

carbonate are supplied to the vicinity of cells, whereby the activity of the cells is activated and high bioactivity is realized.

Prior art references

Patent Literature

[0006]

Patent literature 1: Japanese Patent No. 5179124

Non Patent Literature

[0007]

Non patent literature 1: Walsh et al. β -TCP bone graft substitutes in a bilateral rabbit tibial defect model. Biomaterials 29 (2008) 266-271)

Non Patent Literature 2: Obata et al. Electrospun microfiber meshes of silicon-doped vaterite / poly(lactic acid) hybrid for guided bone regeneration. Acta Biomaterialia 6 (2010) 1248-1257.

Non patent Literature 3: Fujiwara et al. Guided bone regeneration membrane made of polycaprolactone / calcium carbonate composite nano-fibers. Biomaterials 26 (2005) 4139-4147).

Non patent literature 4: Hench LL. Polak JM: Third-generation biomedical materials. Science 2002, 295: 1014 - 1017)

Summary

Problem to be solved by the disclosure

[0008]

Rebuilding a lost bone by utilizing the self-regenerating ability of the bone is an excellent method by which permanent bone repair can be achieved. However, the self-regeneration of a bone needs a long period of time of at least three to six months after a material has been implanted. Therefore, the material for filling a bone defect used for such a method needs to initiate a bone regenerating activity as soon as possible after it was

implanted, and also continue the activity of promoting bone formation by remaining in the defect portion until sufficient bone formation is achieved. However, until now, there has not been obtained any material for filling a bone defect that satisfies these contradicting requirements.

Means to solve the problem

[0009a]

In one aspect, there is provided a material for filling a bone defect comprising a biodegradable fiber produced by electrospinning, wherein the biodegradable fibers comprising calcium phosphate particles of 40-60wt%, silicon releasable calcium carbonate particles of more than 10wt%, and PLLA of 30wt% or more as remainder, and wherein the PLLA has crystalized content of from 75% to 98%, wherein the biodegradable fiber is produced by electrospinning a spinning solution produced by dissolving a composite obtained by kneading the PLLA, silicon releasing calcium carbonate particles and calcium phosphate particles such that silicon releasing calcium carbonate particles and calcium phosphate particles are approximately uniformly distributed in the PLLA polymer.

[0009b]

In another aspect, there is provided a method of producing a material for filling a bone defect, comprising: a step of kneading calcium phosphate particles of 40-60wt%, silicon releasing calcium carbonate particles of 10wt% or more, and PLLA having crystalized content of from 75% to 98% as remainder to produce a mixture in which the calcium phosphate particles and silicon releasing calcium carbonate particles are approximately evenly dispersed in the PLLA polymer, a step of cooling and solidifying the mixture to produce a composite; a step of dissolving the composite by a solvent to produce a spinning solution; and a step of producing a biodegradable fiber from the spinning solution by using electrospinning method.

[0009c]

The material for filling a bone defect of the present disclosure is a material for filling a bone defect that includes biodegradable fibers produced by electrospinning in a cotton-like structure, and the biodegradable fibers contain calcium phosphate particles in an amount of 40% to 60% by weight, preferably 40% by weight, calcium carbonate particles in an amount of 10% by weight or more, preferably 30% by weight, and preferably a poly-L-lactic acid polymer in an amount of 30% by weight or more, preferably 30% by weight or all the remainder. Further, amount of an amorphous phase of the poly-L-lactic acid polymer is 75% to 98%, preferably 85% to 95%, more preferably 88% to 92%.

[0010]

Because Polymer content of the biodegradable fibers used for the material for filling a bone defect of the present disclosure is limited as small as possible as far as fibers can be spun by electrospinning, exposure of calcium phosphate particles and calcium carbonate particles on the surface of a fiber is large, and the area which directly contacts with body fluids is large. As a result, high biological activity is achieved from the particles of calcium phosphate and the calcium carbonate.

[0011]

The calcium carbonate contained in the material for filling a bone defect of the present disclosure is preferably a silicon-releasing calcium carbonate of a

vaterite phase. Because such silicon-releasing calcium carbonate has a fast dissolution rate, calcium ions are released early after being implanted and create a calcium rich environment. On the other hand, silicon species doped in the calcium carbonate are released gradually and stimulate proliferation of osteoblasts and promotes bone formation.

[0012]

The material for filling a bone defect of the present disclosure induces generation of bone-like apatite on a surface of a fiber by releasing a rich amount of calcium ions from the calcium carbonate. Polylactic acid which is a matrix polymer of the fiber has many carboxyl groups, and the polylactic acid is hydrolyzed by contacting with biological fluids, thereby forming a carboxyl group which induces nucleation of bone-like apatite

[0013]

As the calcium carbonate of the material for filling a bone defect of the present disclosure, calcium carbonate of vaterite phase is preferably used. Generally, based on the difference of crystal structure, calcium carbonate is classified into three types: a calcite phase, an aragonite phase, and a vaterite phase. Calcium carbonate of a vaterite phase has the highest solubility in the biological fluid of a human body. Therefore, PLA containing vaterite phase calcium carbonate has a high bone-like apatite forming ability.

[0014]

Bioabsorbable calcium phosphate used for the material for filling a bone defect of the present disclosure is bioabsorbed slowly over time after being implanted in a defect and bone replaced. Because the material for filling a bone defect of the present disclosure contains 40% or more of bioabsorbable calcium phosphate, bone formation by absorption and replacement is performed effectively.

