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(71) Applicant
Farmos-Yhtyma Oy

(Incorporated in Finland)

P.O. Box 425, SF-20101 Turku, Finland

(72) Inventors
Antti Uuno Olavi Yli-Urpo
Harry Gosta Jalonen
Kauko Oiva Antero Kurkela

(74) Agent and/or Address for Service
J A Kemp & Co
14 South Square, Gray's Inn, London, WC1R 5LX, United Kingdom

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(54) Bioceramic system for delivery of a bioactive compound

(57) A bioceramic system for delivery of a bioactive compound, which comprises a combination of bioactive glass or glass ceramic, hydroxyapatite, optionally one or more other calcium phosphate compound and optionally a matrix, may incorporate in the bioceramic system a bioactive compound. The timing of the release of the bioactive compound or compounds can be regulated as desired, and depends on the conditions of the surrounding, the composition of the bioceramic system and the method of preparation of the bioceramic system.

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BIOCERAMIC SYSTEM FOR DELIVERY OF A BIOACTIVE COMPOUND

The present invention relates to a bioceramic system for controlled delivery of a bioactive compound such as a medicine, protein or hormone. The bioceramic system consists wholly or partly of a combination of bioactive glass or glass ceramic, and hydroxyapatite. In addition to hydroxyapatite the system may contain one or more other calcium phosphate compounds, such as rhenanite or tricalcium phosphate. The system may also contain a matrix.

Bioactive glass or glass ceramic is a ternary mixture of SiO_2, Na_2O and CaO or a mixture that contains more than these 3 components which sinters to glass or glass ceramic and reacts with water or tissue fluid by forming a reactive silica-rich layer and a layer rich in calcium and, if present, phosphorous. Bioactive glass is amorphous and bioactive glass ceramic is crystalline.

Bioceramics which consist of wholly water soluble glass compositions are known for example as implants and oral formulations for liberating active compounds at a controlled rate (EP 147932). On the other hand implants made of hydroxyapatite are known to be used for delivering active materials (JP 101145/1984). Muscle tissue has been found to be firmly connected to hydroxyapatite by fibrous tissue and those adhered firmly to each other (S. Negami et al. Abstract World Congress of High Tech Ceramics, Milan,

1986). This means that hydroxyapatite implants do not disappear from soft tissue. The bioceramic system according to the invention resorbs completely and disappears from soft tissue.

It has now been found that by combining hydroxyapatite with bioactive glass or glass ceramic, the activity of which can be regulated, a bioceramic system is produced the resorption rate of which is regulatable, which is distinguished from the resorption rate of the pure bioactive glass or glass ceramic component.

Thus the present invention provides a bioceramic system suitable for the delivery of a bioactive compound which comprises hydroxyapatite and bioactive glass and/or glass ceramic.

The bioceramic system may also contain one or more other calcium phosphate compounds, such as rhenanite or tricalciumphosphate.

The effect of hydroxyapatite in the bioceramic system is dependent on the pH of the surrounding fluid. At low pH-values an increasing amount of hydroxyapatite in the bioceramic system increases the resorption rate. At high pH-values the effect is the opposite: increasing amounts of hydroxyapatite in the bioceramic system decreases the resorption rate.

Medical preparations for oral use decompose in variable pH (pH≈1-7,5); preparations such as implants

decompose in approximately neutral pH surrounding. The combination of hydroxyapatite with bioactive glass or glass ceramic can be used to obtain oral preparations which resorb more rapidly in the stomach than if bioactive glass or glass ceramic alone has been used. The combination of hydroxyapatite with bioactive glass or glass ceramic provides an implant which resorbs more slowly than if bioactive glass or glass ceramic alone is used.

The matrix material which may be used in the bioceramic system may be water, waterglass or any non-toxic polymer or similar compound. The polymer can be a natural polymer, such as gelatine, or a synthetic polymer, such as polyacrylic acid, polymaleic acid, polylactic acid, polytartaric acid or polyglycolic acid.

The bioceramic compound may contain one or more bioactive compound. The bioactive compound which may be delivered using the bioceramic system may be e.g. a medicine, protein or hormone. The system may be used to deliver compounds which are unstable or poorly soluble in simple aqueous solutions. Compounds which it is desirable to administer to only a restricted area may also be delivered using the bioceramic system, preferably as an implant. The system may be designed to allow slow release of a compound.

The surface of the bioceramic system reacts instantly with its surrounding in living tissue, tissue

fluid or in aqueous solution, which leads to resorption the time of which depends on the composition. The resorption can be regulated by changing the ratio of hydroxyapatite and bioactive glass or glass ceramic and, if present, other calcium phosphate compound(s) and the matrix. The release of the bioactive material from the bioceramic system can be restrainedly regulated based on the phenomenon described above. For instance by changing the amount of hydroxyapatite in the bioceramic system the timing of the release of the bioactive compound can be regulated as desired and depends on the conditions of the surroundings, the method of preparation of the bioceramic system or the composition of the bioceramic system.

