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(54) Virsraksts: **Farmaceitiska kompozīcija un tās iegūšanas paņēmiens**

(57) Kopsavilkums: Kompozīcija satur 7-izopropoksiizoflavonu uz porainas hidroksilapatīta un/vai trikalcija fosfāta virsmas. Hidroksilapatīta un/vai trikalcija fosfāta masas attiecība pret 7-izopropoksiizoflavonu ir no 1:9 līdz 9:1, labāk 1:1, un vēlams, lai aktīvie komponenti būtu atsevišķu granulu veidā. Kompozīcija izmantojama tādu kaulu defektu labošanai, kas rodas kaulu patoloģiskas attīstības rezultātā vai mākslīgu kaulu implantācijas gadījumos, kā arī osteoporozes gadījumos.

FARMACEITISKA KOMPOZĪCIJA UN TĀS IEGŪŠANAS PAŅĒMIENS

1. Maisījums kaulu bojājumu, kuri veidojas patoloģiskas attīstības vai mākslīgas pārstādīšanas rezultātā, aizvietošanai, kas atšķiras ar to, ka tajā ietilpst 0 līdz 99,9% pēc svara poraina hidroksilapatīta un/vai trikalcija fosfāta, kā arī 0,001 līdz 100% pēc svara 7-izopropoksiizoflavona, kā aktīvus komponentus, vēlams atsevišķu granulu veidā.

2. Maisījums, saskaņā ar 1.punktu, kas atšķiras ar to, ka tajā ietilpst hidroksil-apatīts un/vai trikalcija fosfāts svara attiecībā pret 7-izopropoksiizoflavonu no 1:9 līdz 9:1.

3. Maisījums, saskaņā ar 1. un 2. punktu, kas atšķiras ar to, ka tajā ietilpst hidroksilapatīts un/vai trikalcija fosfāts svara attiecībā pret 7-izopropoksiizoflavonu 1:1.

4. Kompozīcija kaulu bojājumu, kuri veidojas patoloģiskas attīstības vai mākslīgas pārstādīšanas rezultātā, aizvietošanai, kas atšķiras ar to, ka tajā ietilpst 0,001 līdz 99,9% pēc svara 7-izopropoksiizoflavona, kas atrodas uz 0,1 līdz 99,9% pēc svara poraina hidroksilapatīta un/vai trikalcija fosfāta virsmas.

5. Kompozīcija, saskaņā ar 4. punktu, kas atšķiras ar to, ka tajā ietilpst hidroksilapatīts un/vai trikalcija fosfāts svara attiecībā pret 7-izopropoksiizoflavonu no 1:9 līdz 9:1.

6. Kompozīcija, saskaņā ar 4. un 5. punktu, kas atšķiras ar to, ka tajā ietilpst hidroksilapatīts un/vai trikalcija fosfāts svara attiecībā pret 7-izopropoksiizoflavonu 1:1.

7. Paņēmiens kaulu bojājumu, kuri veidojušies patoloģiskas attīstības vai makslīgas pārstādīšanas rezultātā, aizvietošanai, kas atšķiras ar to, ka tajā ietilpst kaula defekta vietas piepildīšana ar maisījumu, kas sastāv no 0 līdz 99,9% pēc svara poraina hidroksilapatīta un/vai trikalcija fosfāta, kā arī 0,001 līdz 100% pēc svara 7-izopropoksiizoflavona, vēlams atsevišķu granulu veidā, kuras samērcētas ar asinīm, serumu vai seruma (plasmas) aizvietotāju.

8. Paņēmiens, saskaņā ar 7.punktu, kas atšķiras ar to, ka tajā ietilpst hidroksilapatīta un/vai trikalcija fosfāta svara attiecībā pret 7-izopropoksiizoflavonu no 1:9 līdz 9:1 maisījuma izmantošana.

9. Paņēmiens, saskaņā ar 7. vai 8. punktu, it īpaši, kaula bojājuma aizvietošanai periodontā, kas atšķiras ar to, ka tajā ietilpst maisījuma, kas satur

hidroksilapatītu un/vai trikalcija fosfātu svara attiecībā pret 7-izopropoksiizoflavonu 1:1, izmantošana.

