# Original Paper

## Models for physical properties and bioactivity of phosphate opal glasses[1])

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Bioactive glasses are glasses to which bone can attach through a tight chemical bond after implantation. Glasses are, however, brittle and therefore they are preferably used in combination with other ceramic materials or metals. In this work potentially bioactive phosphate opal glasses have been studied. Phenomenological equations describing the influence of glass composition on transition temperature, thermal expansion, chemical durability and bone bonding are developed. The equations may be used for development of various implant materials based on bioactive glass, for example enamels for metal protheses. The corrosion behaviour in body fluid is also discussed and compared with the bone bonding. The role of alumina is briefly considered.

**Modelle für die physikalischen Eigenschaften und die Bioaktivität von Opal-Phosphatgläsern**

Bei den bioaktiven Gläsern handelt es sich um Gläser, die sich nach ihrer Implantierung auf chemischem Wege fest mit dem Knochen verbinden. Da Gläser spröde sind, werden sie bevorzugt in Kombination mit anderen keramischen Werkstoffen oder mit Metallen eingesetzt. In der vorliegenden Arbeit werden bioaktive Opal-Phosphatgläser untersucht. Phänomenologische Gleichungen, die den Einfluß der Glaszusammensetzung auf die Transformationstemperatur, die Wärmeausdehnung, die chemische Beständigkeit und die Knochenbindung beschreiben, werden abgeleitet. Diese Gleichungen können auf die Entwicklung verschiedener Implantatmaterialien, ausgehend von bioaktiven Gläsern, angewendet werden, z. B. Emails für Metallprothesen. Ferner wird das Korrosionsverhalten in der Körperflüssigkeit diskutiert und mit der Knochenbindung verglichen. Die Bedeutung von Aluminium wird kurz gestreift.

### 1. Introduction

A field of materials technology that in recent years has attained an increasing attention is the biomaterials, i.e. materials that may be used in the human body for instance for replacement or augmentation of defect organs or skeletal structures.

In biomedical applications the choice of material depends on a great number of factors. The material has to possess physical and biological properties matching the tissue in contact with which it will be. This is necessary in order to avoid adverse reactions and to achieve beneficial interactions between the implanted material and the host tissue. There is a wide variety of applications for biomaterials possessing very different properties. Depending on the demands a wide range of materials are used, including metals, polymers and ceramic materials. Often it is also necessary to use combinations of these materials in order to get a suitable product.

Bioceramic materials can be divided into three categories depending on their interactions with tissue. Essentially the interactions depend on the stability or the reactivity of the implanted material. Inert materials, such as alumina, are stable and release only very small amounts of degradation products, if any. These materials are surrounded by a thin fibrous membrane and may be mechanically fixed by the ingrowth of tissue into a rough or porous surface. Resorbable materials, such as tricalcium phosphate, are used temporarily in the organism and dissolve as they are gradually replaced by autogenous bone. The bioactive or surface reactive materials provide the most complex interactions with tissue, but also a great potential for use in different applications. These materials show the property of bonding to living tissue through a tight chemical bond. This property is possessed by hydroxoapatite and some glasses. The formation of the bond between glass and bone has been described in the literature [1 to 6]. Also bonding to soft tissue has been reported [7].

For a glass to be bioactive a calcium phosphate surface layer must form on it when exposed to the body fluid. By the formation of this surface layer the implant gets a surface to which bone can bind and furthermore the glass will be protected from further dissolution. In the initial stage of the corrosion process alkali is preferentially leached out from the glass surface leaving behind a layer rich in silica. After this a surface film rich in calcium phosphate starts to build up as $Ca^{2+}$ and $PO_4^{3-}$ ions that, migrating from the bulk of the glass, reach the surface. The film increases in thickness as calcium and phosphate present in the body fluid precipitates on the surface. Simultaneously collagen is incorporated into the silica-rich gel and the calcium phos-