The bioceramic system incorporating a bioactive compound, may be administered to a human or animal patient orally, by implanting into tissue in various ways or it may act by releasing a bioactive compound through mucous membrane. The bioceramic system may be used in various forms such as a monolithe, multi-particle system, tablet, pill, granule, suppository or suspension. The bioceramic system may be attached to e.g. a tooth; it may also be implanted or connected into plant tissue.

The structure of the bioceramic system may be based on a single or multi-layer system, a homogenic material or a combination of particles of different type and/or size. The bioceramic system may also be coated with matrix.

The bioceramic system containing a bioactive compound may be administered to a subject in an amount sufficient to release the desired amount of bioactive compound at a particular time or at a particular rate. For a known medicine the desired dose can be calculated and the bioceramic system can be produced which will release the desired dose under the ambient conditions resulting from its administration to the subject.

The bioceramic system is prepared by combining ground and sieved bioactive glass or glass ceramic, hydroxyapatite and, if present, matrix, and pressing, e.g. forming a tablet using a mould. The bioactive compound is combined with the components of the bioceramic system before pressing. The bioceramic system may also be prepared by sintering a combination of bioactive glass or glass ceramic, hydroxyapatite and optionally a few drops of water as a matrix. The bioceramic system made by sintering is then impregnated with a bioactive compound.

In the examples used to illustrate the invention the bioactive glass used for sample preparation was ground in a ball mill and sieved. The fraction under 53 micrometers was used. The bioactive glass used in the examples was a mixture of SiO_2 (52,7 w-%), Na_2O (20,75 w-%), CaO (15,60 w-%), P_2O_5 (6,8 w-%), Al_2O_3 (0,8 w-%) and B_2O_3 (3,3 w-%) except in Experiment 7 where the bioactive glass was a mixture of SiO_2 (55,26 mol-%), Na_2O (26,21 mol-

%), CaO (12,01 mol-%), P_2O_5 (2,4 mol-%), Al_2O_3 (1,24 mol-%) and B_2O_3 (2,9 mol-%). The hydroxyapatite used was specially synthesized and pure. The fraction under 100 micrometers was used. The water glass used was of normal technical grade. Gelatine was used as a matrix either as a dry powder or as a gel.

For preparing the samples two different methods of tablet preparation were used depending on the consistency of the wet mixture. The more solid mixtures were pressed into tablets in a press normally used for making tablets for IR-analysis. The content of the bioactive compound was 1 wt-%. The tablets were keep under constant pressure in the press for 1 minute.

Further two different methods were used when preparing samples containing gelating. The first method consisted of mixing the solid components with solid gelatine followed by moistening this mixture in the tablet press with a few drops of water. This method gave good solid tablets. In the second method the gelatine was mixed with water to form a 2 % solution. the gelatine was allowed to dissolve by letting the mixture stand overnight. This solution was then used as matrix when pressing the tablets. An extruder method may also be used.

The samples that were too liquid to be pressed were molded using a plate of silicon rubber with cylindrical holes. The mixture was spread in the mold using a spatula.

The tablets were allowed to harden before they were removed from the mold. The tablets prepared by this technique varied somewhat in size. Since the content of the bioactive compound was constant the exact amount of the bioactive compound could be calculated for each tablet from its total weight.

The methods described above to prepare the samples are not restricting.

The following experiments illustrate the invention. All the experiments except Experiment 7 were carried out in room temperature.

The samples were analyzed with Hewlett-Packard 1081 B liquid chromatograph.

EXPERIMENT 1.

Tablets each containing 20 mg of selegiline hydrochloride, were made by pressing. The proportion of hydroxyapatite in each batch is shown in table 1.

The tablets were placed in phosphate buffer pH 7.4 (USP) and shaken by hand for a few seconds once a day to dissolve the tablet and release the selegiline hydrochloride.

As shown in table 1 increasing the amount of hydroxyapatite decreases the amount of the selegiline hydrochloride released when the time is constant.

TABLE 1: The amount of selegiline hydrochloride released from the total amount (%) in 15 days when the ratio of hydroxyapatite (HA) is changed.

No.	bioactive glass/%	HA/%	gelatine/%	selegiline released
1	88	10	2	59
2	68	30	2	37
3	28	70	2	16

EXPERIMENT 2.

The dissolution of selegiline hydrochloride as a function of time in phosphate buffer pH 7,4 (USP) is presented in Figure 1. The selegiline hydrochloride powder was mixed with the components of the bioceramic system before pressing. Each tablet contained about 18 mg of selegiline hydrochloride. The components of the system are presented in Table 2. The dissolution was carried out as described in Experiment 1.

