(VPGVG) and the analog with L-alanine substituted in position 3, poly(VPAVG) and mole fraction combinations thereof to achieve elastomeric matrices of varying elastic moduli. *And in the third year polypentapeptides containing chemical clocks are to be characterized for their rate of breakdown and their effects on drug release profiles.*

Peptide Syntheses: The three sets of syntheses are:

1) Synthesis of the basic polypentapeptides, poly(VPGVG) and poly(VPAVG) and mole fraction combinations thereof, poly[f_{A3}(VPAVG),f_{G3}(VPGVG)], and compounding of these polymers to fabrics such as gauze.

2) Synthesis of analogs of poly(VPAVG) with different hydrophobicities.

3) Synthesis of analogs with functional side chains to achieve chemical control of contraction under isothermal conditions.

4) *Synthesis of polymers containing chemical clocks to gain control of the rate of degradation.*

Physical Studies: The physical studies include:

1) Determination of the temperatures of transition.

2) Evaluation of the properties of aerosol sprays and foams on 37°C surfaces and cavities.

3) Determination of the rates of water loss through the synthetic elastic matrices or membranes (for those materials with potential for use as wound coverings or as vascular sleeves).

4) Mechanical studies including: stress strain, temperature dependence of length at constant force, temperature dependence of force at constant length and rates of contraction.

5) *Determination of the relative rates of degradation in relevant media.*

6) *The release of model drugs from cross-linked matrices and coacervates with and without chemical clocks*

B. SYNTHESES COMPLETED OR BEGUN IN THE SECOND TRIMESTER OF YEAR 03:

The synthesis of 10 grams of the following two polymers has been completed to facilitate production of matrices of increased strength:

1. poly[0.9(AVGVP),0.1(AFGVP)] CG149WR
2. poly[0.8(AVGVP),0.2(AFGVP)] CG150WR

The synthesis of 35 grams each of the following two polymers has begun:

1. poly[(AVGVP)
2. poly(GVGIP)

These latter syntheses are to be used to determine the biocompatibility of these polymers.

C. PROGRESS

1. Determination of Transition temperatures T_t

The transition temperatures for CG149WR and CG150WR are 26.6°C and 23.0°C, respectively.

2. Stress/strain characterization of X^{20}-poly(GVGIP) and X^{20}-poly[0.25(GFGVP),0.75(GVGVP)].

Figure 1 contains the stress/strain curve for X^{20}-poly(GVGIP) where a sigmoid shaped curve is obtained. The Young's (elastic) modulus obtained from the initial slope is 7.2 x 10^6 dynes/cm^2, that from 60 to 100% extension is 3.9 x 10^6 dynes/cm^2, and that at high extensions is 8 x 10^6 dynes/cm^2. Failure began at just over 180% extension.

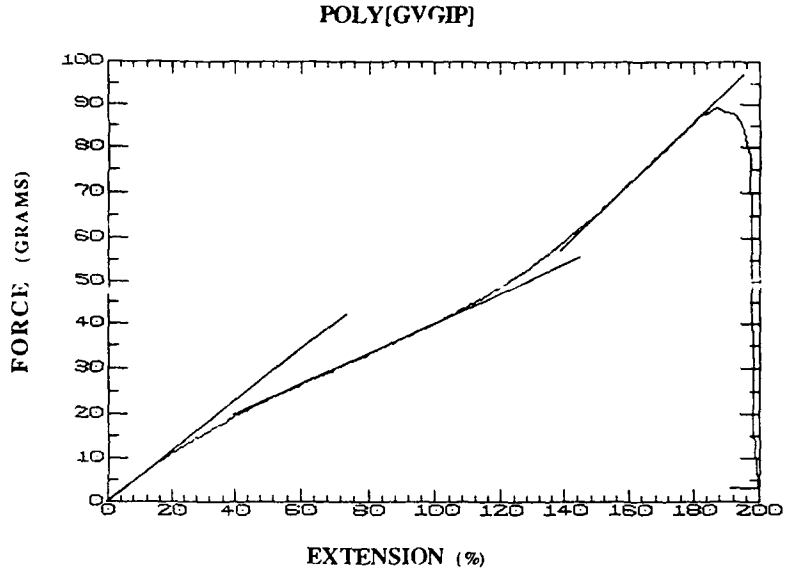

Figure 1

Figure 2 contains the stress/strain curve for X^{20}-poly[0.25(GFGVP),0.75(GVGVP)]. The elastic modulus obtained from the initial slope is 8.4 x 10^6 dynes/cm^2, and that in the 70 to 90% extension range is 4.9 x 10^6 dynes/cm^2. Failure for this elastic matrix began just above 90% extension.

