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Original Article

The effect of fibrin sealant on bioactive glass S53P4 particles – pH impact and dissolution characteristics *in vitro*

Jussi Sarin [a, *], Leena Björkvik [b], Markus Hiltunen [c], Leena Hupa [b], Jaakko Pulkkinen [a], Pekka K. Vallittu [c, d, e]

[a] Department of Otorhinolaryngology – Head and Neck Surgery, Turku University Hospital and University of Turku, Finland
[b] Process Chemistry Centre, Laboratory of Inorganic Chemistry, Åbo Akademi University, Finland
[c] BioCity, Turku Biomaterials Research Program, Turku Clinical Biomaterials Centre – TCBC, Finland
[d] Department of Biomaterials Science, Institute of Dentistry, University of Turku, Turku, Finland
[e] City of Turku Welfare Division, Oral Health Care, Turku, Finland

A B S T R A C T

Fibrin glue, a two-component tissue adhesive, has a range of clinical indications. Bioactive glass (BG) S53P4 has been approved for clinical use in several craniomaxillofacial and orthopedic applications. Although sometimes used simultaneously, there is no data available regarding the possible interaction of these two biocompatible substances. In this *in vitro* study, using a BG particle concentration of 4 mg/ml, a 0.4 unit pH increment ($p < 0.001$) was observed in simulated body fluid (SBF) after a 7-day incubation period. The addition of fibrin glue (0.13 g, SD 0.04; or 3.7 mg/ml) on top of the BG particles raised further the pH by 0.5 units ($p < 0.001$). The difference between these groups was statistically significant ($p = 0.008$). With a BG concentration of 25 mg/ml and a fibrin glue concentration of 18 mg/ml during a 14-day incubation period, a pH increment of 0.6 units and SBF ion concentration change of Ca, K, Mg, Na, P and Si ions was seen. Moreover, a penetration depth between 4 and 6 mm was observed when fibrin glue was applied on top of a bed of BG particles. Conclusions: Fibrin glue is not likely to have a distracting effect on BG-induced pH increase of the SBF although it might delay early BG surface reactions based on ion concentration measurements. Fibrin glue penetrated to the interparticle space to some extent, binding the particles together for easy clinical use of BG.
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1. Introduction

Fibrin sealant or fibrin glue, is a two-component tissue adhesive consisting of fibrinogen and thrombin. It has a variety of clinical indications including hemostasis, colonic sealing and skin graft attachment [1]. Additional, clinical and experimental uses are being continuously developed, and the current literature on fibrin sealant exceeds 4900 indexed articles.

Various types of bioactive glass (BG) and bioactive glass ceramics have been in clinical use since the 1980's [2,3]. BG S53P4 has been approved for clinical use in Europe (European conformity CE-mark) and in USA (US Food and Drug administration approval, 510k clearance) for several craniomaxillofacial and orthopedic

applications. As a bone cavity filling material, bioactive glass is biocompatible [4], induces new bone formation [5] and has significant antibacterial effects [6–9]. Antibacterial properties are related to the pH increase near the BG particles as well as increased alkali metal and alkali earth metal ion concentration, released from the BG particles [8].

When the treatment of a challenging chronic middle ear infection requires canal wall-down mastoidectomy [10], it is sometimes necessary to fill the bony cavity with a suitable material. When bioactive glass S53P4 particles are used as a filling material, BG particles can be used as such moistened with physiological saline solution before application, or in tandem with fibrin glue. The latter method is currently preferred by ear surgeons, head and neck surgeons in order to bind the BG particles and allow an easy clinical application of the material [11–14].

Although a favourable osteoinductive interaction between fibrin glue and one type of BG has been shown by Abiraman et al. in a mouse model [15], the data collected via *in vivo* experiments

examining whether using BG together with fibrin glue is or isn't of benefit, has been controversial [16]. Only recently, new data has been published by Zazgyva et al. to support the use of fibrin glue with BG S53P4 [17]. To our knowledge, there is no data available addressing the absorption characteristics of fibrin sealant used on top of BG particles. Also, considering that BG slowly dissolves, creating a rise in pH of the surrounding liquid environment which facilitates its antibacterial effects [18], there is a need to understand the possible impact of using fibrin glue simultaneously with BG not only on pH values but also on ion concentration of the surrounding environment. The purpose of this study was to test a hypothesis that the use of fibrin glue with BG S53P4 particles does not have a negative influence on the pH change of simulated body fluid.