TABLE 2:

No.	bioactive glass/%	HA/%	H_2O
1	100	0	2-4 drops
2	95	5	2-4 drops
3	90	10	2-4 drops
4	50	50	2-4 drops

EXPERIMENT 3.

The dissolution of selegiline hydrochloride as a function of time in pH 1,2 (0,1 M hydrochloric acid) is presented in Figure 2. The tablets were pressed and the contents of the bioceramic system are presented in Table 3. Each tablet contained about 15 mg of selegiline hydrochloride. The dissolution was carried out by shaking in a linear shaker at a speed of 110/min.

TABLE 3:

No.	bioactive glass/%	HA/%	gelatine/%	H_2O
1	88	10	2	2-4 drops
2	68	30	2	2-4 drops
3	28	70	2	2-4 drops

EXPERIMENT 4

The dissolution of selegiline hydrochloride as a function of time in pH 1,2 (0,1 M hydrochloric acid) is presented in Figure 3. The tablets were made by molding and the components of the bioceramic system are presented in Table 4. Each tablet contained about 15 mg of selegiline hydrochloride. The dissolution was carried out as described in Experiment 3.

TABLE 4:

No.	bioactive glass/%	HA/%	waterglass/%
1	80	10	10
2	20	70	10

EXPERIMENT 5

The dissolution of nifedipine as a function of time in pH 1,2 (0.1 M hydrochloric acid) is presented in Figure 4. The tablets were made by pressing and the components of the bioceramic system are presented in Table 5. Each tablet contained about 5 mg of nifedipine. The dissolution was carried out as described in Experiment 3.

TABLE 5:

No.	bioactive glass/%	HA/%	gelatine/%
1	88	10	2
2	28	70	2

EXPERIMENT 6.

The dissolution of nifedipine as a function of time in pH 1,2 (0.1 M hydrochloric acid) is presented in Figure 5. The tablets were made by molding and the components of the bioceramic system are presented in Table 6. Each tablet contained about 4 mg of nifedipine. The dissolution was carried out as described in Experiment 3.

TABLE 6:

No.	bioactive glass/%	HA/%	waterglass/%
1	80	10	10
2	20	70	10

EXPERIMENT 7.

The dissolution of methotrexate as a function of time in water is presented in Figure 6. The bioceramic system which consisted of 50 % of bioactive glass and 50 % of hydroxyapatite was sintered at 930 ^{o}C for 3 min and above 730 ^{o}C for 6 min and after that impregnated with methoxtrexate solution. The tablet contained about 10 mg of methoxtrexate. The dissolution was carried out by a dissolution method with baskets according to USP (50 rpm, 37 ^{o}C).

CLAIMS

1. A bioceramic system suitable for delivery of a bioactive compound, which system comprises (i) hydroxyapatite and (ii) a bioactive glass and/or bioactive ceramic.

2. A bioceramic system according to claim 1 wherein the system comprises hydroxyapatite, bioactive glass or bioactive ceramic, and a matrix.

3. A bioceramic system according to claim 2 wherein the matrix is gelatine and/or water.

4. A bioceramic system according to claim 2 wherein the matrix is waterglass.

5. A bioceramic system according to any one of the preceding claims which further comprises one or more calcium phosphate compound other than hydroxyapatite.

6. A pharmaceutical preparation comprising a bioceramic system as claimed in claims 1 to 5 in combination with at least one bioactive compound.

7. A pharmaceutical preparation according to claim 6 wherein the bioactive compound is a medicine.

8. A pharmaceutical preparation according to claim 7 wherein the medicine is selegiline.

9. A pharmaceutical preparation according to claim 7 wherein the medicine is methotrexate.

10. A pharmaceutical preparation according to claim 7 wherein the medicine is nifedipine.

11. A monolithe, multiparticle system, tablet, pill, suppository, granule or suspension comprising a bioceramic system or preparation as claimed in any one of the preceding claims.

12. A process for producing a bioceramic system as claimed in any one of claims 1 to 5 comprising sintering (i) hydroxyapatite and (ii) a bioactive glass and/or bioactive ceramic, and optionally (iii) water as a matrix.

13. A process for producing a preparation as claimed in any one of claims 6 to 10 comprising producing a bioceramic system according to claim 12 and impregnating the system with a bioactive compound.

14. A process for producing a preparation as claimed in any one of claims 6 to 10 comprising combining the bioactive compound, hydroxyapatite, and at least one of a bioactive glass and a bioactive ceramic and pressing this combination.

15. A process for administering a bioactive compound to a subject to whom such administration is desired comprising administering a preparation as claimed in any one of claims 6 to 10 or monolithe, multi-particle system, tablet, pill, suppository, granule or suspension as claimed in claim 11.

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