Surprisingly, it has been found that calcium hydroxyapatite particles which have been sintered, but not subjected to a temperature of more than 1030°C, bear a particularly high collagen stimulating effect.

In one aspect, the present disclosure provides calcium hydroxyapatite particles having porous surfaces, wherein the surfaces of the calcium hydroxyapatite particles have pores of an average diameter between 10 and 500 nm at the surface as determined by Hg-porosimetry, each calcium hydroxyapatite particle bears at least 10 of such pores at its surface, and the calcium hydroxyapatite particles have a mean particle diameter in the range of 1 to 1000 µm, as determined by light scattering.

In another aspect, the present disclosure provides an injectable composition comprising:

(A) one or more types of calcium hydroxyapatite particles as described herein as component A; and

(B) one or more pharmaceutically acceptable carriers as component B.

(C) optionally one or more local anesthetics as component C; and

(D) optionally one or more pharmaceutically acceptable additives other than components A, B and C as component D.

In another aspect, the present disclosure provides a cosmetic method for improving appearance of the skin and/or contour of a part of interest of the face or body of a subject, said method including the following steps:

(i) providing an injectable composition as described herein; and

(ii) injecting said injectable composition into the skin of the part of interest of the face or body of a subject.

In another aspect, the present disclosure provides the calcium hydroxyapatite particles as described herein or the injectable composition as described herein for use as a medicament.

In another aspect, the present disclosure provides use of the calcium hydroxyapatite particles as described herein or the injectable composition as described herein in the manufacture of a medicament for treating a pathologic condition associated with pathologic deterioration of connective tissue, wherein the pathologic condition is selected from the group consisting of urinary incontinence, vesicoureteral reflux, vocal cord augmentation, lipotrophy, in particular in a patient suffering from human immunodeficiency virus (HIV), a pathologic condition associated with age-related or pathologic deterioration of connective tissue, and combinations of two or more thereof.

In another aspect, the present disclosure provides a cosmetic use of the calcium hydroxyapatite particles as described herein for the production of collagen in fibroblast cells.

As provided above, the present disclosure relates to calcium hydroxyapatite particles which have been sintered at a temperature in the range of from 910 to 1030°C and have not been subjected to a temperature of more than 1030°C.

Accordingly, there may be no heating to a temperature of more than 1030°C, which may further alter the material properties, preferably not heated above the indicated sintering temperature. The present invention also relates to calcium hydroxyapatite particles which have been sintered at a temperature in the range of from 910 to 1030°C and have not been subjected to a temperature of more than 1030°C, wherein the weight average particle diameter is from 1 to 500 µm as determined by sieving or light scattering.

The calcium hydroxyapatite particles of the present invention may have a well-defined higher surface area which may enable increase of the collagen synthesis of fibroblasts and, thus, bears particularly high biostimulation.

As used herein, the terms “calcium hydroxyapatite”, “calcium hydroxylapatite” and “basic calcium orthophosphate”, “calcium hydroxyphosphate”, “calcium phosphate tribasic”, “hydroxyapatite”, “hydroxylapatite”, and “tribasic calcium phosphate” and the abbreviations “CaHA” and “HAp” should be interchangeably understood in the broadest sense as commonly understood in the art. Calcium hydroxyapatite may be expressed by the formulae $Ca_5(PO_4)_3(OH)$ and $Ca_5[OH|(PO_4)_3]$, respectively.

The claimed invention is:

1. Calcium hydroxyapatite particles having porous surfaces, wherein the surfaces of the calcium hydroxyapatite particles have pores of an average diameter between 10 and 500 nm at the surface as determined by Hg-porosimetry, each calcium hydroxyapatite particle bears at least 10 of such pores at its surface, and the calcium hydroxyapatite particles have a mean particle diameter in the range of 1 to 1000 µm, as determined by light scattering.

2. Calcium hydroxyapatite particles according to claim 1, wherein the porous surfaces are the result of sintering the calcium hydroxyapatite particles at a temperature in the range of from 960 to 995°C without subjecting them to a temperature of more than 995°C.

3. The calcium hydroxyapatite particles of claim 1 or 2, wherein the calcium hydroxyapatite particles are spherical or ellipsoid, more preferably spherical, in particular spherical having a D-ratio above 0.7.

4. The calcium hydroxyapatite particles of any of claims 1 to 3, wherein the surfaces of the calcium hydroxyapatite particles have pores of an average diameter between 50 and 220 nm at the surface as determined by Hg-porosimetry and each calcium hydroxyapatite particle bears at least 100 of such pores at its surface.

5. The calcium hydroxyapatite particles of any of claims 1 to 4, wherein the calcium hydroxyapatite particles have a mean particle diameter of from 5 to 500 µm, 1 to 150 µm, or of from 2 to 100 µm, or of from 5 to 80 µm, or of from 10 to 60 µm, or of from 15 to 50 µm, or of from 20 to 45 µm, or of from 25 to 45 µm, as determined by light scattering.

