

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 March 2010 (18.03.2010)

PCT

(10) International Publication Number
WO 2010/029307 A1

(51) International Patent Classification:
A61K 9/14 (2006.01) *A61K 31/282* (2006.01)

(21) International Application Number:
PCT/GB2009/002180

(22) International Filing Date:
11 September 2009 (11.09.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0816772.8 12 September 2008 (12.09.2008) GB

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— with international search report (Art. 21(3))

(54) Title: MEDICAL PRODUCT

(57) Abstract: An active medical component of low or moderate thermal stability is incorporated in a body of phosphate-based glass which is in the form of an amorphous solid oxide material comprised of metal cations and phosphate anions. The glass is degradable by water to release the active medical component. The active medical component is particularly a platinum complex such as cisplatin. The metal oxide composition of the glass, in mole per cent and expressed as P2O5 and metal oxides, is for example (i) P2O5 35 - 65%, preferably 40 - 60% (ii) alkaline earth metal oxide or oxides 20 - 60%, preferably 25 - 60% (iii) metal oxides other than alkaline earth metal oxides 5 - 35%, preferably 10 - 30%. The product may be made by a sol-gel process.



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Medical Product

5 **Field of the invention**

This invention relates to a medical product, such as a pharmaceutical product, and to a method of making such a product, and is particularly applicable to a product containing cisplatin or another platinum-based anticancer drug in a form deliverable to a mammal.

Background to the invention

Cisplatin is a widely used and successful anticancer drug. It was initially developed for treatment of testicular cancer, and has been used also in treatment of head and neck cancer, small cell lung cancer and ovarian cancer. It is a potent antineoplastic but is also very toxic. Because of its side effects, there have been searches for other platinum-based drugs which are analogues of cisplatin. Iproplatin, tetraplatin and carboplatin are, or have been, in clinical use. Others have been proposed. All of these compounds are electroneutral platinum complexes, with four or six coordination of the platinum atom. Bis-platinum complexes have also been proposed.

Anticancer therapies using cisplatin and its analogues have usually involved intravenous delivery. This tends to cause debilitating side effects due to the systemic administration of the drug. Broadly speaking the drug is transported not only to the tumor site but also to other tissues. Therapies targeting only certain tissues with drug carriers which release the drug in a controlled manner are therefore sought. Proposals for loading cisplatin into organic polymer systems, e g poly(methylmethacrylate) have been made.

Cisplatin has an advantage of high thermal stability but tends to be reactive and unstable in solvents.

Ceramics based on calcium phosphate have been developed for slow-release delivery of bioactive materials. An example is hydroxyapatite ceramic, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, which has a high compatibility with human tissue. The bioactive material is absorbed at the surface of the hydroxyapatite cement, and is released by

washing out, not by degradation of the cement. Calcium phosphate cements containing drugs for example are described in US patent 6730324. US patent 5296026 describes phosphate glass cements which may include a drug, such as an antibiotic, which is released as the cement degrades.

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Summary of the invention

The present invention seeks to provide a delivery system for drugs and other medical agents, specifically cisplatin and its analogues, which can avoid problems arising in manufacture and in storage, and provide effective delivery into a mammalian body.

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According to the invention in one aspect there is provided a medical product containing an active medical component, for example one having a low or moderate thermal stability, incorporated in a body of phosphate-based glass in the form of an amorphous solid oxide material comprised of metal cations and phosphate anions, the glass being degradable by water to release the active medical component.

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The rate of release of the active medical component can be modified by adaptation of the chemical composition of the glass.

20

According to the invention in another aspect there is provided a method of making a medical product comprising the steps of:

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- (i) forming a metal phosphate sol,
- (ii) incorporating an active medical component in said metal phosphate sol,
- (iii) gelling said sol, and
- (iv) heating the resultant gel to convert the gel into a phosphate-based glass in the form of amorphous solid oxide material comprising metal cations and phosphate anions, the active medical component being incorporated in the glass, and the glass being degradable by water to release the medical component.

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The invention provides a delivery system which avoids a problem of degradation of an active component due to action of a liquid solvent in which the component is held for storage or due to the use of an elevated temperature associated with conventional glass formation by melt-quenching. The product of the invention is easy to handle and store and can be injected in finely divided form, e.g. as beads. It may

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also be produced in the form of a fibre or fibres or as a larger solid body such as a rod.

