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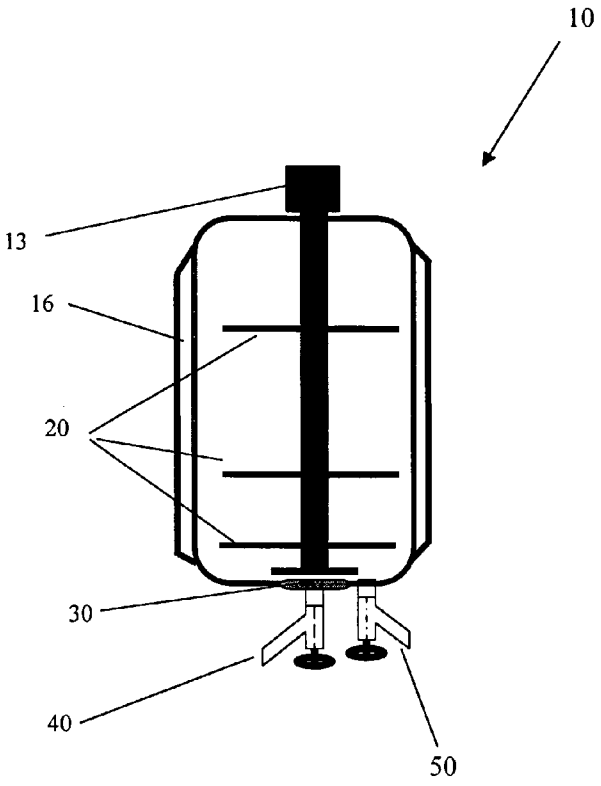
(54) Title: METHODS FOR MAKING INJECTABLE POLYMER HYDROGELS

(57) Abstract: Methods for preparing injectable hydrogels, particularly hydrogels containing hyaluronan, are described herein. Also described are hydrogel products made by the methods provided herein.



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Methods For Making Injectable Polymer Hydrogels

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority from U.S. Provisional Application Serial No. 60/572,944, filed May 20, 2004.

TECHNICAL FIELD

This document relates to processes for preparing injectable polymer hydrogels.

BACKGROUND

Injectable gels often are used for soft tissue augmentation. For example, injectable gels and be used as facial fillers for wrinkles and folds, lip enhancement and body contour correction, as well as in arthritis prostheses. Biocompatible polymers such as alginate acid, chitosan, polyacrylamide, and hyaluronan (hyaluronic acid, HA) have been used to prepare injectable gels for various applications. Injectable gels often are prepared by covalently crosslinking polymers in solution to form a rubber-like network structure, which is then mechanically homogenized to form injectable microparticles. Typically, each operation of these multi-step processes is separated, involving various pieces of equipment and product transfers.

SUMMARY

This document provides simple, rapid and low cost processes for preparation of injectable hydrogels (*e.g.*, injectable hyaluronan hydrogels). The processes can include the steps of crosslinking one or more polymers and washing the subsequently formed gel, followed by purification and homogenization to produce an injectable hydrogel. The processes can be carried out in a single reaction vessel as continuous processes, and thus can result in elimination of the need to carry out any product transfer. In addition, no organic solvent or drying step is required. The processes also can provide an easily controllable and repeatable operation for very quick and low cost production of injectable gels, with different polymer concentrations and different particle sizes for various applications. One production cycle may take as little as three days.

Also provided herein are hydrogels made by the processes described herein. The hydrogels can have a high degree of cross linking but a very deformable soft structure and superior biostability. As such, the gels can be used in soft tissue augmentation and medical prostheses. The swelling degree of the gels in PBS can be about 4000-5000%. The gels can have particle sizes on the order of 500 micrometers, and can be easily injected through G30 ½ needles (inner diameter 150 micrometer). Injectable hyaluronan gels produced by the processes provided herein can have superior viscoelasticity. The elastic modulus G′ can be much higher than the viscous modulus G″, the complex viscosity can be from about 2 x 10^4 Pa.s to 35 Pa.s, and the phase angle delta (δ) can be very low (around 10), over a range of 0.01-10 Hz. In addition, the injectable hyaluronan gels prepared by the processes provided herein can exhibit a large degree of biostability to hyaluronidase as compared with injectable hyaluronan gels such as Restylane® (Medicis Aesthetics, Inc., Scottsdale, AZ) and Hylaform® (Inamed Aesthetics, Santa Barbara, CA).

In one aspect, this document features a process for the preparation of an injectable hydrogel. The process can include the steps of crosslinking one or more polymers to form a gel, washing the gel, purifying the gel, and homogenizing the gel to produce the hydrogel, wherein the process is carried out in a single reaction vessel as a continuous process. The polymer can have one or more reactive groups selected from hydroxyl groups, carboxyl groups and amine groups. The polymer can be a polysaccharide (*e.g.*, hyaluronic acid, chitosan, alginate acid, starch, dextran, or salts or water soluble derivatives thereof), a protein or a synthetic polymer, such as poly(acrylic acid) or poly(vinyl alcohol).

The crosslinking reaction can be carried out with a bi- or polyfunctional crosslinking agent, such as an epoxide, aldehyde, polyaziridyl or divinyl sulphone. The crosslinking agent can be 1,4-butanediol diglycidyl ether (BDDE). The process can be carried out at a pH of 11 or higher. The crosslinking reaction can be carried out at a temperature of 37-60°C (*e.g.*, 50°C), for at least 4 hours.

The process can further include preparing a solution of the polymer in NaOH and adding the crosslinking agent with stirring. The process can further include cutting the formed gel into pieces using one or more impellers in the reaction vessel, and washing and purifying the gel with one or more changes of PBS solution. The washing and

purifying process can be carried out over 2 to 3 days with at least six changes of PBS solution.

The polymer can be hyaluronic acid. The process can be carried out with a solution of hyaluronic acid in 0.25 M NaOH, at a concentration up to 20% by weight. The initial concentration of hyaluronic acid can be 11-14% by weight. The molar ratio of crosslinking agent to polymer can be 0.5-2.4.

In another aspect, this document features an injectable hydrogel produced using a process described herein. In addition, this document features a biomaterial containing an injectable hydrogel as described herein. The biomaterial can be in the form of a sheet, bead, sponge, or formed implant.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. Although methods and materials similar or equivalent to those described herein can be used to practice the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF DRAWINGS

FIG. 1 is a drawing a stirrer vessel suitable for use in the continuous processes for preparing injectable hyaluronan gels as described herein.

FIG. 2 is a graphical representation of the rheological data described in Example 1.

DETAILED DESCRIPTION

Hyaluronan is a naturally occurring polysaccharide containing alternating N-acetyl-D-glucosamine and D-glucuronic acid monosaccharide units. As used herein

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