10. Kompozīcijas, kas derīga kaulu bojājumu, kuri veidojas patoloģiskas attīstības vai mākslīgas pārstādīšanas rezultātā, aizvietošanai, iegūšanas paņēmiens, kas atšķiras ar to, ka tajā ietilpst 0,001 līdz 99,9% pēc svara 7-izopropoksiizoflavona, kas atrodas uz 0,1 līdz 99,9% pēc svara poraina hidroksilapatīta un/vai trikalcija fosfāta virsmas.

11. Paņēmiens, saskaņā ar 10. punktu, kas atšķiras ar to, ka tajā ietilpst hidroksilapatīta un/vai trikalcija fosfāta svara attiecībā pret 7-izopropoksiizoflavonu no 1:9 līdz 9:1 maisījuma izmantošana.

12. Paņēmiens, saskaņā ar 10. vai 11. punktu, kas atšķiras ar to, ka tajā ietilpst hidroksilapatīta un/vai trikalcija fosfāta svara attiecībā pret 7-izopropoksiizoflavonu 1:1 maisījuma izmantošana.

PHARMACEUTICAL COMPOSITION AND PROCESS

The invention relates to a combination useful for the substitution of bone defects which have pathologically developed or have been artificially established as well as compositions containing these combinations and the process for the preparation thereof.

During the last decade, a demand has become more and more pronounced to prevent the loss of teeth or groups of teeth instead of substituting them by removable prostheses.

Because of the disease of the periodontium, the alveolar walls and thereby the mandibles atrophize after removal or loss of a tooth or teeth being close to each other. The solid fixation of a metal implant in atrophized, bone-deficient jaws is problematic.

In the cases of certain diseases, e.g. bone tumours, the bone defect is artificially established by removing the tumour tissue or by a bone fracture.

It is known that porous hydroxylapatite (e.g. CEROS^{R} 80) or tricalcium phosphate (e.g. CEROS^{R} 82), respectively are useful bone-substitutive materials in dentistry and maxillary surgery. The drawback of this method consists in that after filling the bone-defective region with a porous hydroxylapatite or tricalcium phosphate by suitable techniques, an amount of new bone providing a safe implantation bed has formed only after 20 months.

Thus, the aim of this invention is to develop a combination, which is useful: to substitute artificially established bone defects [e.g. oral (dental) surgery, removal of bone tumours, bone fractures or the like]; to accelerate the regenerative process of bone defect-substitution carried out with hydroxylapatite or tricalcium phosphate known in the art; and/or to achieve a new bone adapted to the demand of bone hardness locally suitable.

It is known that orally administered 7-isopropoxyisoflavone (generic name: IPRIFLAVONE) can be used for the treatment of osteoporosis.

Thus, the present invention relates to a combination useful for substituting bone defects having pathologically developed or being artificially established, which comprises 0 to 99.9% by weight of porous hydroxylapatite and/or tricalcium phosphate and 0.001 to 100% by weight of 7-isopropoxyisoflavone, optionally in the form of discrete granules. The combination according to the invention contains in a weight ratio of 1:9 to 9:1 hydroxylapatite and/or tricalcium phosphate related to 7-isopropoxyisoflavone.

Optionally, the combination according to the invention contains the active ingredients as discrete (physically separate) granules, where the suitable weight ratio is adjusted by varying the amounts of the different granules.

If the composition contains the active ingredients according to the invention together, the composition can preferably be prepared by applying the required amount of 7-isopropoxyisoflavone onto the surface of the porous hydroxylapatite or tricalcium phosphate in a manner known per se (e.g. by wet granulation).

When 7-isopropoxyisoflavone is used in the form of discrete granules, these granules may contain, if de-

sired, also auxiliaries (additives). Useful additives are e.g. polyvinylpyrrolidone, Avicel, Aerosil, methylcellulose, (hydroxypropyl)cellulose, (hydroxymethyl)-propylcellulose, starch, mannitol or the like. For the substitution of bone defects, the bone-deficient region is filled by applying suitable surgical techniques with a combination containing porous hydroxylapatite and/or tricalcium phosphate as well as 7-isopropoxyisoflavone, optionally in the form of discrete granules wetted by blood, serum or plasma-substitute.