The phosphate-based glass used can be highly biocompatible. The product may be targeted to specific sites in the body, for example by injection of the glass as beads into a blood vessel entering a tumour, resulting in entrapment of the bead in the blood vessels (e.g. capillaries) in or near the tumour. For example it can provide continuous delivery of the active component at an appropriate rate directly to the tumour site, if inserted directly as a rod or other solid body implanted directly into or near the tumour. The glass in bead form may be delivered to a desired site by biopsy.

Particularly it has been found that cisplatin can be incorporated into the phosphate-based glass in a convenient manner using a sol-gel process and when incorporated in the phosphate based glass remains at least partially unaffected by the process and by the glass during storage and is released in a useful manner and a useful quantity when the glass is contacted with saline solution.

The physical form of the glass product can be selected according to the desired use.

One suitable form is as small beads, e.g. of micrometre or nanometre size, which are simple to deliver by injection. Larger beads of a suitable size may provide a second therapeutic effect of embolisation of blood vessels, in addition to the therapeutic effect of the released drug, for example the chemotherapy effect of a released platinum drug. A procedure involving embolisation using beads is described in European Journal of Pharmaceutical Sciences, Vol. 30, January 2007, pages 7-14.

Preferred size range or ranges for the beads are 50nm to 1000µm, more preferably 500nm to 1000µm, particularly 10 to 1000µm, more particularly 50 to 500µm. A size range suitable for entrapment in capillaries may be 1 to 50µm, preferably 5 to 20µm.

Other deliverable forms which the glass may take are as mentioned as a fibre or fibres, preferably of diameter in the range 10nm to 10µm and a larger solid body having for example dimensions of at least 1mm in each of three orthogonal directions.

The active medical component is typically distributed throughout the body of amorphous-phase phosphate-based glass and may be distributed homogeneously

(with uniform concentration) throughout the glass body. This allows good control of its release as the glass degrades.

The glass body may be a single phase body, and may be a discrete body
5 unconnected to another solid phase (for example, a bead). The glass body may be non-porous, or may have porosity.

The active medical component is typically one or more chemical compounds and may be a drug (pharmaceutically active agent) having therapeutic effect, or a medical
10 diagnostic agent, e.g. an X-ray contrast agent, a tracer or a marker. A tracer or marker is for example an agent containing a radioactive element.

The invention is especially applicable in the case where the active medical agent has moderate thermal stability and can sufficiently withstand the process of incorporation
15 into the phosphate-based glass body. The method of the invention provides a procedure for the production of the glass incorporating the active medical component at a low temperature, compared with conventional glass formation temperatures. Preferably the active medical component is thermally stable at 100°C (e.g. for at least
one hour) and more preferably thermally stable at 150°C (e.g. for at least *one hour*).

Since inorganic compounds having very high thermal stability can be incorporated in a glass by other methods, the active medical component is typically not a metal oxide which is a component of the glass and is typically not an inorganic metal salt. A
20 typical active medical compound used in the invention is a compound including organic carbon chemistry, for example including one or more bonds selected from carbon-carbon bonds, carbon-oxygen bonds and carbon-hydrogen bonds. Typically the active medical compound is not stable at 400°C.

The active medical component is preferably one soluble in a non-aqueous solvent,
30 since water is undesirable in the sol-gel method here described.

The invention is particularly suitable for platinum-containing drug compounds useful for cancer treatment, such as cisplatin and its analogues. Such compounds include

35 cisplatin (cisdiamminedichloridoplatinum(II)),
iproplatin (cis-dichloro-trans-dihydroxy-cis-bis(isopropylamine)platinum(IV)),
[cis-PtCl₂(NH₃)₂H₂N(CH₂)₄NH₂,

carboplatin (diammine(1,1-cyclobutane-dicarboxylato)platinum(II),
(aquo)sulfato(1,1-bis-aminomethycyclohexane)platinum(II),
tetraplatin, also known as ormaplatin,
oxaliplatin,

- 5 (cis-amminedichloro(cyclohexylamine)platinum(II),
cis-amminedichloro(cyclohexylamine)-trans-dihydroxoplatinum(IV),
bis-acetato-cis-amminedichloro(cyclohexylamine)platinum(IV),
trans-amminedichloro(cyclohexylamine)dihydroxoplatinum(IV),
transplatin,
10 *cis, trans, cis*-Pt(NH₃)(C₆H₁₁NH₂)(OOCCH₃)₂Cl₂,
nedaplatin,
malanato-1,2-diaminocyclohexaneplatinum(II),
5-sulfosalicylato-trans-(1,2 diaminocyclohexane)platinum(II),
poly-[(trans-1,2-diaminocyclohexane)platinum]-carboxyamylose, and
15 4-hydroxy-sulfonylphenylacetato(trans-1,2-diaminocyclohexane)platinum(II).

