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(54) Title: A COLLAGEN/HYDROXYAPATITE COMPOSITE SCAFFOLD, AND PROCESS FOR THE PRODUCTION THEREOF

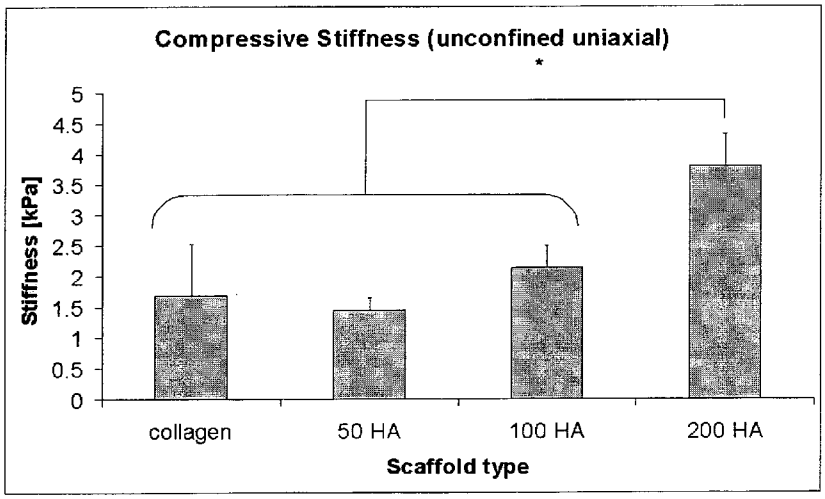

Fig. 2

(57) Abstract: A process for producing a collagen/hydroxyapatite (HA) composite scaffold comprises the steps of forming a homogenous suspension of collagen and HA in an acidic solution, lyophilising the suspension at a constant cooling rate until a desired final freezing temperature is reached to produce the composite scaffold, wherein the ratio of HA to collagen is at least 1 : 10 (w/w). Also provided is a collagen/hydroxyapatite (HA) composite scaffold comprising a homogenous distribution of hydroxyapatite within a porous, collagen matrix, wherein the ratio of HA to collagen is at least 1 : 10 (w/w). Suitably, the composite scaffold has a porosity of at least 99% (v/v), and a compressive stiffness of at least 0.3KPa. Composite scaffolds of the invention may be used to provide osteoconductive bone implants, tissue engineering implants, maxillofacial bone graft substitute, dental bone graft substitute, cartilage defect repair implant and osteochondral defect repair implant.

WO 2008/096334 A3

WO 2008/096334 A3

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Claims

1. A process for producing a collagen/hydroxyapatite (HA) composite scaffold, comprising the steps of mechanically mixing collagen and HA in an acidic solution to form a homogenous suspension of collagen and HA in an acidic solution, freezing the suspension at a constant cooling rate until a final freezing temperature of between -10°C and -70°C is reached, and heating the frozen suspension to a sublimation temperature where an ice phase in the frozen suspension is sublimated under vacuum for a suitable period of time to produce the composite scaffold, wherein the ratio of HA to collagen in the suspension is at least 1:10 (w/w), and wherein the amount of collagen in the suspension is from 3g/L to 8g/L (w/w).

2. A process as claimed in Claim 1 in which the acidic solution has a molarity of at least 0.1M.

3. A process as claimed in Claim 1 or 2 in which the molarity of the acidic solution is from 0.4M to 0.6M.

4. A process as claimed in any preceding Claim in which the ratio of HA to collagen in the suspension is from 1:10 (w/w) to 50:10 (w/w).

5. A process as claimed in any preceding Claim in which the ratio of HA to collagen in the suspension is from 5:10 to 30:10 (w/w).

6. A process as claimed in Claim 5 in which the ratio of HA to collagen in the suspension is from 10:10 (w/w) to 30:10 (w/w).

7. A process as claimed in any preceding Claim in which the homogenous suspension of Collagen/HA is formed in conditions suitable for minimising gelatinisation of the collagen.

8. A method as claimed in Claim 7 in which the method of ensuring minimal gelatinisation of collagen during the production of the homogenous suspension comprises maintaining the suspension at a temperature between 1° and 5°C.

9. A process as claimed in any preceding Claim in which the freezing is carried out at a constant cooling rate of between 0.1°C/min to 10°C/min.

10. A process as claimed in any preceding Claim in which freezing is carried out at a constant cooling rate of between 0.5°C/min to 1.5°C/min.

11. A process as claimed in any preceding Claim in which freezing is carried out at a constant cooling rate of between 0.8°C/min to 1.1°C/min.

12. A process as claimed in any preceding Claim in which the desired final freezing temperature is between -30°C and -50°C.

13. A process as claimed in any preceding Claim in which the desired final freezing temperature is between -35°C and -45°C.

14. A process as claimed in any preceding Claim further comprising an annealing step that comprises increasing the temperature in the lyophilisation chamber after the final freezing temperature has been reached to an annealing temperature that is intermediate the final freezing temperature and the sublimation temperature, and holding the temperature at the annealing temperature for a period of time before increasing the temperature to the sublimation temperature.

15. A process as claimed in any preceding Claim in which the HA employed in the present invention is in powder form.

16. A process as claimed in Claim 15 in which the HA powder is selected from the group consisting of: sintered HA powder; and unsintered HA powder.