The locally suitable bone hardness can be achieved by varying the weight ratio or the particle size of hydroxylapatite and/or tricalcium phosphate used in relation to 7-isopropoxyisoflavone.

In dentistry or in surgery of the jaws, respectively, it is preferred to use a combination, wherein the weight ratio of hydroxylapatite and/or tricalcium phosphate related to 7-isopropoxyisoflavone is 1:1 and the particle size of hydroxylapatite and/or tricalcium phosphate is 0.5 to 0.8 mm.

The combination according to the invention can be used for the substitution of the following bone defects.

In stomatology:

- to fill the dental alveolus remaining after removal of a tooth or teeth, thereby preventing the atrophy of the walls of the dental alveolus;
- to rebuild toothless, severely atrophic dental alveoli for rehabilitation of the set of teeth by using prosthesis or implantation;

In other bone-deficient diseases:

- to substitute bone defects occurring as a consequence of pathologic, inflammatory, tumour diseases or fractures and the like.

During the use of the combination according to the invention it is advantageous to administer 7-isopropoxy-isoflavone p.o. as well.

The combination according to the invention and the results achieved by the use thereof, respectively are illustrated by the following non-limiting Example.

Example 1

Investigation of the direct mechanism of action on the bone of hydroxylapatite (HA) and ipriflavone (IP)

This experiment was carried out on female Beagle dogs weighing 9 to 15 kg each in the following arrangement of groups.

Groups of dogs	Ratio of HA : IP
I.	1 : 1
II.	6 : 4
III.	9 : 1
IV.	8 : 2
V.	IP alone
VI.	HA alone
VII.	empty bone cavities

All groups consisted of 4 dogs each. Thus, a total of 28 dogs was operated on and evaluated later on.

Description of the surgical intervention

After a first incision made on the subjugular mucous membrane of the teeth of proper appropriate size, the bone cavities were established entering the vestibular bone surface on the right side of the lower

jaw-bone of the dogs at the site of the roots of the 4th bicuspid by amputating both roots of this tooth and closing the root canal of the amputation root-stump by a retrograde root filling well established in the human dentistry.

Dimensions of the bone cavities in all dogs were:

- about 20 mm in length;
- about 8 mm in width;
- about 5 mm in depth.

The inlet orifice of the bone cavity was shaped to an elliptic or form. Hydroxylapatite and ipriflavone mixed together in a ratio corresponding to the respective group were introduced in the form of discrete granules in such a way that the amount of material soaked by blood reached the bone surface level. The wound of the mucous membrane was tightly closed by a suture of 11 knots in average.

On the 25th day, bone tissue was taken out from all of the 28 dogs for histological examination, in some cases together with the above-lying soft tissues by using the commonly employed method of biopsy sample taking. The following results were obtained: 1. Up to a ratio of 1:1, the higher the amount of ipri-

flavone was in the ratio of the two substances, the more significant were both the quality and quantity of the newly developed bone. The bone was more compact and its colour became more and more similar to that of the nearly intact native bone (it became more and more pale yellow) and the soft, vascularized interstitial elements (showing a reddish-brown colour) in the bone structure gradually decreased. From the point of view of ossification, the material obtained by 1:1 weight ratio gave the best results.

2. The regions being in various phases of maturation and the borderlines thereof, were very well discernible

on the biopsy bone cylindre.

3. No hydroxylapatite or ipriflavone granules were observed on the bone surfaces recovered or in the depth as well as on the surface of the biopsy cylindre.
4. In the bone cavities containing ipriflavone alone, the newly formed bone was relatively hard and uniform but not to the same degree as the one obtained with combinations of hydroxylapatite and ipriflavone. There were more loose tissue regions among the separate ossifying islets.
5. The consistency of tissues formed in the bone cavity and the connection thereof to the surrounding bone can be characterized as a function of the ratio used as follows.