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Table 1. Composition of glasses in wt%

| glass no. | $SiO_2$ | $Na_2O$ | CaO | $P_2O_5$ | $Al_2O_3$ | $B_2O_3$ |
|---|---|---|---|---|---|---|
| 1 | 68.05 | 15.15 | 11.42 | 2.31 | 2.49 | 0.75 |
| 2 | 48.24 | 25.13 | 18.19 | 2.31 | 3.31 | 2.82 |
| 3 | 62.93 | 17.11 | 13.66 | 4.61 | 0.00 | 1.70 |
| 4 | 56.70 | 19.00 | 15.83 | 4.61 | 1.64 | 2.25 |
| 5 | 47.51 | 27.29 | 20.57 | 4.63 | 0.00 | 0.00 |
| 6 | 56.73 | 24.59 | 8.90 | 6.76 | 0.81 | 2.21 |
| 7 | 52.68 | 20.75 | 15.64 | 6.79 | 0.81 | 3.33 |
| 8 | 51.53 | 22.23 | 13.12 | 8.85 | 3.18 | 1.09 |
| 9 | 52.47 | 18.53 | 17.65 | 8.93 | 2.41 | 0.00 |

Table 2. Coefficients of thermal expansion

| glass no. | clear glass $\alpha$ in $10^{-5}\,K^{-1}$ (calculated) | opal glass $\alpha$ in $10^{-5}\,K^{-1}$ (determined) | difference in % |
|---|---|---|---|
| 1 | 1.00 | 0.92 | − 8.0 |
| 2 | 1.42 | 1.29 | − 9.2 |
| 3 | 1.13 | 0.97 | −14.2 |
| 4 | 1.21 | 1.11 | − 8.3 |
| 5 | 1.56 | 1.31 | −16.0 |
| 6 | 1.37 | 1.30 | − 5.1 |
| 7 | 1.29 | 1.18 | − 7.8 |
| 8 | 1.35 | 1.35 | 0.0 |
| 9 | 1.27 | 1.14 | −10.2 |

phate surface layer. The bone bonding takes place as the amorphous calcium phosphate crystallizes and the collagen mineralizes [4]. In both processes apatite is formed.

The main drawback of glass lies in its poor mechanical properties. As a failure of an implant will demand a reparative operation, which is likely to be a lot more difficult than the initial one, the mechanical weakness severely restricts the use of these materials. This can, however, to some extent be overcome by using them as coatings on ductile metal substrates. By coating a metal with a bioactive glass on the one hand the metal can be protected from corroding and on the other hand it can be attached to bone. By using bioactive glass in the attachment of metal implants to bone the need for polymeric bone cements can be eliminated.

In order to develop a successful coating there are various factors to take into consideration. As the glass surface may be leached to a considerable depth and as this may result in exposition of the metal substrate to the physiological environment it would be desirable to design a ground enamel of high durability. Also the other properties of interest, like the coefficient of thermal expansion and the transition temperature, should be achieved without interfering with the bioactivity. That is, there is a restriction to use mainly matter occuring naturally in the human body and to stay within the composition range showing bioactivity.

The objective of this work was to develop phenomenological equations describing the relationship between glass composition and physical as well as bone-bonding properties. It has long been known that several physical properties may be described as functions of the glass composition. The hypothesis was that also the bone-bonding behaviour may be expressed in the same way.

## 2. Experimental

In this work nine glasses in the system $SiO_2$–$Na_2O$–CaO–$P_2O_5$–$B_2O_3$–$Al_2O_3$ were studied. The compositions in table 1 were chosen by a method described by Plackett and Burman [8] in order to provide a basis for a statistical evaluation of the results.

The raw materials used were Belgian sand, $Na_2CO_3$, $CaCO_3$, $Ca(H_2PO_4)_2 \cdot H_2O$, $Al_2O_3$ and $Na_2B_4O_7$. For each glass 200 to 250 g batch was prepared and melted in a ceramic crucible at 1400 °C for 4 h. Some changes in the composition due to corrosion of the crucible did take place. The increase in $Al_2O_3$ and $SiO_2$ contents was estimated to be 1.0 to 1.5 wt%. This increase was, however, not counted in when developing the models, but the theoretical compositions were used.

