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 which have been sintered at a temperature in the range of from 910 to 1030°C and which have not been subjected to a temperature of more than 1030°C.

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 in treating a pathologic condition associated with pathologic deterioration of connective tissue, preferably 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 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, preferably 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.

~~Accordingly, a first aspect of~~As provided above, the present ~~invention~~ 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 calcium hydroxyapatite particles may have any shape. These may be spherical, ellipsoid, crystalline, random (also: irregular), or a mixture of two or more thereof. In a preferred embodiment, the calcium hydroxyapatite particles are (essentially) spherical or (essentially) ellipsoid. In a preferred embodiment, the calcium hydroxyapatite particles are (essentially) spherical.

In a preferred embodiment, the calcium hydroxyapatite particles are spherical having a D-ratio above 0.7. Thus, the calcium hydroxyapatite particles preferably have a D-ratio above 0.7, more preferably above 0.8, in particular above 0.9. In this context, a D-ratio of 1.0 indicates perfect roundness.

The claimed invention is:

1. Calcium hydroxyapatite particles which have been sintered at a temperature in the range of from 910 to 1030°C and which have not been subjected to a temperature of more than 1030°C.

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

3. The calcium hydroxyapatite particles of any of claims 1 or 2, wherein the calcium hydroxyapatite particles have porous surfaces.

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 10 and 500 nm at the surface as determined by Hg-porosimetry.

5. The calcium hydroxyapatite particles of any of claims 1 to 4, wherein the calcium hydroxyapatite particles have a mean particle diameter of from 1 to 500 µm, or 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 calcium hydroxyapatite particles have been sintered at a temperature in the range of from 910 to 995°C, or of from 920 to 995°C, or from 930 to 990°C, or from 940 to 985°C, or from 950 to 980°C, or from 960 to 975°C, and wherein the calcium hydroxyapatite particles have not been subjected to temperatures above the sintering temperature.

7. The calcium hydroxyapatite particles of any of claims 1 to 6, wherein the calcium hydroxyapatite particles have been sintered for 1 to 24 hours, 2 to 12 hours, or 3 to 16 h

8. An injectable composition comprising:
   (A) one or more types of calcium hydroxyapatite particles of any of claims 1 to 7 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.

9. The injectable composition of claim 8, 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.

10. The injectable composition of any of claims 8 or 9, 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.

11. The injectable composition of any of claims 8 to 10, 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.

12. 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 8 to 11; and
(ii) injecting said injectable composition into the skin of the part of interest of the face or body of a subject.

13. The cosmetic method of claim 12, 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.

14. The cosmetic method of any of claim 12 or 13, 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.

15. The calcium hydroxyapatite particles of any of claims 1 to 7 or the injectable composition of any of claims 8 to 11 for use in ~~a method of~~ treating a pathologic condition associated with pathologic deterioration of connective tissue, preferably 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.

16. Use of the calcium hydroxyapatite particles of any of claims 1 to 7 or the injectable composition of any of claims 8 to 11 in the manufacture of a medicament for treating a pathologic condition associated with pathologic deterioration of connective tissue, preferably 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.