

[54] **INJECTABLE CROSS-LINKED COLLAGEN IMPLANT MATERIAL**

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**Related U.S. Application Data**

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[52] **U.S. Cl.** ..... **260/123.7; 514/773; 514/801; 128/DIG. 8**

[58] **Field of Search** ..... **260/123.7; 424/177, 424/359; 128/DIG. 8; 514/2, 773, 801**

[56] **References Cited**

**U.S. PATENT DOCUMENTS**

|           |         |                |             |
|-----------|---------|----------------|-------------|
| 3,949,073 | 4/1976  | Daniels et al. | 424/177     |
| 4,140,537 | 2/1979  | Luck et al.    | 260/123.7   |
| 4,233,360 | 11/1980 | Luck et al.    | 260/123.7   |
| 4,424,208 | 1/1984  | Wallace et al. | 260/112.5 R |

**OTHER PUBLICATIONS**

Schechter, I., et al, "Prolonged Retention of Glutaral-

dehyde-Treated Skin Homografts in Humans", *Brit. Journal of Plas. Surg.*, (1975) 28, 198-202.

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[57] **ABSTRACT**

Cross-linked atelopeptide collagen that is substantially free of residual cross-linking agent is prepared by: reconstituting atelopeptide collagen from solution by neutralizing the solution at a reduced temperature and a hypotonic ionic strength; cross-linking the reconstituted fibers in an aqueous medium at a concentration of 0.1 to 10 mg/ml with glutaraldehyde under conditions that produce cross-linked collagen that when in suspension in physiological saline at a concentration of 35 mg/ml exhibits a shear viscosity whose log varies linearly with the log of the shear rate and is approximated by the formula

$$\log \eta \cong -0.96 \log \gamma + 2.3$$

where  $\gamma$  is the shear rate in  $\text{sec}^{-1}$ ,  $\log \gamma$  is in the range of  $-6$  to  $+2$  and  $\eta$  is the viscosity of the suspension in Pascal-sec; optionally quenching the cross-linking reaction with an amino acid; and separating the cross-linked atelopeptide collagen from the reaction mixture. This collagen is dispersed in an isotonic aqueous medium for use in soft tissue dermal augmentation and is injectable and forms implants that have excellent persistence.

**31 Claims, No Drawings**