To crystallize the glasses they were nucleated for 2 h at 700 °C. Then the temperature was raised to 750 or 800 °C, depending on the glass. This temperature was held for 3 h.

## 3. Determined properties

### 3.1. Thermal expansion

The coefficient of thermal expansion of glasses can with acceptable accuracy be estimated from a known oxide composition. A number of methods have been developed for this purpouse, that of Appen [9 and 10] being one of the most reliable. However, all available models have been developed for homogeneous glasses. The coefficient of thermal expansion of the phase-separated glasses was therefore determined experimentally. The results are shown in table 2 together with the expansion calculated with Appen's method. As can be seen the coefficient of thermal expansion, $\alpha$, is about 10 % lower for the phase-separated glasses than for the clear ones. The influence of the composition (in wt%) on the thermal expansion of the phase-separated glasses can satisfactorily be described by the equation

$$\alpha = 0.734377 + [1.56974\,Na_2O - 0.509946\,CaO - \\ - 21.8829/P_2O_5 + 1.84830\,Al_2O_3]/SiO_2\,;$$

$$R^2 = 99.47\%,\ \sigma = 0.01592 \cdot 10^{-5}\,K^{-1}\,,$$

where $\alpha$ is given in $10^{-5}\,K^{-1}$, $R$ is the correlation coefficient and $\sigma$ is the standard deviation.

Table 3. Glass transition temperature and chemical durability

| glass no. | $T_g$ in °C | $P_{98}$ in ml |
|---|---|---|
| 1 | 542 | 0.40 |
| 2 | 493 | 0.78 |
| 3 | 522 | 0.48 |
| 4 | 525 | 0.42 |
| 5 | | 1.93 |
| 6 | 482 | 2.75 |
| 7 | 525 | 0.56 |
| 8 | 501 | 1.66 |
| 9 | 639 | 0.87 |

### 3.2. Glass transition temperature

The glass transition temperatures, $T_g$, were determined from the dilatometric measurements and are shown in table 3. The dependence between the glass transition temperature and the composition (in wt%) can be described by

$$T_g = 1286.72 - 14.5209\,Na_2O - 84.9158\,CaO + \\ + 3.35623\,(CaO)^2 + 0.939346\,(P_2O_5)^2\,;$$

$$R^2 = 99.82\,\%,\ \sigma = 3.132\,K\,,$$

where $T_g$ is given in °C.

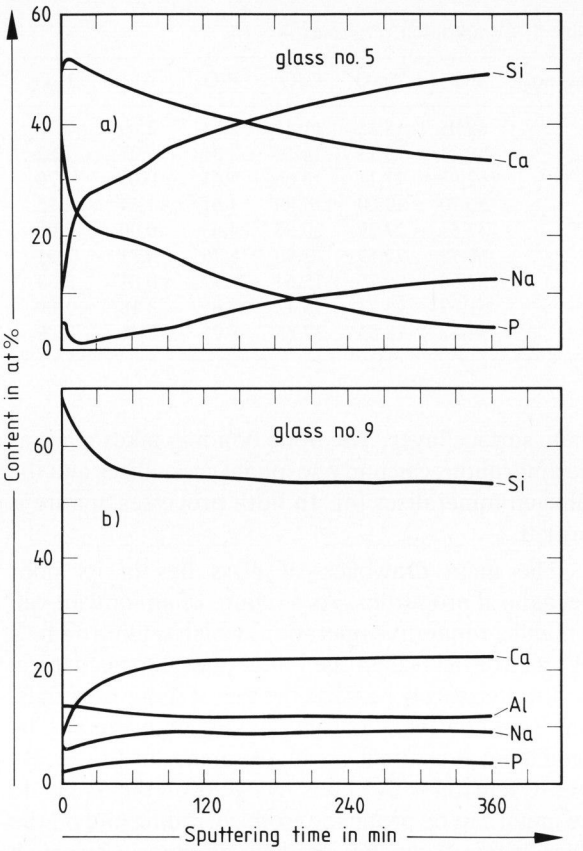
### 3.3. Corrosion behaviour

In order to develop a model for the chemical durability a standard method was used. The glass was crushed to 297 to 500 µm grain size and leached 1 h in demineralized water at 98 °C. The $P_{98}$ value expresses the volume (in ml) of 0.01 M HCl per gram glass used to neutralize the leaching solution (table 3). The following model gives the $P_{98}$ value as a function of the glass composition in wt%.