Such platinum compounds may be employed in the product of the invention singly or
in combination of two or more, and also in combination with one or more other active
pharmaceutical compounds.

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The platinum-containing compounds which may be used in the invention are typically
electroneutral and have four or six coordination of the Pt atom or atoms.

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Other pharmaceutical agents have thermal stability enabling them to be used in the
product and method of the invention. An example is tetracycline.

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The amount of active medical compound, particularly the amount of platinum
compound or compounds, e. g. the amount of cisplatin, in the phosphate-based glass
is preferably in the range 0.2 to 5 weight per cent, more preferably 0.5 to 2 weight per
cent.

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The phosphate-based glass used in the invention is usually defined herein as
comprising metal cations and phosphate anions, but it may equally well be expressed
as an oxide solid solution, e g (CaO)_x(Na₂O)_y(P₂O₅)_{x+y}.

Preferably the glass is at least 90% by weight of metal cations and phosphate anions, and may consist substantially entirely of metal cations and phosphate anions.

The metal cations of the phosphate based glass are usually of at least two metals.

Preferably the cations consist of or include at least one alkali metal and at least one alkaline earth metal. The alkaline earth metal cations may be one or more of Ca^{++} , Mg^{++} and Sr^{++} . The alkali metal cations may be one or both of K^+ and Na^+ . Most preferably the cations consist of or include Ca^{++} and at least one of K^+ and Na^+ .

Other cations may be present, for example cations of at least one metal having a valency of greater than 2. Metal cations of valency of 3 or more, for example transition metal cations preferably of valency 3 or 4, may be employed to decrease the water-solubility of the glass. Examples are Fe^{3+} , Ti^{4+} , Ga^{3+} and Ta^{5+} . Ga^{3+} can provide an antibiotic property.

Suitably, the metal oxide composition of the glass, in mole per cent and expressed as P_2O_5 and metal oxides, is

(i) P_2O_5 35 - 65%, preferably 40 - 60%

(ii) alkaline earth metal oxide or oxides 20 - 60%, preferably 25 - 60%

(iii) metal oxides other than alkaline earth metal oxides 5 - 35%, preferably 10 - 30%.

This composition can provide suitable water-solubility. Preferably in this metal oxide composition the amount of metal oxides other than alkaline earth metal oxides and alkali metal oxides is not more than 5 mole %, more preferably not more than 3 mole %.

The phosphate anions are preferably orthophosphate (PO_4^{3-}), pyrophosphate ($\text{P}_2\text{O}_7^{4-}$), metaphosphate (PO_3^-) or ultraphosphate (P_2O_5), or mixtures of these. The anion ultraphosphate is conventionally expressed as P_2O_5 . Other anions, such as F^- , may be present, provided that the desired degradation by water is obtained. Such other anions are preferably not more than 5 mole % of the anions. The glass used in

the invention may be an ultraphosphate glass, i.e. one containing 50 mole% or more P_2O_5 in the phosphate anions.

The phosphate-based glass is water-degradable and therefore is biologically
5 degradable to release the active drug component, for example when in contact with blood. A suitable test for this biodegradability is the ability to release the active drug component when the product is immersed in saline solution.

The solution rate of the phosphate-based glass in distilled water at 37°C is preferably
10 in the range 1×10^{-4} to 1×10^{-2} mg/mm²/hr.

In the method of the invention step (i) is preferably performed by combining alkyl
phosphate material and an organic alcohol oxide of at least one metal. Preferably
step (i) is carried out in organic alcohol solution. Preferably step (ii) is performed by
15 adding a non-aqueous solution of the drug component to the sol. A suitable non-aqueous solvent for cisplatin is DMF. Step (iii) may be performed by allowing the sol to stand at a temperature in the range of 40 to 150°C, more preferably 40 to 100°C, most preferably 50 to 100°C. The time of standing is preferably at least one day,
preferably at least two days. Step (iv) may be performed by heating the gel to a
20 temperature of at least 100°C, in order to remove solvent and water and organic molecules derived from the sol materials, preferably at 150°C or above. Cisplatin is thermally stable up to 270°C, and therefore can withstand the heating step. The upper limit of heating temperature in step (iv) is determined by the thermal stability of the active medical component, and may be for example 250°C. In general the heating
25 temperature and time should be such that a substantial proportion of the active medical component is not thermally degraded.

