substitute by new tissue. A dermal substitute is not, like a regenerative device for promoting soft tissue volume augmentation in the oral region, exposed during wound healing to pressure created by the above mentioned complex mechanical forces.

The problem or objective of the invention is to find a regenerative collagen device for promoting soft tissue volume augmentation in the oral region that is biocompatible, resorbable *in vivo*, allows gingival ingrowth, shows a good level of tissue integration such as to allow uneventful healing (without excessive inflammation or dehiscence) and be able to withstand mechanical forces by acting as a scaffold that maintains tissue volume during a sufficient time during the wound healing process after implantation, generally at least about 3 months.

The above problem is solved by the invention as defined in the appended claims.

Summary

In one aspect, there is provided a resilient resorbable chemically crosslinked collagen sponge, comprising 60-96 % (w/w) collagen and 4-40 % (w/w) elastin, which shows by mercury intrusion porosimetry interconnected pores with a median pore diameter between 50 and 90 μm and at least 80 % porosity with a pore diameter more than 10 μm, an onset temperature of 45 to 57 °C and a density in dry state from 50 to 65 mg/cm^3.

In another aspect, there is provided a process for preparing a resilient resorbable chemically crosslinked collagen sponge of the present invention, which comprises the following steps:

(a) Submitting a porcine or bovine peritoneum or pericardium membrane to a basic treatment in a sodium hydroxide solution at a pH above 12, an acid treatment in a hydrochloric solution of pH of 1 to 3, a dehydrating

(b) treatment with a water soluble organic solvent and a degreasing treatment with an organic solvent, milling the dry membrane obtained with a cutting mill, sieving through a 0.5-2 mm sieve and suspending the powder obtained in an acidified water solution of pH from 2.5 to 3.5, such as to obtain a slurry of collagen fibres,

(c) Submitting grinded bovine or porcine dermis to a dehydrating treatment with a water soluble organic solvent, a degreasing treatment with an organic solvent, a basic treatment in a strong inorganic base at a pH above 12, an acid treatment in a strong inorganic acid at a pH from 0 to 1, rinsing with water and suspending the collagen fibres, freeze-drying, cleaning the dried collagen fibres with an organic solvent and grinding the cleaned dried fibres in an acidified solution of pH from 3 to 4, such as to obtain a slurry of collagen fibres,

(d) Mixing 3.5 to 4.5 parts of the collagen fibres slurry obtained in (a) with 0.5 to 1.5 parts of the collagen fibres slurry obtained in (b), such as to obtain a resulting slurry,

(e) Freeze-drying the resulting slurry obtained in (c) and crosslinking the freeze-dried product in a solution containing a crosslinking agent, washing with water and freeze-drying, and

Optionally sterilizing the freeze-dried product obtained in (e) by γ irradiation or X-ray irradiation.

In a further aspect, there is provided use of the resilient resorbable chemically crosslinked collagen sponge according to the present invention in the manufacture of an implant for promoting soft tissue volume augmentation in the oral region.

Description

The invention relates to a resilient resorbable chemically crosslinked collagen sponge for promoting soft tissue volume augmentation in the oral region, comprising 60-96 % (w/w) collagen and 4-40 % (w/w) elastin, which shows by mercury intrusion porosimetry interconnected pores with a median pore diameter between 50 and 90 μm and at least 80 % porosity with a pore diameter more than 10 μm, an onset temperature of 45 to 57 °C and a density in dry state from 50 to 65 mg/cm^3.

The chemically crosslinked collagen sponge comprises 60-96 % (w/w) collagen and 4-40 % (w/w) elastin. The elastin content is here measured by desmosine/iodesmosine determination according to a modification of a known method involving hydrolysis and RP-HPLC (see e.g. Guida E. *et al.* 1990 *Development and validation of a high performance chromatography method for the determination of desmosines in tissues* in Journal of Chromatography or Rodriguqe P 2008 *Quantification of Mouse Lung Elastin During Prenatal Development* in The Open Respiratory Medicine Journal). To determine the desmosine/isodesmosine content of dry elastin, the elastin

CLAIMS

1. A resilient resorbable chemically crosslinked collagen sponge, comprising 60-96 % (w/w) collagen and 4-40 % (w/w) elastin, which shows by mercury intrusion porosimetry interconnected pores with a median pore diameter between 50 and 90 μm and at least 80 % porosity with a pore diameter more than 10 μm, an onset temperature of 45 to 57 °C and a density in dry state from 50 to 65 mg/cm^3.