$$P_{98} = -4.65818 + 0.167403\,Na_2O + 25.0815/CaO + \\ + 0.251367\,P_2O_5 - 0.016014\,(P_2O_5)^2 - \\ - 0.234179\,B_2O_3\,;$$

$$R^2 = 99.85\,\%,\ \sigma = 0.05219\,ml\,.$$

The corrosion behaviour of surface reactive glasses can preferably be studied applying methods for surface analysis, like Auger Electron Spectroscopy (AES) [11 and 12] or Electron Spectroscopy for Chemical Analysis (ESCA) in combination with ion-milling. ESCA was used in this work for studying glasses no. 5 and 9 after corrosion in blood serum for 1 h at 36.5 °C. The obtained profiles are shown in figures 1a and b. As can be seen a surface layer rich in calcium and phosphorus has formed on glass no. 5. The chemical profiles in glass no. 9 are quite different showing only a dealkalisation of the surface. The very different corrosion behaviour during the first hour indicates that there should also be a significant difference in the bone-bonding behaviour of these glasses.

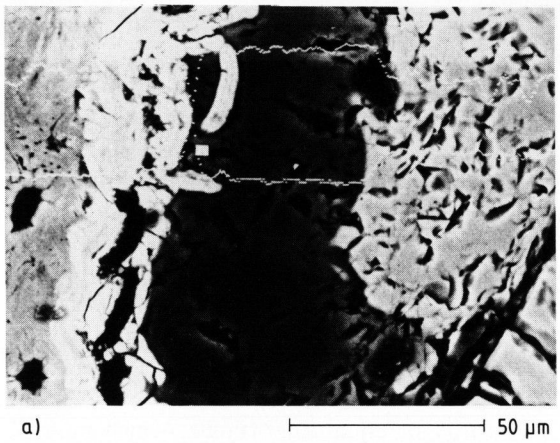


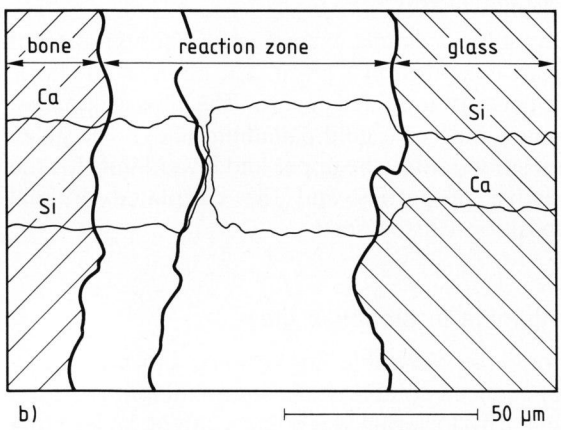

Figures 1a and b. Chemical profiles obtained by ion-milling and ESCA after 1 h corrosion in serum (36.5 °C), a) on glass no. 5 a calcium-phosphate-rich surface layer has formed, b) on glass no. 9 the surface is dealkalized.

### 3.4. Bone-bonding behaviour

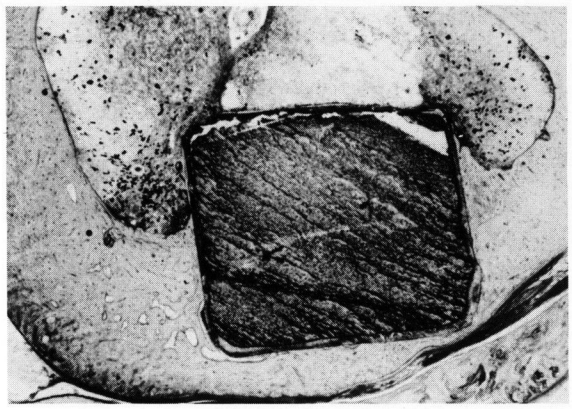
The bone-bonding behaviour of the glasses was studied in vivo by implantation in rabbit tibia [13]. For each rabbit three holes were drilled in each tibia and glass cylinders ($l = 4$ mm, cross section = 4.2 mm) were inserted. Three specimens of each glass were implanted. After eight weeks the rabbits were sacrificed. The implants were excised as blocks with surrounding bone, fixed in buffered formaldehyde and embedded in methylmethacrylate. From each specimen a 30 to 50 µm thick slice was cut and stained for examination by optical microscopy. Remaining material was studied using Scanning Electron Microscopy (SEM) and Energy Dispersive X-ray Analysis (EDXA).