2. Materials and methods

The fibrin glue (Tisseel Duo Quick, Baxter AG, Vienna, Austria) used in this study is a two-component sealant made of pooled human plasma. The active ingredients consist of human fibrinogen with fibrinolysis-delaying synthetic aprotinin (sealer protein solution) and thrombin (thrombin solution). After the frozen, pre-filled syringes are warmed, preferably to a 33–37 °C temperature using a water bath or an incubator, the product is ready for application.

The BG S53P4 particles used in this study were produced by BonAlive Biomaterials Ltd., Turku, Finland. Particle size Varies between 0.5 and 0.8 mm and the manufacturer lists the following composition by weight for BG S53P4 particles: silicon dioxide 53%, sodium oxide 23%, calcium oxide 20%, and phosphate pentoxide 4%.

2.1. Absorption test

The absorption depth of fibrin glue in between BG particles was studied by first creating a solid polyvinyl siloxane mould (Coltène® Lab-Putty, Coltène/Whaledent AG, Altstätten, Switzerland) for BG particles with a cylindrical hole of 5.0 mm in diameter and 10 mm in depth. Exactly 0.14 g of BG granules, moistened with a physiological saline solution, were applied tightly inside each mould. Fibrin glue was then incubated in water to temperature of either 9, 21 or 37 °C and a drop of fibrin glue was applied on top of the BG-particle layer covering the whole particle bed surface. As BG particles filled the moulds completely, the thickness of each particle bed before fibrin glue application was approximately 10 mm. The BG–fibrin glue-combination was left to solidify for 24 h at 21 °C room temperature. The penetration depth of fibrin glue was assessed by removing the solid BG–fibrin glue-piece from the mould and releasing all loose particles from the piece, followed by the height measurement of the solid piece. This measurement was used to indicate the penetration depth of fibrin glue into the interparticle space of BG particles. These solid particles were then examined and photographed using light microscopy, and at this stage, the maximum BG–fibrin glue-combination thickness was measured. The penetration depth was measured for fibrin glue temperatures of 9, 21 and 37 °C, using two samples at each temperature.

2.2. pH test

To investigate the effect of fibrin glue on pH values in a liquid environment, a two-stage-protocol was used. Using a XS105 Dur −laboratory scale (Mettler Toledo, United States), 0.14 g (SD 0.00) of BG S53P4 particles were weighed for each six test tubes. Then 35 ml of simulated body fluid (SBF) was added, prepared according to the Kokubo protocol [19], with a seventh control test tube containing only SBF without BG. Using a Grant OLS200 shaking incubator (Grant Instruments, United Kingdom) test tubes were kept at 37 °C

with a 100 rpm shaking frequency. For each test tube, SBF pH values were measured at 21 °C room temperature after 1, 2, 3, 4 and 7 days, with a PHM220 Lab pH Meter (Radiometer, Copenhagen, Denmark). This protocol represented a control series, where only BG was tested in SBF without fibrin glue.

In a second series, six samples of BG S53P4 particles, weighing 0.14 g (SD 0.00) per sample as well, in tandem with 0.13 g (SD 0.04) of fibrin glue, were tested as in the previous description. A feature of fibrin glue is its rapid coagulation on the tip of the application cannula, and consequently the exact dosing and direct weighing presented a challenge. The amount of used fibrin glue was determined by weighing the two-syringe system before and after application and thus calculating the weight difference. The temperature of the SBF test tubes was also maintained at 37 °C and pH values were measured accordingly. In addition, as a control, two samples of fibrin glue alone without BG were incubated in the same manner to see whether the glue by itself had any effect on SBF pH.

2.3. Ion dissolution test

Dissolution characteristics of BG–fibrin glue-combination were determined for 22 BG–fibrin glue-samples. Using a similar protocol as described above, a cylindrical mould was created for each sample, 8 mm in diameter and 6 mm in height, and 0.25 g of BG S53P4 particles (SD 0.00) were weighed into each mould. An average of 0.18 g of fibrin glue (SD 0.04), warmed to 37 °C temperature was applied on top of each sample and these BG–fibrin glue-mixtures were left to solidify under a 0.125 mm thick Mylar® polyester film for 18 h at 21 °C room temperature. Each sample was then immersed in 10 ml of SBF and kept in shaking incubator for up to 14 days in the same manner previously described.