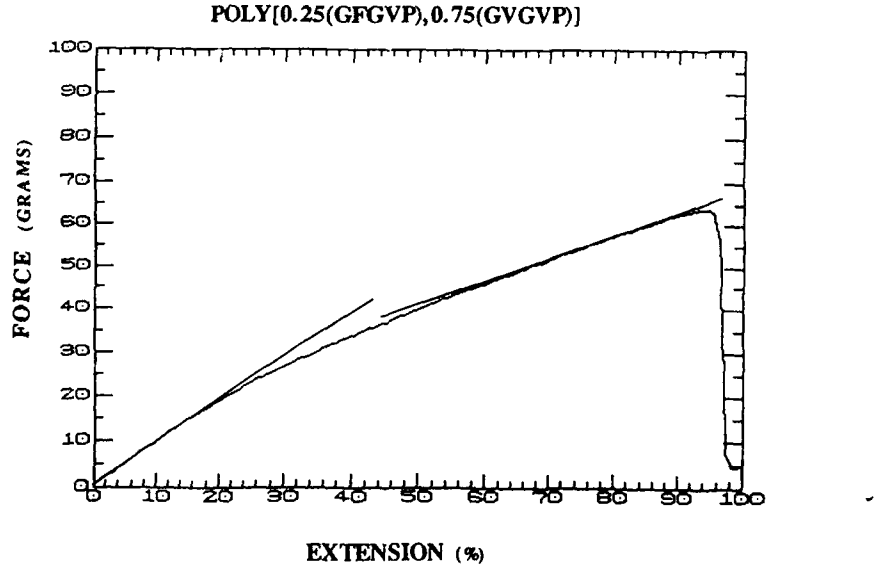

Figure 2

These elastic moduli are well placed with regard to viable vascular wall which is in the 4 to 6 x 10^6 dynes/cm^2 range. As the vascular wall under diastolic pressure is near 30% extension, this puts the operating range of the material at or slightly above the elastic modulus of a functional artery. The gamma-irradiation dose can be lowered slightly to reduce the elastic modulus, or the wall thickness can be slightly less than that of the vascular wall to arrive at the desired compliance match.

D. FURTHER STUDIES

1. Biocompatibility

The above results suggest that either of these compositions are well suited to function as sleeves for concomitant veins as was suggested in the original proposal. It is now important to take the next step which is to carry out extensive biocompatibility studies. This effort has started with the synthesis of 35 grams of poly(GVGIP). Next, similar quantities of poly[f_V(GVGVP),f_F(GFGVP)] will be synthesized with some variation of the mole fractions to optimize elastic modulus and extensibility, and the biocompatibilities will also be investigated. It is planned that the mole fraction f_F will have the values in four different syntheses – 0.1, 0.2, 0.3 and 0.4.

2. Degradability

In terms of the perspective of the temporary functional vascular sleeve, it is now planned to synthesize poly[f_V(GVGIP),f_N(GNGIP)] where asparagine (Asp,N) is introduced to result in a spontaneous surface carboxamide hydrolytic cleavage to carboxylate. This will raise the value of T_t and cause surface swelling with resulting increased rate of degradation.

E. PUBLICATION SINCE LAST REPORT (Copy Attached):

Dan W. Urry, D. Channe Gowda, Cynthia M. Harris and R. Dean Harris, "Bioelastic Materials and the ΔT_t Mechanism in Drug Delivery," *Am. Chem. Society Books, Poly. Chem. Div. Mtg. Proceedings in Symp. Series* 1993 (in press).