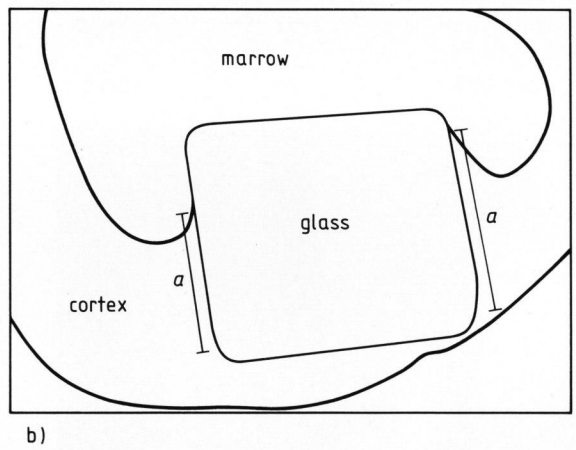
In figures 2a and b a SEM micrograph and a drawing of the interface between glass no. 6 and bone are shown. A good bonding has resulted. Due to the leaching in the physiological environment a 50 µm thick silica-rich layer has formed. Migration of $Ca^{2+}$ and $PO_4^{3-}$ ions from the bulk to the surface of the glass and deposition of soluble calcium phosphate




Figures 2a and b. The interface between tissue and glass is shown by a) a SEM micrograph, b) a drawing of chemical profiles (EDXA).




Figures 3a and b. Result of implantation of glass no. 5 in rabbit tibia after 8 weeks; a) optical micrograph, b) sketch of the same sample showing the area taken into account.

from the solution has resulted in a 20 µm thick calcium phosphate layer on top of the silica-rich layer. As one application for these glasses is for coating of metals and as the leaching of the glass in only eight weeks has extended to a depth comparable to the thickness of an enamel, there is an apparent need for a ground enamel of high durability.

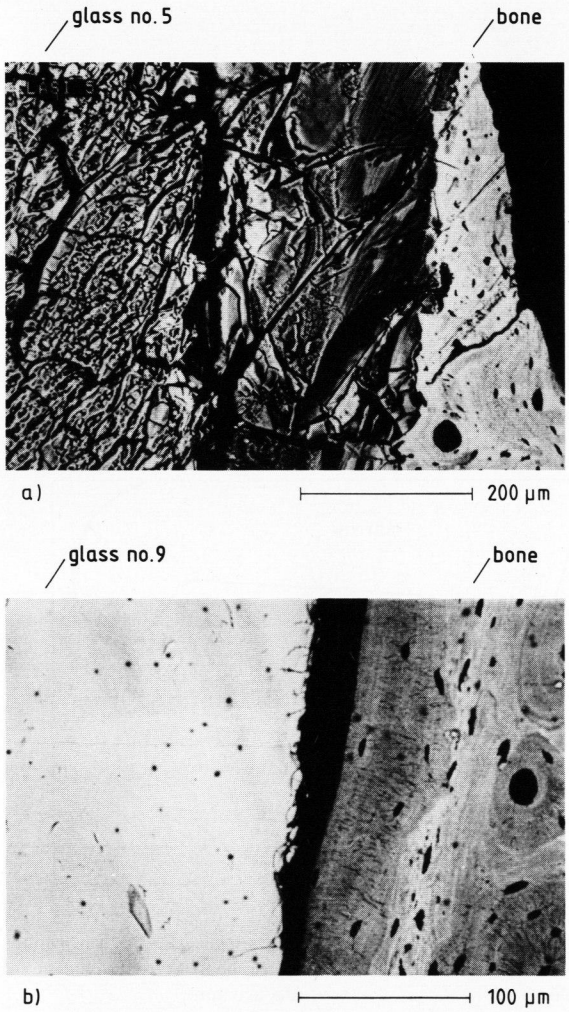
From the histological sections the relative amounts of connective tissue, osteoid and maturated bone developed in contact with the mantle area of the glass cylinder was determined. Hence, not only the area that initially had been in contact with the cortex was taken into account (figures 3a and b). The results of the planimetric measurements are shown in table 4. As can be seen there are glasses showing very good bone bonding as well as glasses showing very poor or no bonding at all. The large differences between the glasses allow to develop a model describing the bone bonding from 0 to 100 %. However, the results for each glass show large scattering and a large standard deviation for this model is the consequence. The model gives the maturated bone (MB in %) developed in contact with the implant after 8 weeks in rabbit tibia as a function of the composition in wt%.