The composition of the starting materials, including the metal elements present, is selected in accordance with the desired composition of cations and anions in the
30 glass product, described above.

The alkyl group of the alkyl phosphate material preferably used in step (i) may be an alkyl of 1 to 10 carbon atoms, preferably 1 to 4 carbon atoms, may be straight or
35 branched chain and is preferably unsubstituted. Propyl, isopropyl, n-butyl and isobutyl are preferred. The phosphate of the alkyl phosphate is preferably mono- or di-substituted by the alkyl group.

The organic alcohol of the metal oxide of organic alcohol which may be used is preferably an alkanol of 1 to 6 carbon atoms, more preferably 1 to 4 carbon atoms. It may be unsubstituted or may be substituted with –OR where R is an alkyl group of 1 to 4 carbon atoms. Preferred are methanol, ethanol and 2-methoxyethanol.

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In the method, the presence of water in the sol is undesirable and is very preferably avoided.

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The sol containing the active drug component may be subjected to electrospraying to form beads, which are then gelled and then heated to dry them and form the glass. Electrospraying may be performed by ejecting a stream of the sol from a nozzle through a heated zone onto a substrate, with a voltage applied between the nozzle and the substrate, e.g. 10-30kV. Bead size can be controlled in this process.

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The beads may be of a suitable size, e.g. up to 500µm, to embolise blood vessels when injected into the patient, thus for example providing an additional therapy to the platinum treatment, by embolisation of blood vessels associated with a tumour. To cause embolisms in this way is known to be of advantage in some cancer treatments. *The embolisation may have the advantage of preventing or restricting the spread of* the active drug component to other sites, thereby increasing efficiency of treatment at a selected site.

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The dosage amounts of the pharmaceutical product of the invention in its use may be according to the established principles, if any, for the particular drug.

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The invention also extends to products for use in the medical treatments herein described, particularly products containing a platinum compound for use in the treatment of cancer, such as testicular cancer, head and neck cancer, small cell lung cancer and ovarian cancer. The invention further extends to the methods of medical treatment herein described.

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Introduction of the drawings

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Fig 1 shows a reaction scheme for the sol-gel synthesis of a product of the invention. Fig 2 shows Pt LIII-edge EXAFS fluorescence data. Fig 3 is graphs of UV/vis spectroscopy study of cisplatin release.

Description of embodiments

Preparation of cisplatin in $(\text{CaO})_{0.3}(\text{Na}_2\text{O})_{0.2}(\text{P}_2\text{O}_5)_{0.5}$

The following precursors are used, without further purification, in the sol-gel preparation: 2.5 ml of 1:1 molar mixture of mono- and di-substituted n-butyl phosphate ($\text{OP}(\text{OH})_2(\text{OBu}^n)$ and $\text{OP}(\text{OH})(\text{OBu}^n)_2$, Alfa Aesar, ~98%), 1.15 ml sodium methoxide solution (NaOMe, Aldrich, 30 wt% in methanol) and 4.95 ml calcium methoxyethoxide solution ($\text{Ca}(\text{methoxyethoxide})_2$), 17.5 wt% in 2-methoxyethanol). The Ca-methoxyethoxide solution is prepared by reacting the appropriate amount of calcium metal (Riedel-de Haën, 98%) with 2-methoxyethanol (Aldrich, 99.8%) under argon at 80 °C for 24 hr. The concentration of the resultant solution can be confirmed gravimetrically by evaporating the solvent and heating to 1050 °C for 12 hr to convert the alkoxide to CaO.

The sol-gel preparation is shown by the flowchart in Fig 1. The n-butyl phosphate is first added dropwise using a syringe through a septum to a vessel containing the NaOMe solution: the solution is stirred magnetically throughout this addition. After one hour, the Ca-methoxyethoxide solution is added using the same method. The sol is then allowed to gel at room temperature, which typically takes ~ 2 hrs, and left overnight. During this period the gel liquefies, allowing the cisplatin solution to be added and mixed in. The cisplatin solution is 15 mg cisplatin in 1 ml dimethylformamide (DMF) (equivalent to 17mM), corresponding to 1 wt% cisplatin relative to the $(\text{CaO})_{0.3}(\text{Na}_2\text{O})_{0.2}(\text{P}_2\text{O}_5)_{0.5}$ glass formed later. The resultant sol is cast in a polypropylene container and aged at 60°C for one week, during which time the final gellation occurs, before drying at 120°C for two weeks. The dried gel is heated to 200°C at a ramp rate of 5°C/min and this temperature maintained for 1 hr to remove solvent, water and organic molecules deriving from the sol materials.

Evidence of cisplatin encapsulation and release

Pt L_{III} -edge EXAFS (Extended X-ray Absorption Fine Structure) data (collected in fluorescence mode) verified the encapsulation of cisplatin in the $(\text{CaO})_{0.3}(\text{Na}_2\text{O})_{0.2}(\text{P}_2\text{O}_5)_{0.5}$ glass (PBG). The data were fitted using a model based on the premise that some of the Cl^- ligands are replaced by oxygens during the sol-gel

processing. The structural parameters obtained from the fitting process are given in Table 1 below and the data shown together with the fits in Fig 2. From the Pt-Cl coordination number we can estimate that ~65% of the cisplatin is encapsulated unchanged in the dried gel, and that heat treatment to 200°C causes further Cl⁻ ligand exchange.

Fig 2 shows the Pt L_{III}-edge EXAFS fluorescence data: (top) cisplatin, (middle) dried cisplatin doped phosphate gel and (bottom) cisplatin doped PBG. The experimental data are depicted by solid lines and the fits by dashes line.

Table 1 Structural parameters obtained from fitting the fluorescence EXAFS data.

The parameters in italics were fixed. N = coordination number, R = atomic separation and A = Debye-Waller factor. The units are Angstroms (10⁻¹⁰ m).

Data	Shell	N / Å	R / Å	A / Å ²	R _{fit}
Cisplatin	Pt-N	2	2.043	0.004	36.18
	Pt-Cl	2	2.319	0.005	
Cisplatin loaded sol-gel PBG (dried gel)	Pt-N	2	2.000	0.007	51.02
	Pt-O	0.7	2.035	0.004	
	Pt-Cl	1.3	2.314	0.007	
Cisplatin loaded sol-gel PBG (heated to 200°C)	Pt-N	2	1.999	0.011	53.11
	Pt-O	1.5	2.026	0.010	
	Pt-Cl	0.5	2.313	0.008	

The release of cisplatin into saline solution from the phosphate-based glass (PBG) was monitored using UV/vis spectroscopy. Fig 3(a) shows the evolution with time of the absorption spectra of the saline solution exposed to the cisplatin-loaded PBG together with the spectrum from pure cisplatin dissolved in saline for comparison (broken line); the graph clearly shows the release of cisplatin as a function of time. The solid lines in Fig 3(a) are, from the bottom to the top, the absorption curves at 1 day, 2 days, 3 days and 6 days respectively. The release profile, obtained by plotting the absorption at 301 nm against time, is shown in Figure 3(b). The results show sustained release of cisplatin for three days before the release profile reaches a plateau.

Claims

1. A medical product containing an active medical component of low or moderate thermal stability incorporated in a body of phosphate-based glass in the form of an amorphous solid oxide material comprised of metal cations and phosphate anions, the glass being degradable by water to release the active medical component.
2. A medical product according to claim 1 wherein said phosphate ions are selected from orthophosphate, pyrophosphate, metaphosphate, ultraphosphate and mixtures of two or more of these.
3. A medical product according to claim 1 or 2 wherein said metal cations consist of or include cations of at least one alkali metal and at least one alkaline earth metal.
4. A medical product according to claim 3 wherein the alkaline earth metal cations are selected from Ca^{++} , Mg^{++} and Sr^{++} .
5. A medical product according to claim 3 wherein said cations consist of or include Ca^{++} and at least one of K^{+} and Na^{+} .
6. A medical product according to any one of claims 3 to 5 wherein said cations further include cations of at least one metal having a valency greater than 2.
7. A medical product according to any one of claims 3 to 6 wherein the metal oxide composition of the glass, in mole per cent and expressed as P_2O_5 and metal oxides, is
 - (i) P_2O_5 35 - 65%, preferably 40 – 60%
 - (ii) alkaline earth metal oxide or oxides 20 – 60%, preferably 25 – 60%
 - (iii) metal oxides other than alkaline earth metal oxides 5 – 35%, preferably 10 – 30%.