Consistency of the tissue	Connection to the surrounding bone	HA : IP ratio
Compact new bone	Rounded angles; no sharp borderline between the old and new bone	1 : 1
Loose new bone	Sharp angles with a well-pronounced borderline	9 : 1
Loose new bone with many soft, vascularized tissues	Sharp angles	1: 0
Invaginations of soft parts	Blunted bone borders	-

It has unambiguously been proven by the above data that the combination according to the invention accelerated bone formation in comparision to the controls.

Claims

1. Combination for substituting bone defects having pathologically developed or being artificially established, which comprises 0 to 99.9% by weight of porous hydroxylapatite and/or tricalcium phosphate as well as 0.001 to 100% by weight of 7-isopropoxyisoflavone, optionally in the form of discrete granules of the active ingredients.

2. A combination as claimed in claim 1, which comprises in a weight ratio of 1:9 to 9:1 hydroxylapatite and/or tricalcium phosphate in relation to 7-isopropoxyisoflavone.

3. A combination as claimed in claim 1 or 2, which comprises in a weight ratio of 1:1 hydroxylapatite or tricalcium phosphate in relation to 7-isopropoxyisoflavone.

4. Composition for substituting bone defects having pathologically developed or being artificially established, which comprises 0.001 to 99.9% by weight of 7-isopropoxyisoflavone applied on the surface of 0.1 to 99.9% by weight of porous hydroxylapatite and/or tricalcium phosphate.

5. A composition as claimed in claim 4, which comprises in a weight ratio of 1:9 to 9:1 hydroxylapatite and/or tricalcium phosphate in relation to 7-isopropoxyisoflavone.

6. A composition as claimed in claim 4 or 5, which comprises in a weight ratio of 1:1 hydroxylapatite and/or tricalcium phosphate in relation to 7-isopropoxyisoflavone.

7. Method for substitution of bone defects having pathologically developed or being artificially established, w h i c h c o m p r i s e s filling of the bone-deficient region with a combination containing 0 to 99.9% by weight of porous hydroxylapatite and/or tricalcium phosphate as well as 0.001 to 100% by weight of 7-isopropoxyisoflavone, optionally in the form of discrete granules, wetted by blood, serum or serum (plasma) substitute.

8. A method as claimed in claim 7, w h i c h c o m p r i s e s using a combination containing in a weight ratio of 1:9 to 9:1 hydroxylapatite and/or tricalcium phosphate in relation to 7-isopropoxyisoflavone.

9. A method as claimed in claim 7 or 8, particularly for the substitution of a bone defect in the periodontium, w h i c h c o m p r i s e s using a combination containing in a weight ratio of 1:1 hydroxylapatite and/or tricalcium phosphate in relation to 7-isopropoxyisoflavone.

10. Process for the preparation of a composition useful for substituting bone defects having pathologically developed or being artificially established, w h i c h c o m p r i s e s applying 0.001 to 99.9% by weight of 7-isopropoxyisoflavone onto the surface of 0.1 to 99.9% by weight of porous hydroxylapatite and/or tricalcium phosphate.

11. A process as claimed in claim 10, w h i c h c o m p r i s e s using in a weight ratio of 1:9 to 9:1 hydroxylapatite and/or tricalcium phosphate in relation to 7-isopropoxyisoflavone.

12. A process as claimed in claim 10 or 11, w h i c h c o m p r i s e s using in a weight ratio of 1:1 hydroxylapatite and/or tricalcium phosphate in relation to 7-isopropoxyisoflavone.

PHARMACEUTICAL COMPOSITION AND PROCESS

A b s t r a c t

The invention relates to a combination useful for the substitution of bone defects having pathologically developed or being artificially established as well as compositions containing these combinations.

The combinations of the invention preferably contain in a weight ratio of 1:9 to 9:1, most preferably 1:1 porous hydroxylapatite and/or tricalcium phosphate in relation to 7-isopropoxyisoflavone, optionally in the form of discrete granules of the active ingredients.

The composition contains 7-isopropoxyisoflavone applied onto the surface of porous hydroxylapatite and/or tricalcium phosphate.

An advantageous member of the combination according to the invention is 7-isopropoxyisoflavone (generic name: ipriflavone) known as an anti-osteoporotic drug.