Table 4. Biological response

| | connective tissue | | | osteoid | | | maturated bone | | |
|---|---|---|---|---|---|---|---|---|---|
| glass no. | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| 1 | 45 | – | – | 37 | – | – | 18 | – | – |
| 2 | 27 | – | 21 | 18 | – | 69 | 60 | – | 10 |
| 3 | 96 | 100 | 43 | 3 | 0 | 20 | 1 | 0 | 37 |
| 4 | – | 54 | 35 | – | 0 | 52 | – | 46 | 13 |
| 5 | 11 | 28 | 4 | 7 | 0 | 4 | 82 | 72 | 92 |
| 6 | 18 | 36 | 36 | 4 | 0 | 11 | 78 | 64 | 53 |
| 7 | 2 | 5 | 0 | 0 | 0 | 0 | 98 | 95 | 100 |
| 8 | – | 100 | – | – | 0 | – | – | 0 | – |
| 9 | 49 | 52 | 72 | 44 | 48 | 22 | 7 | 0 | 6 |

$$MB = 1660.08 - 32.0095\,Na_2O - 26.3001\,P_2O_5 + \\ + 1015.17\,Al_2O_3 - \\ - 889.808\,(Al_2O_3)^2 + 181.034\,(Al_2O_3)^3 - \\ - 123.263\,(B_2O_3)^2 - 12.2229\,SiO_2\,;$$

$$R^2 = 88.97\,\%,\ \sigma = 15.58\ \text{wt\%}\ .$$




Figures 4a and b. SEM micrographs of the interface between bone (right) and a) glass no. 5, b) glass no. 9 (left). Glass no. 5 has induced bone growth to a surface that did not have initial contact to the cortex, whereas glass no. 9 shows no bonding to bone.

The equation gives a reasonable fit for the experimentally investigated glasses. In the bioactive range, however, this equation gives values exceeding 100 %, which of course must be read as 100 %. To blunt the curve in this range, the power of the polynomial terms should be increased. This was, however, disregarded as it increases the risk of an oscillating behaviour of the equation.

As suggested in paragraph 3.3. the different corrosion behaviour of the glasses no. 5 and no. 9 (figures 1a and b) should also be reflected in the biological behaviour. This is also the case. Glass no. 5, on top of which a calcium phosphate-rich surface layer formed during the first hour of corrosion in vitro, showed 82 % of maturated bone at its surface, whereas there was only about 5 % of maturated bone in contact with glass no. 9. In figures 4a and b typical interfaces for these glasses and bone are shown. This indicates a possible applicability of in vitro testing and surface analysis in the prediction of tissue response to glass.

## 4. Optimisation of glass compositions

The equations in section 3. describe the properties as functions of glass composition. They allow, however, also to tackle the opposite problem of finding the composition of the most bioactive glass suitable for enamelling of a given metal or suitable for use in composites. The method of solving the optimisation has been described previously [14 and 15]. Usually some deviation in the properties can be tolerated. The programme allows specifying the limits within which the respective property may vary and an opportunity to fix one or more of the oxides at specified levels. Furthermore, all the properties are not necessarily of equal importance, which may be counted for by giving the different properties different weight factors.

