

crosslinked atelopeptide collagen is a preferred biomaterial and is used as an exemplary material in the following disclosure.

The term "extrusion plot" refers to a graph of syringe plunger travel in cm versus force in newtons applied to the plunger obtained by loading a test aqueous suspension of particulate biomaterial in a 1.25 cc Burrton syringe fitted with a 32 gauge needle and applying such force as to give a constant plunger displacement rate of 30 mm/min. Suspensions that may be used in the invention exhibit an extrusion plot in which there is a smooth (i.e. substantially free of spikes or transient increases (see U.S. Pat. No. 4,642,117)) linear increase or ramp up in force from zero force to a substantially constant force (i.e. a plateau) in the range of 5 to 30 newtons.

B. Collagen Suspension

The collagen suspension that may be employed as a particulate biomaterial in the invention is made from sterile CIS. For example, one may use VITROGEN® 100 collagen-in-solution (CIS), which is commercially available from Celtrix Pharmaceuticals, Inc. Palo Alto, Calif., and is a sterile solution containing 3 mg/ml atelopeptide bovine hide collagen in a pH 2 buffer. Alternatively, one may prepare CIS by methods known in the art. In general, cowhide is dehaired, ground, and soaked in acid (e.g., aqueous HCl) to swell the collagen fibers. The product is then treated with a suitable protease (other than collagenase) such as pepsin or trypsin, and then sterile filtered.

Fibrillar atelopeptide collagen (also referred to as "reconstituted" collagen) is prepared from CIS by raising the pH to about 7.4 by adding a sufficient quantity of a Na₂PO₄ buffer, thus precipitating the fibers from solution. The concentration of collagen in the resulting suspension is about 3 mg/ml. The suspension is then passed continuously through a 50 mesh (0.013 in. openings) screen until it has passed 90 times through the screen (flow rate and time depend on the volume of suspension and diameter of the screen) and concentrated by centrifugation to about 70 mg/ml. The screening breaks up large fibrils, making the fiber size more uniform. This results in improved flow characteristics providing enhanced extrudability for fine gauge needles and improved intrudability into the skin. The concentrate is then homogenized with phosphate-buffered saline (optionally including an anesthetic agent such as Lidocaine) to a concentration of 10 to 50 mg/ml, preferably 30-40 mg/ml, and then loaded into the syringe.

C. Syringes

The syringes used in this invention comprise a barrel, a plunger received in the barrel, and a fine gauge needle attached to the leading end of the barrel via an appropriate fitting such as a Luer lock fitting. Burrton syringes with a 4 to 10 mm I.D. diameter barrel 4 to 8 mm long are preferred because of their smallness and compactness. The fine gauge needle is 31-33 gauge of about 0.90 to 1.3 cm in length (e.g., approximately $\frac{3}{8}$ to $\frac{1}{2}$ inch). The needle is typically made from stainless steel and is pre-sterilized. The use of such a fine gauge needle reduces or eliminates trauma/bruising at the treatment site, provides more control (precision) in the injection, and is less intimidating to some patients.

Clinical experience indicated that a volume of approximately 0.7 cc of collagen suspension is optimal to achieve full correction of fine lines in a first treatment. In some instances, a following "touch-up" injection

may be needed. Such treatments require less volume, typically on the order of about 0.4 cc.

Quantitative confirmation of the flow characteristics of the suspension may be carried out by running extrusion tests on samples of the loaded syringes as follows. The loaded syringes are refrigerated at 2°-10° C. for 12 hours prior to testing. They are allowed to warm at room temperature for 5 minutes prior to testing. The sample syringe is placed on an extrusion test device similar to an Instron machine. The device is adapted to plunge the plunger at a constant rate of travel (linear displacement), measure the force applied to the plunger during its travel, and plot the force versus plunger travel on a chart recorder. As indicated above, at a linear plunger displacement of 30 mm/min the plot should appear as a smooth linear ramp up in force from zero force to a constant force plateau of 5 to 30 newtons in magnitude, preferably 10 to 30 newtons with an average of about 25 newtons.

D. Administration

The region of fine superficial facial lines is located and preferably placed under magnification. The tissue at the site is then stretched to give a taut surface. The needle is then inserted into the skin site as superficially as possible. The position of the needle bevel (up or down) is dictated by physician preference—the objective being to achieve superficial placement of the injectate.

The suspension is then injected using a steady pressure on the syringe plunger until a slight blanch occurs. Multiple serial punctures in the area are advisable. When injecting into a periorbital region care should be taken to not overcorrect (inject excessive volume of suspension).

CLINICAL RESULTS

A blind study was conducted to compare treatment of fine superficial facial lines using commercially available ZYDERM® I collagen implant (Collagen Corp.) (this product had a 1 cc syringe fitted with a 30 gauge needle and the collagen was not screened) and devices made according to this invention (1.25 cc Burrton syringes, 32 gauge needle loaded with reconstituted atelopeptide collagen having an extrusion plot as described above. The collagen concentration was 35 mg/ml in both projects.

The study involved 103 patients who were treated with unmarked invention devices in the periorbital area on one side and with unmarked ZYDERM® I product on the other side. Neither physicians nor patients knew which material was used. The results of the comparison showed significantly less post-treatment trauma experienced with the invention, with most investigators preferring the invention device over the ZYDERM® I product. Many investigators reported less lumping and beading of injected material with the invention than with the ZYDERM® I product. Interviews with investigators also showed there was a perception (not supported by clinical data) that the invention device was less painful than the ZYDERM® I product.

Modifications of the above-described modes for carrying out the invention that are obvious to those of skill in the fields of medical devices, injectables, and biomaterial formulation are intended to be within the scope of the following claims.

We claim: