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Controlled release of cobalt ions from polyphosphate glasses

Wolfram Hartramph [a], Kristin Griebenow [a], Yuki Oi [b,a], Thilo Grammes [a], Nuttawan Sawangboon [a], Efstratios I. Kamitsos [c], Toshihiro Kasuga [b], Delia S. Brauer [a,*]

[a] *Otto Schott Institute of Materials Research, Friedrich Schiller University, Lessingstr. 12 (AWZ), 07743 Jena, Germany*
[b] *Division of Advanced Ceramics, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya, Aichi 466-8555, Japan*
[c] *Theoretical and Physical Chemistry Institute, National Hellenic Research Foundation, 48 Vasileos Konstantinou Avenue, 11635 Athens, Greece*

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ABSTRACT

Owing to their tuneable solubility, phosphate glasses are of interest for the controlled release of therapeutic ions. Here, we investigate the release of cobalt ions, which may stimulate blood vessel formation. Substituting cobalt for calcium in soda lime polyphosphate glasses resulted in minor structural changes as shown by IR spectroscopy and molar volume calculation. Cobalt release during immersion increased linearly with substitution, confirming that released amounts can be tuned easily via glass composition.

1. Introduction

As people live longer and want to remain physically active well past their retirement age, the need for new biomaterials keeps growing. Inorganic glasses, owing to their amorphous structure, not only show tuneable solubility. They can also accommodate a wide range of therapeutic ions, releasing them into the body when in contact with body fluids [1]. Sodium-calcium phosphate glasses dissolve in aqueous media [2], and their solubility can easily be tailored *via* their chemical composition [3,4]. Unlike silicate bioactive glasses, e.g. Bioglass 45S5 [5], they dissolve congruently without any preferential leaching of certain ions [6]; making them of interest as controlled release devices [7,8].

Cobalt-releasing bioactive glasses have been shown to mimic a hypoxic, i.e. low oxygen pressure, environment *in vitro* [9,10], known to activate various processes, among them angiogenesis, i.e. blood vessel formation [11]. The controlled release of hypoxia-mimicking Co^{2+} ions from non-apatite forming glass systems such as phosphate glasses is therefore of interest for various *in vitro* or *in vivo* soft tissue applications, e.g. wound healing, where mineralisation is not a requirement. This study investigates how Co^{2+} for Ca^{2+} substitution affects the glasses' dissolution behaviour.

2. Experimental procedure

Polyphosphate glasses ($45P_2O_5$–$25Na_2O$–(30-x)CaO–xCoO; x = 0–10 mol%) were prepared by melt-quenching as described previously [12]. To avoid reactions with atmospheric humidity, all samples were stored in a desiccator.

Glass density was measured on monoliths using helium pycnometry (AccuPyc1330, Micromeritics). Infrared spectra in the medium- and far-infrared range were recorded using 1 mm thick polished glass pieces on a vacuum Fourier transformation IR spectrometer in specular reflectance mode (Vertex80v, Bruker). Absorption coefficient spectra were calculated from the merged reflectance spectra by performing the Kramers-Kronig transformation as described previously [13]. These calculations yielded absolute values for the absorption coefficient spectra.

0.025 M tris(hydroxymethyl)aminomethane-HCl buffer solution was prepared as described previously [6]. Tris-HCl was chosen as it is a common buffer used in biomedical research and free of any of the ions present in the glass, unlike e.g. simulated body fluid. The powders for dissolution tests (size 125–250 µm) were cleaned several times using 10 mL of isopropanol in an ultra-sonic bath for 15 min each, rinsed with acetone and dried in an oven at 70 °C overnight.

For dissolution experiments, PE containers were filled with 50 mL of 0.025 M Tris-HCl buffer solution and 75 mg of glass and stored in a shaking incubator at 37 °C for six hours, one, three, seven or 14 days. Afterwards, the solutions were filtered. The filtrate was prepared for inductively coupled plasma optical emission spectroscopy analysis by mixing 30 mL of filtrate with 0.5 mL concentrated nitric acid (Merck, 65 %).

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* Corresponding author.
E-mail address: delia.brauer@uni-jena.de (D.S. Brauer).

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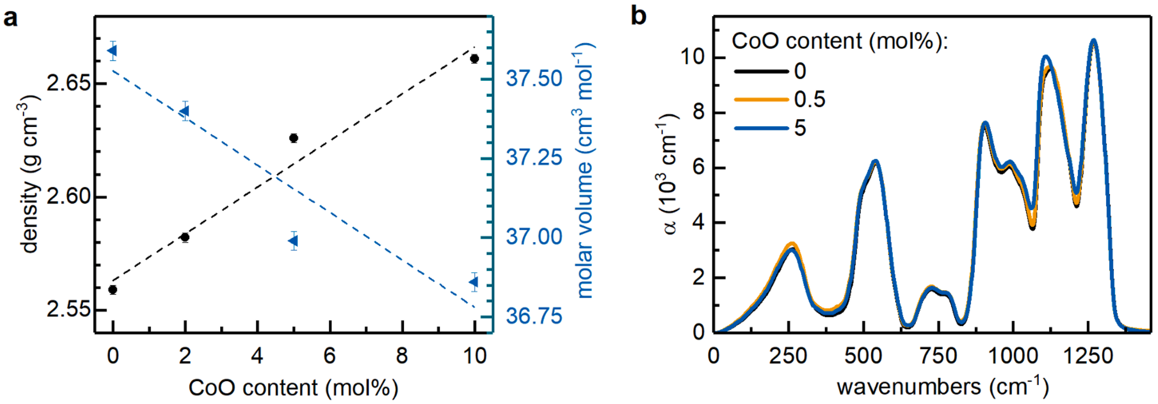

Fig. 1. (a) Density and molar volume; lines are linear regression ($R^2 = 0.972$ and 0.895). (b) IR absorption coefficient spectra.

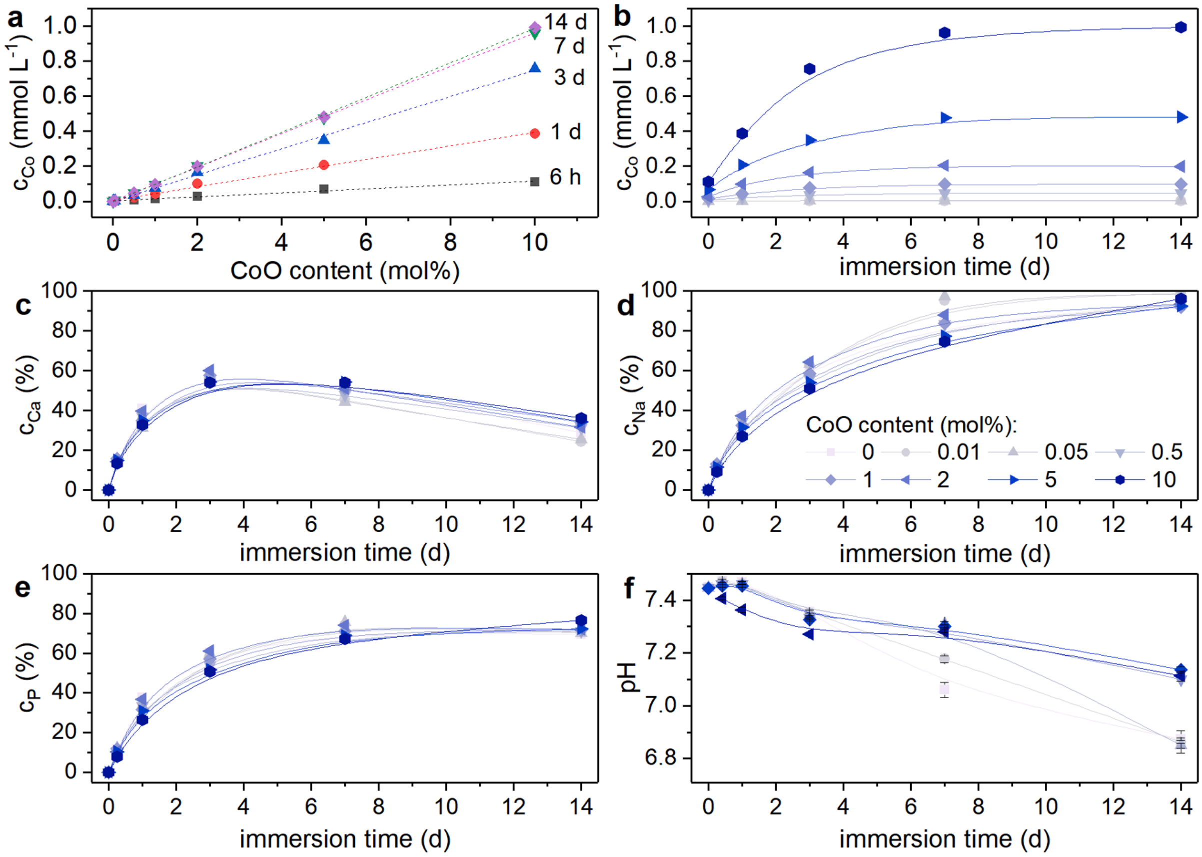

Fig. 2. Absolute cobalt concentration in solution as a function of (a) substitution and (b) immersion time. Relative concentrations of (c) calcium, (d) sodium and (e) phosphate (normalised to the amount of the respective ion present in the glass) and (f) pH as a function of immersion time. Lines are (a) linear regression (6 h: $R^2 = 0.988$; 1d-14d: $R^2 > 0.996$) and (b-f) visual guides.