17. A process as claimed in Claim 15 or 16 in which the HA powder has a particle size of between 10nm and 100μm.

18. A process as claimed in any preceding Claim in which the collagen employed in the present invention comprises collagen fibres.

19. A process as claimed in any preceding Claim in which the homogenous suspension of collagen/HA is formed by the steps of forming an acidic homogenous suspension of collagen, and subsequently adding the HA to the collagen suspension under conditions of mixing to ensure homogenous distribution of the HA within the collagen suspension.

20. A process as claimed in Claim 19 in which the HA is provided in the form of an acidic HA suspension.

21. A process as claimed in Claim 19 or 20 in which the collagen suspension is centrifugally mixed, and wherein the HA is added to the vortex of the suspension during centrifugal mixing.

22. A process as claimed in of Claims 19 to 21 in which the HA is added in aliquots.

23. A process as claimed in Claim 22 in which the aliquots are added to the collagen suspension at intervals of between 30 and 240 minutes.

24. A process as claimed in Claim 22 to 23 in which the HA is added to the collagen suspension in between 2 and 5 aliquots.

25. A process as claimed in any preceding Claim in which the composite scaffold is cross-linked.

26. A process as claimed in Claim 25 in which the composite scaffold is cross-linked by a means selected from the group consisting of: dehydrothermal cross-linking; and chemical cross-linking.

27. A process as claimed in Claim 25 in which the composite scaffold is cross-linked with 1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (EDAC).

28. A collagen/hydroxyapatite (HA) composite scaffold obtainable by the method of any of Claims 1 to 27.

29. A collagen/hydroxyapatite (HA) composite scaffold comprising a homogenous distribution of hydroxyapatite within a porous, collagen matrix, wherein the ratio of HA to collagen is at least about 1:10 (w/w), and wherein composite scaffold has a porosity of at least 95% (v/v) and a compressive stiffness of at least 1.5KPa.

30. A collagen/hydroxyapatite (HA) composite scaffold as claimed in Claim 29 having a ratio of HA to collagen of at least about 10:10 (w/w).

31. A collagen/hydroxyapatite (HA) composite scaffold as claimed in Claim 30 having a ratio of HA to collagen of at least about 10:20 (w/w).

32. A collagen/hydroxyapatite (HA) composite scaffold as claimed in any of Claims 29 to 31 having a porosity of at least or 96% (v/v).

33. A collagen/hydroxyapatite (HA) composite scaffold as claimed in any of Claims 29 to 31 having a porosity of at least or 98% (v/v).

34. A collagen/hydroxyapatite (HA) composite scaffold as claimed in any of Claims 29 to 31 having a porosity of at least or 99% (v/v).

35. A collagen/hydroxyapatite (HA) composite scaffold as claimed in any of Claims 29 to 34, being dehydrothermally and EDAC crosslinked,

36. A collagen/hydroxyapatite (HA) composite scaffold as claimed in Claim 35, being dehydrothermally and EDAC crosslinked, having a compressive stiffness of at least 2.0kPa

37. A collagen/hydroxyapatite (HA) composite scaffold as claimed in Claim 36, being dehydrothermally and EDAC crosslinked, having a compressive stiffness of at least 3.0kPa

38. A collagen/hydroxyapatite (HA) composite scaffold as claimed in any of Claims 29 to 37 in which the ratio of HA to collagen in the composite scaffold is from 1:10 (w/w) to 50:10 (w/w).

39. A collagen/hydroxyapatite (HA) composite scaffold as claimed in Claim 38 in which the ratio of HA to collagen in the composite scaffold is from 5:10 (w/w) to 30:10 (w/w).

40. A collagen/hydroxyapatite (HA) composite scaffold as claimed in any of Claims 29 to 39 in which the composite scaffold is characterised by a level of proliferation of MC3T3 osteoblasts in the scaffold at 28 days incubation minus the level at 7 days of at least 0.5 x 10^6 cells .

41. A collagen/hydroxyapatite (HA) composite scaffold as claimed in any of Claims 29 to 40 in which the composite scaffold is characterised by having a flow conductivity under pressure through the scaffold of at least 1 x 10^{-10} m^4/Ns.

42. A collagen/hydroxyapatite (HA) composite scaffold as claimed in any of Claims 29 to 41 in which the scaffold is produced in the form of a sheet.

43. A collagen/hydroxyapatite (HA) composite scaffold as claimed in any of Claims 29 to 42 that is seeded with at least 1 x 10^6 cells per 500mm^3 volume of scaffold.

44. A collagen/hydroxyapatite (HA) composite scaffold as claimed in any of Claims 29 to 43 that is crosslinked.

45. An osteoconductive bone implant comprising a collagen/hydroxyapatite composite scaffold of any of Claims 29 to 44.

46. A tissue engineering implant comprising a collagen/hydroxyapatite composite scaffold of any of Claims 29 to 44.

47. A maxillofacial bone graft substitute comprising a collagen/hydroxyapatite composite scaffold of any of Claims 29 to 44.

48. A dental bone graft substitute comprising a collagen/hydroxyapatite composite scaffold of any of Claims 29 to 44.

49. A cartilage defect repair implant comprising a collagen/hydroxyapatite composite scaffold of any of Claims 29 to 44.

50. A osteochondral defect repair implant comprising a collagen/hydroxyapatite composite scaffold of any of Claims 29 to 44.