[0015]

Biodegradable polymer used for the material for filling a bone defect of the present disclosure remains in a defect portion while maintaining a skeleton structure until calcium phosphate is absorbed and bone replaced, and works as a scaffold where bone cells perform their activity during formation of the bone. Because PLLA is not easily hydrolyzed, the concern that PLLA will disappear immediately after implantation by being decomposed and absorbed upon contacting with body fluid is small.
[0016]

Outer diameter of the biodegradable fibers of the material for filling a bone defect of the present disclosure is preferably from 10 to 50 μm , more preferably from 30 to 50 μm .
[0017]

A method of producing a material for filling a bone defect of the present disclosure includes the steps of: providing a mixture of calcium phosphate particles and SiV particles in a melted polymer solution in a kneader such that weight ratio of the three components are 40% to 60% by weight of calcium phosphate, 10% by weight or more of silicon-releasing calcium carbonate, and remainder is 30% by weight or more of poly L lactic acid; kneading the components in that state; cooling and solidifying the kneaded mixture to produce a composite body in which the molecular weight of the polymer is 200,000 to 250,000 and the amount of amorphous phase of the polymer is 75% or more, preferably 85% or more; producing a spinning solution by dissolving the composite by using a solvent; producing biodegradable fibers by spinning the spinning solution by using an electrospinning method; and producing the material for filling a bone defect in a cotton-like structure by receiving the biodegradable fibers in a collector filled with ethanol and accumulating the biodegradable fibers thereon.
[0018]

The method of producing the material for filling a bone defect of the present disclosure includes the steps of kneading a solution containing silicon-releasing calcium carbonate particles, calcium phosphate particles, and melted poly lactic acid in a predetermined amounts respectively for a predetermined time at a predetermined temperature in a kneader by using the kneader; and during this process amino group portion of siloxane contained in the silicon-releasing calcium carbonate particles and a carboxy group at an end of the poly(lactic acid) structure is bonded (amino bonding). By using this process, the orderly structure of polylactic acid contained in the spinning solution is disturbed and the ratio of an amorphous phase of the polylactic acid becomes high, and solubility increases. As a result, the material for filling a bone defect produced by electrospinning method by using the spinning solution thus produced has a higher absorptivity in a living body. The amount of amorphous phase in the poly L lactic acid of the material for filling bone defect of the present disclosure is preferably from 75% to 98%, more preferably from 85% to 95%, further more preferably from 88% to 98%.
[0019]

In the material for filling a bone defect of the present disclosure, approximately spherical TCP particles (preferable average particle diameter is about from 3 to 4 μm) and approximately spherical SiV particles (preferable average particle diameter is about 1 μm) are dispersed almost homogeneously in a matrix polymer in the composite fiber having a diameter of about 10 to 50 μm produced by electrospinning. Preferably, both the TCP particles and the SiV particles are dispersed almost homogeneously in the matrix polymer without being unevenly distributed in a specific portion. As a result, minute TCP particles and SiV particles are homogeneously dispersed widely near the surface of a fiber and over the vicinity of the center of

CLAIMS

1. A material for filling a bone defect comprising a biodegradable fiber produced by electrospinning,
wherein the biodegradable fibers comprising calcium phosphate particles of 40-60wt%, silicon releasable calcium carbonate particles of more than 10wt%, and PLLA of 30wt% or more as remainder, and wherein the PLLA has crystalized content of from 75% to 98%,
wherein the biodegradable fiber is produced by electrospinning a spinning solution produced by dissolving a composite obtained by kneading the PLLA, silicon releasing calcium carbonate particles and calcium phosphate particles such that silicon releasing calcium carbonate particles and calcium phosphate particles are approximately uniformly distributed in the PLLA polymer.
2. The material for filling a bone defect of claim 1, wherein the calcium phosphate is β -TCP.
3. The material for filling a bone defect of claim 1 or 2, wherein the silicon releasing calcium carbonate comprises 2-4wt% of siloxane.
4. The material for filling a bone defect of any one of the claims 1-3, wherein molecular weight of the PLLA polymer is 200,000 to 250,000.
5. The material for filling a bone defect of claim 4, wherein the material for filling a bone defect is subjected to sterilization treatment by being irradiated with γ rays with a dose of 25 kGy to 35 kGy, whereby the molecular weight of the poly L lactic acid reduces to 70,000 to 120,000.
6. The material for filling a bone defect of any one of the claims 1-5, wherein the

biodegradable fibers has an outer diameter of 10 to 50 μm .

7. The material for filling a bone defect of any one of the claims 1-6, wherein diameter of the silicon releasing calcium carbonate particles is about 1 μm .

8. A method of producing a material for filling a bone defect, comprising:

a step of kneading calcium phosphate particles of 40-60wt%, silicon releasing calcium carbonate particles of 10wt% or more, and PLLA having crystalized content of from 75% to 98% as remainder to produce a mixture in which the calcium phosphate particles and silicon releasing calcium carbonate particles are approximately evenly dispersed in the PLLA polymer,

a step of cooling and solidifying the mixture to produce a composite;

a step of dissolving the composite by a solvent to produce a spinning solution; and

a step of producing a biodegradable fiber from the spinning solution by using electrospinning method.

9. The method of producing a material for filling a bone defect of claim 8, wherein the calcium phosphate is β -TCP.

10. The method of producing a material for filling a bone defect of claim 8 or 9, further comprising a step of subjecting the material of filling bone defect to sterilization treatment by being irradiated with γ rays with a dose of 25 kGy to 35 kGy, whereby the molecular weight of the poly L lactic acid is reduced.

11. The method of producing a material for filling a bone defect of any one of the claims 8-10, wherein diameter of the calcium phosphate particle is about 1-6 μm , and diameter of the silicon releasing calcium carbonate particles is about 1 μm .