3. Results & discussion

Glasses were X-ray amorphous with analysed compositions close to nominal ones, as shown previously [12]. When substituting Co^{2+} for Ca^{2+}, owing to the larger atomic weight of Co^{2+} compared to Ca^{2+}, glass density increased linearly (Fig. 1a). The smaller ionic radius of Co^{2+} ions (0.6 and 0.7 Å for 4- and 6-fold coordination [14]) compared to Ca^{2+} ions (1 Å for 6-fold coordination [14]) caused a small reduction in glass molar volume, calculated from the density (Fig. 1a) [15].

In absorption coefficient (α) spectra of selected glasses (Fig. 1b), the far-infrared (FIR) region <400 cm^{-1} shows an asymmetric band arising from the combined vibrations of modifier cations within their oxygen polyhedra: Na^+ ~200 cm^{-1}, Ca^{2+} ~250 cm^{-1} and Co^{2+} between 190 and 280 cm^{-1} depending on its coordination [16–19]. As Co^{2+} has a larger ionic field strength than Ca^{2+} (Co^{2+}(IV) 3.1 or Co^{2+}(VI) 3.6 Å^{-2} *vs* Ca^{2+}(VIII) 1.6 Å^{-2}), one would expect more pronounced changes in the FIR region of the spectra. However, either differences in field strength or substitutions were too small to cause significant changes to the envelope of the three overlapping bands.

The remaining IR bands are related to phosphate vibrations, e.g. δ(P–O) between 400 and 600 cm^{-1} and ν_s(P–O–P) between 700 and 800 cm^{-1}. The broad feature between 900 and 1000 cm^{-1} is assigned to ν_{as}(P–O–P) in chain and ring formation, respectively [16,18,19]. Based on nominal glass compositions, theoretical phosphate chain length [20] is 9 groups, which we recently showed to agree with results from ^{31}P MAS NMR measurements for the Co^{2+}-free glass [21]. The highest-intensity IR bands at ~ 1125 and ~ 1270 cm^{-1} are related to $\nu_{as}(Q^1)$ and $\nu_{as}(Q^2)$ [16,18,19]. The former feature shifts to lower wavenumbers and gains relative intensity when $x = 5$, indicating that Co^{2+} promotes Q^1 instead of Q^2, but the overall effect of Co^{2+} substitution on glass structure here was marginal.

Cobalt concentrations in solution increased linearly with increasing cobalt content in the glass (Fig. 2a), showing that the amount released can easily be tailored via glass composition. Over time, cobalt concentrations increased until reaching a plateau (Fig. 2b).

Calcium concentrations (Fig. 2c) initially increased rapidly, reaching a maximum at three days and then decreased owing to precipitation of, likely, calcium phosphates of probably poor crystallinity [6]. Sodium and phosphate concentrations (Fig. 2d,e) showed no decrease, suggesting that calcium (not phosphate) ions were the limiting factor for precipitation. For up to three days, dissolution was congruent, shown by comparable percentages of calcium, sodium and phosphate in solution (Fig. 2c-e).

Time-dependent solution pH changes (Fig. 2f) show that glass dissolution caused a pH decrease from ~7.4 to ~7.2–6.9, originating from P-O-P hydrolysis during formation of dissolution products like trimetaphosphate or orthophosphate, as shown for cobalt-free glasses [6,21].

4. Conclusions

Phosphate glass solubility in aqueous solutions can be tailored *via* glass composition. We show that Co^{2+}, which can enhance blood vessel formation (angiogenesis) *in vitro* and *in vivo*, can easily be incorporated into and released from Na-Ca phosphate glasses, its concentrations in solution increasing linearly with substitution. The effect on glass structure at the present substitution levels were minor. Taken together, phosphate glasses are a promising means to deliver Co^{2+} for enhancing blood vessel formation.

CRediT authorship contribution statement

Wolfram Hartramph: Writing – review & editing, Investigation. **Kristin Griebenow:** Writing – review & editing, Writing – original draft. **Yuki Oi:** Investigation. **Thilo Grammes:** Writing – review & editing, Investigation. **Nuttawan Sawangboon:** Writing – review & editing, Supervision, Investigation. **Efstratios I. Kamitsos:** Writing – review & editing, Supervision, Investigation. **Toshihiro Kasuga:** Writing – review & editing, Supervision, Funding acquisition. **Delia S. Brauer:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in the paper.

Data availability

Data will be made available on request.

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