2. The resilient resorbable chemically crosslinked collagen sponge according to claim 1 which shows an onset temperature from 46 to 53 °C.

3. The resilient resorbable chemically crosslinked collagen sponge according to claim 1 or 2, which shows a density in dry state from 50 to 60 mg/cm^3.

4. The resilient resorbable chemically crosslinked sponge according to any of claims 1 to 3, which comprises 70-90 % (w/w) collagen and 10-30 % (w/w) elastin.

5. The resilient resorbable chemically crosslinked sponge according to any of claims 1 to 4, which shows at least 90 % porosity with a pore diameter more than 10 μm.

6. The resilient resorbable chemically crosslinked sponge according to any of claims 1 to 5 which was obtained using a crosslinking agent selected from the group consisting of gluteraldehyde, EDC (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide) and a mixture of EDC and NHS (N-hydoxysuccinimide).

7. The resilient resorbable collagen chemically crosslinked sponge of any of claims 1 to 5, which was derived from tissues of natural origin by a process comprising freeze drying and chemical crosslinking, optionally followed by γ sterilisation or X-ray sterilization.

8. The resilient resorbable chemically crosslinked collagen sponge of claim 6 or 7 wherein the tissues of natural origin include porcine or bovine peritoneum or

pericardium membranes, porcine or bovine placenta membrane, or porcine or bovine SIS or dermis .

9. The resilient resorbable chemically crosslinked collagen sponge of any of claims 1 to 9, which wetted by a PBS solution retains at least 70 % of initial thickness after 49 cycles of compression to a pressure of 12.1 kPa.

10. The resilient resorbable chemically crosslinked collagen sponge of any of claims 1 to 9, which wetted by a PBS solution retains less than 55 % hysteresis with respect to the first loading after 49 cycles of compression to a pressure of 12.1 kPa.

11. A process for preparing a resilient resorbable chemically crosslinked collagen sponge of any of claims 1 to 10, which comprises the following steps:

(a) Submitting a porcine or bovine peritoneum or pericardium membrane to a basic treatment in a sodium hydroxide solution at a pH above 12, an acid treatment in a hydrochloric solution of pH of 1 to 3, a dehydrating treatment with a water soluble organic solvent and a degreasing treatment with an organic solvent, milling the dry membrane obtained with a cutting mill, sieving through a 0.5-2 mm sieve and suspending the powder obtained in an acidified water solution of pH from 2.5 to 3.5, such as to obtain a slurry of collagen fibres,

(b) Submitting grinded bovine or porcine dermis to a dehydrating treatment with a water soluble organic solvent, a degreasing treatment with an organic solvent, a basic treatment in a strong inorganic base at a pH above 12, an acid treatment in a strong inorganic acid at a pH from 0 to 1, rinsing with water and suspending the collagen fibres, freeze-drying, cleaning the dried collagen fibres with an organic solvent and grinding the cleaned

dried fibres in an acidified solution of pH from 3 to 4, such as to obtain a slurry of collagen fibres,

(c) Mixing 3.5 to 4.5 parts of the collagen fibres slurry obtained in (a) with 0.5 to 1.5 parts of the collagen fibres slurry obtained in (b), such as to obtain a resulting slurry,

(d) Freeze-drying the resulting slurry obtained in (c) and crosslinking the freeze-dried product in a solution containing a crosslinking agent, washing with water and freeze-drying, and

(e) Optionally sterilizing the freeze-dried product obtained in (e) by γ irradiation or X-ray irradiation.

12. The process according to claim 11, wherein the crosslinking agent is selected from the group consisting of gluteraldehyde, EDC (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide) and a mixture of EDC and NHS (N-hydoxysuccinimide).

13. The process according to claim 11 or 12, wherein the slurry of collagen fibres prepared in step (a) contains 2.5 to 3.75 (w/w) % collagen and the slurry of collagen fibres prepared in step (b) contains from 4.0 to 6.0 (w/w) % collagen.

14. Use of the resilient resorbable chemically crosslinked collagen sponge according to any claims of 1 to 10 in the manufacture of an implant for promoting soft tissue volume augmentation in the oral region.

15. The use of claim 14, wherein the implant is an implant for the oral cavity.

16. The use of claim 14 or 15, wherein the resilient resorbable chemically crosslinked collagen sponge shows the same volume retention in the oral region as SCTG (Subepithelial Connective Tissue Graft) after implantation.