6. The calcium hydroxyapatite particles of any of claims 1 to 5, wherein the porous surfaces are the result of sintering the calcium hydroxyapatite particles at a temperature in the range of from 960 to 990°C, or from 960 to 985°C, or from 960 to 980°C, or from 960 to 975°C, without subjecting them to temperatures above 995°C.

7. The calcium hydroxyapatite particles of any of claims 1 to 6, wherein the porous surfaces are the result of sintering the calcium hydroxyapatite particles for 1 to 24 hours, 2 to 12 hours, or 3 to 16 hours.

8. The calcium hydroxyapatite particles of claim 7, wherein the surfaces of the calcium hydroxyapatite particles have pores of an average diameter between 50 and 220 nm at the surface as determined by Hg-porosimetry and each calcium hydroxyapatite particle bears at least 100 of such pores at its surface, and the calcium hydroxyapatite particles have a mean particle diameter of from 1 to 150 μm, as determined by light scattering.

9. The calcium hydroxyapatite particles of claim 8, wherein the surfaces of the calcium hydroxyapatite particles have pores of an average diameter from 2 to 100 μm, as determined by light scattering.

10. The calcium hydroxyapatite particles of claim 9, the surfaces of the calcium hydroxyapatite particles have pores of an average diameter from 15 to 50 μm, as determined by light scattering.

11. An injectable composition comprising:
    (A) one or more types of calcium hydroxyapatite particles of any of claims 1 to 10 as component A; and
    (B) one or more pharmaceutically acceptable carriers as component B.
    (C) optionally one or more local anesthetics as component C; and
    (D) optionally one or more pharmaceutically acceptable additives other than components A, B and C as component D.

12. The injectable composition of claim 11, wherein the one or more pharmaceutically acceptable carriers are selected from the group consisting of one or more polysaccharide derivatives or pharmaceutically acceptable salts thereof, one or more polysaccharides or pharmaceutically acceptable salts thereof, glycerol, water, one or more aqueous buffers, and combinations or two or more thereof.

13. The injectable composition of any of claims 11 or 12, wherein the one or more pharmaceutically acceptable carriers are selected from the group consisting of carboxymethyl cellulose or pharmaceutically acceptable salts thereof, glycerol, water, and combinations or two or more thereof.

14. The injectable composition of any of claims 11 to 13, wherein said injectable composition consists of:
    (A) 1 to 80% by weight, referred to dry matter, referred to the injectable composition, of one or more types of the calcium hydroxyapatite particles as component A;
    (B) 1 to 80% by weight, referred to the injectable composition, of one or more pharmaceutically acceptable carriers as component B comprising at least one pasty, viscous or liquid carrier;
    (C) 0 to 10% by weight, referred to the injectable composition, of one or more local anesthetics as component C; and
    (D) 0 to 50% by weight, referred to the injectable composition, of one or more pharmaceutically acceptable additives other than components A, B, C and D as component D.

15. A cosmetic method for improving appearance of the skin and/or contour of a part of interest of the face or body of a subject, said method including the following steps:
    (i) providing an injectable composition of any of claims 11 to 14; and
    (ii) injecting said injectable composition into the skin of the part of interest of the face or body of a subject.

16. The cosmetic method of claim 15, wherein said method is further characterized in that it is a method for a purpose selected from the group consisting of filling of wrinkles, improving facial lines, breast reconstruction or augmentation, rejuvenation of the skin, buttocks augmentation, remodeling of cheekbones, soft tissue augmentation, filling facial wrinkles, improving glabellar lines, improving nasolabial folds, improving marionette lines, improving buccal commissures, oral commissures, improving peri-lip wrinkles, improving crow’s feet, improving subdermal support of the brows, malar and buccal fat pads, improving tear troughs, nose, augmentation of lips, augmentation of cheeks, augmentation of peroral region, augmentation of scars such as acne scars, augmentation of infraorbital region, resolving facial asymmetries, improving jawlines, augmentation of chin, and combinations of two or more thereof,
    in particular wherein said method is a method for filling of wrinkles of interest of a subject, said method injecting said injectable composition subcutaneously or intradermally into the wrinkles of interest.

17. The cosmetic method of any of claim 15 or 16, wherein the step (ii) is injecting the injectable composition in connective tissue of the subdermal skin and thereby stimulating the production of collagen, in particular collagen selected from collagen type III, collagen type I, or a combination of collagen type I and III.

18. The calcium hydroxyapatite particles of any of claims 1 to 10 or the injectable composition of any of claims 11 to 14 for use as a medicament .

19. Use of the calcium hydroxyapatite particles of any of claims 1 to 10 or the injectable composition of any of claims 11 to 14 in the manufacture of a medicament for treating a pathologic condition associated with pathologic deterioration of connective tissue, wherein the pathologic condition is selected from the group consisting of urinary incontinence, vesicoureteral reflux, vocal cord augmentation, lipotrophy, in particular in a patient suffering from human immunodeficiency virus (HIV), a pathologic condition associated with age-related or pathologic deterioration of connective tissue, and combinations of two or more thereof.

20. A cosmetic use of the calcium hydroxyapatite particles of any of claims 1 to 10 for the production of collagen in fibroblast cells.