8. A medical product according to claim 7 wherein in said metal oxide composition the amount of metal oxides other than alkaline earth metal oxides and alkali metal oxides is not more than 5 mole %, preferably not more than 3 mole %.

9. A medical product according to any one of claims 1 to 8 wherein the glass
5 body is a single phase body.

10. A medical product according to any one of claims 1 to 9, wherein said single phase body is a discrete body, unconnected to another solid phase.

11. A medical product according to any one of claims 1 to 10 wherein the phosphate based glass is non-porous.

10 12. A medical product according to any one of claims 1 to 11 wherein the active medical component is selected from a drug having therapeutic effect and a medical diagnostic agent.

13. A medical product according to any one of claims 1 to 12 wherein the active medical component is thermally unstable at 400°C.

15 14. A medical product according to any one of claims 1 to 13 wherein the active medical component is a platinum compound.

15 A medical product according to claim 14 wherein the platinum compound is a platinum complex, e.g. cisdiamminedichloridoplatinum (II) (cisplatin) or an analogue thereof.

20 16. A medical product according to claim 15 wherein the amount of the platinum compound in the phosphate-based glass is in the range 0.5 to 2% by weight.

17. A method of making a medical product comprising the steps of:

(i) forming a metal phosphate sol

(ii) incorporating an active medical component in said metal phosphate
25 sol,

(iii) gelling said sol, and

(iv) heating the resultant gel to convert the gel into a phosphate-based

glass in the form of amorphous solid oxide material comprising metal cations and phosphate anions, the active medical component being incorporated in the glass.

18. A method according to claim 17 wherein step (i) is performed by combining
5 alkyl phosphate material and an organic alcohol oxide of at least one metal,

19. A method according to claim 17 or 18 wherein in step (i) the metal of the metal phosphate sol comprises at least one alkali metal and at least one alkaline earth metal.

20. A method according to any one of claims 17 to 19 wherein step (i) is carried
10 out in organic alcohol solution.

21. A method according to any one of claims 17 to 20 wherein step (ii) is performed by adding a non-aqueous solution of the active medical component to the sol.

22. A method according to any one of claims 17 to 21 wherein step (iii) is
15 performed by allowing the sol to stand at a temperature in the range of 40 to 150°C, preferably 40 to 100°C, more preferably 50 to 100°C.

23. A method according to any one of claims 17 to 22 wherein step (iii) is performed by allowing the sol to stand for at least one day, preferably at least two days

20 24. A method according to any one of claims 17 to 23 wherein step (iv) is performed by heating the gel to a temperature of at least 100°C.

25. A method according to any one of claims 17 to 24 wherein the active drug component is a platinum compound.

26. A method according to claim 25 wherein the platinum compound is
25 cisdiamminedichloridoplatinum (II) (cisplatin) or an analogue thereof.