In table 5 a simple example of an optimisation of the glass composition is given. The alumina and boric oxide contents are fixed at zero. The glass is intended for enamelling of a gold-palladium alloy. The given composition range, the upper and lower limits for the respective properties and the calculated optimal composition can be seen.

## 5. Alumina in bioactive glass

It would be desirable to produce bioactive glasses of reduced solubility. Reduced solubility can be achieved by lowering the alkali content and adding di- or trivalent metal oxides.

In order to control the solubility and other physical properties, alumina was included in the present work. However, from a biological point of view this may not be acceptable. As can be seen in table 4 there is only a small amount of osteoid, which is bone-like but not mineralised tissue, in contact with glasses no. 3 and 5 to 8. This indicates that the osteoid is either not formed at all (glasses no. 3 and 8) or that, once it is formed, it transforms into bone (glasses no. 5 to 7). The rest of the glasses show a great amount of osteoid indicating that there is some mechanism inhibiting the mineralisation and the transformation into bone. In the latter glasses the alumina content is higher than in the former ones. The strong correlation suggests that aluminium retards or inhibits the transformation of osteoid into bone. This finding supports the results presented by Gross and Strunz [5] showing a disturbance of the bone-forming process as metal oxides such as $Al_2O_3$, $Ta_2O_5$, $Sb_2O_3$ and $ZrO_2$ are added to the glass. They showed that tissue could be transformed into osteoid but that the mineralisation of the osteoid was disturbed.

The negative effects of aluminium on the bone-bonding properties are accounted for by the presented model giving lower bone-bonding percentages as the alumina content is increased. However, the presence of small amounts (up to 1.6 wt%) of

Table 5. Example of optimisation of glass composition. The alumina and the boric oxide contents are fixed at zero. The glass is intended for enamelling of a gold-palladium alloy. The minimum and maximum limits for the compositions are set by the experimentally investigated range (c.f. table 1), the limits for the properties by the requirements on the enamel

| composition | remark | minimum content | feedrate | maximum content |
|---|---|---|---|---|
| $B_2O_3$ | fixed | 0.00 | 0.00 | 3.30 |
| $Al_2O_3$ | fixed | 0.00 | 0.00 | 3.30 |
| $Na_2O$ | | 15.00 | 27.50 | 27.50 |
| CaO | | 9.00 | 10.19 | 21.00 |
| $P_2O_5$ | | 2.50 | 5.26 | 9.00 |
| $SiO_2$ | | 47.00 | 57.05 | 68.00 |
| Total: | | | 100.00 | |

| properties | weight factor | property values for | | |
|---|---|---|---|---|
| | | minimum content | actual content | maximum content |
| viscosity at 600 °C given in lg $\eta$ ($\eta$ in dPa s) | 1 | 5.000 | 5.634 | 10.300 |
| viscosity at 800 °C given in lg $\eta$ ($\eta$ in dPa s) | 1 | 1.000 | 2.844 | 5.500 |
| thermal expansion in $10^{-5}\,K^{-1}$ | 100 | 1.350 | 1.327 | 1.400 |
| transition temperature in 100 °C | 1 | 3.500 | 4.108 | 6.000 |
| chemical durability ($P_{98}$ value) in ml HCl/g | 0 | 0.010 | 3.311 | 5.000 |
| maturated bone in wt% | 100 | 100.000 | 100.000 | 100.000 |

alumina in the glass does not seem to be fatal for the development of a bond between glass and bone.

## 6. Conclusions

Equations describing some physical properties and biomedical behaviour of phosphate opal glasses have been developed. The models provide a tool for the development of glasses with optimal biomedical properties as well as physical properties important for successful coating of metal implants or for manufacture of composites.

ESCA in combination with ion-milling proved to be a promising tool in the study of potentially bioactive glasses. Aluminium seems to retard the transformation of osteoid into matured bone. The present investigation, however, suggests that the use of small amounts of alumina may be tolerated.

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