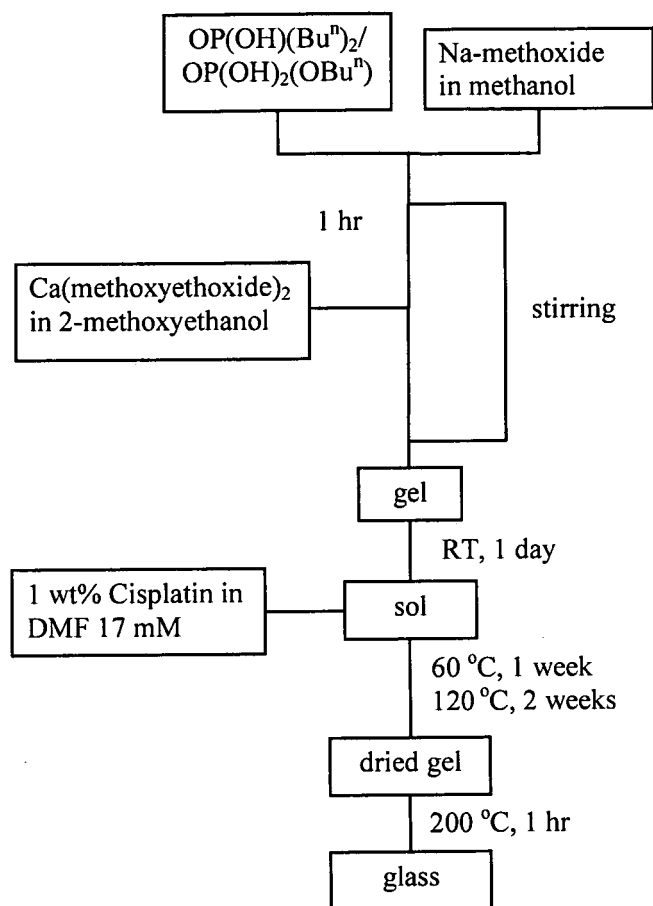


FIG 1

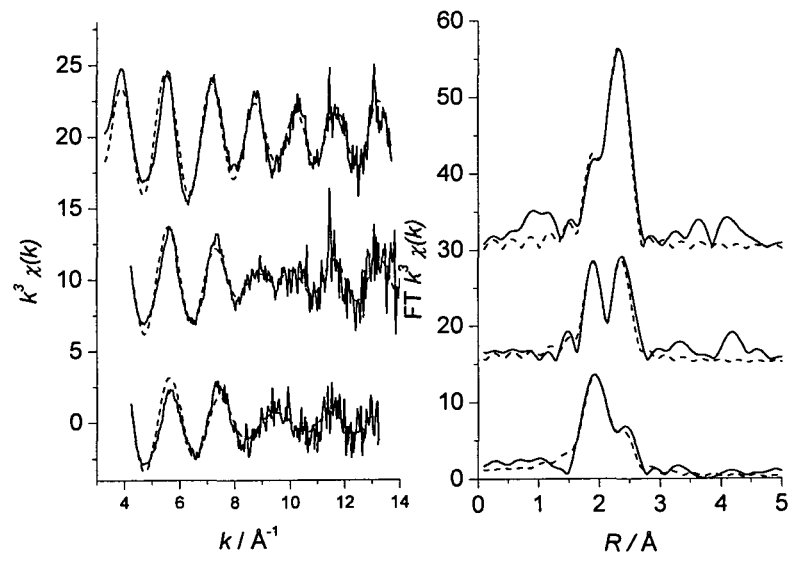


FIG 2

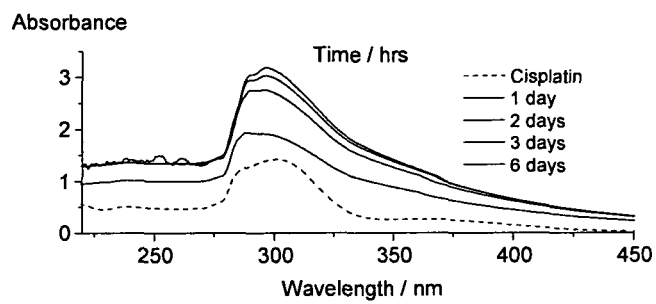


FIG 3(a)

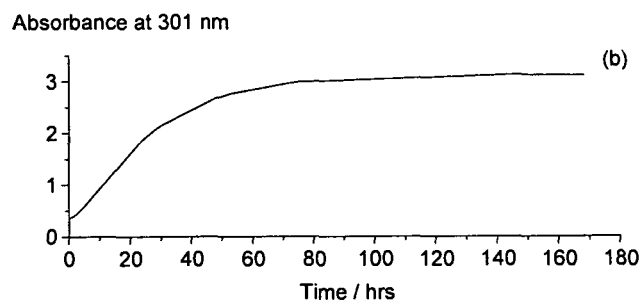


FIG 3(b)

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2009/002180

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/14 A61K31/282

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 374 427 A (STILLE WOLFGANG [DE] ET AL) 20 December 1994 (1994-12-20)	1-6,9-16
Y	claims 13,19-21	7,8, 17-26
	table 1	
	example 1	
	column 5, lines 20-34,50-54	
	column 7, lines 26-60	
	column 2, line 7 - line 10	

X	EP 1 872 798 A (SANGI KK [JP]) 2 January 2008 (2008-01-02)	1-6,9-16
	preparation examples 1,2	
	examples 1-1 to 1-4	

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Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

20 November 2009

Date of mailing of the international search report

30/11/2009

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International application No

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