After incubation, concentration of calcium, potassium, magnesium, sodium, phosphorus and silicon ions in the solution were measured for samples immersed for 2, 5, 9 and 14 days, using inductively coupled plasma optical emission spectrometry (ICP-OES, PerkinElmer Optima 5300 DV, United States). Weights of the BG–fibrin glue-combinations were measured by collecting the solid sample and any detached BG particles from SBF for this purpose. In addition, pH values (37 °C) were measured at 0, 1, 2, 4, 5, 6, 7, 8, 12 and 14 days.

2.4. Statistical analysis

Statistical analysis was performed using SPSS Statistics software (IBM Corporation, New York, United States). The comparison of the daily SBF pH change within and between the two groups (BG only versus BG and fibrin glue) in the 7-day-incubation experiment was performed with repeated measures analysis of variance (rm ANOVA). The statistical significance was set at the $p < 0.05$ level.

3. Results

The measured penetration depths of fibrin glue within BG particles were 4.2 and 6.4 mm for 9 °C fibrin glue; 3.2 and 5.6 mm for 21 °C fibrin glue and 3.72 and 4.05 mm for 37 °C fibrin glue, respectively (Fig. 1).

When only fibrin glue was kept in SBF, no change in pH was observed as pH values stayed between 7.48 and 7.49 for both samples at 1, 2, 3, 5 and 7 days. In contrast, when immersing only BG S53P4 particles in SBF, the pH rose continuously from the initial average value of 7.6–8.0 (SD 0.1), measured after seven days of incubation (Table 1). The pH change was statistically significant ($p < 0.001$).

When incubating BG S53P4 particles together with fibrin glue, the average pH of the solution increased after seven days from 7.5
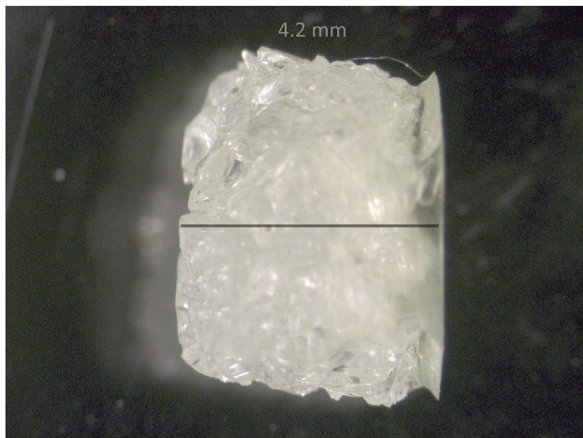
Fig. 1. Light microscopy image of a BG granule–fibrin glue-compound, with a measured maximum fibrin glue (incubated at 9 °C) absorption depth.

to 8.0 (SD 0.0; Table 2). As in the previous group, the pH change within this group was statistically significant (p < 0.001). When comparing the pH change pattern between the two test groups on a daily basis, a statistically significant difference was found (group × time interaction effect, p = 0.008), although the final increment in pH values was of the same order, being 0.4 in the BG-protocol and 0.5 in the BG–fibrin glue-protocol.

As the BG–fibrin glue-combos were immersed, a rapid initial weight reduction took place during the first two days, after which the weight was stable (Fig. 2). At the start of the experiment, the pH of SBF was in the vicinity of 7.4. This pH value was slightly lower than the pH of the solutions used for the 7-day test protocols thus

reflecting typical differences measured for various SBF batches. Also for these samples, the average pH value rose to around 8.0 (Fig. 2).

Ion concentration changes in SBF during the 14-day incubation period of the BG–fibrin glue-combinations are shown in Fig. 3 and Table 3. Calcium ion concentration increased from the original value of 68 mg l^{-1} reaching a near maximum value of 150 mg l^{-1} over a two-day-period, and started to decrease after 5 days. Silicon ion concentration increased up to 9 days, while phosphorus ion concentration decreased over time. In addition, the concentration of other inorganic ions in the solution, K, Mg and Na, stayed at a relatively constant level.

4. Discussion

Results from previous experimental work in the field of tissue engineering seem promising, when the potential benefits of using two bioactive components, fibrin glue and BG together, are considered. The endeavour to produce artificial organs has led the research, among other things, towards suitable polymer scaffolds to be used as their base structure. As part of such a scaffold, the use of a fibrinogen layer seems suitable for generating smooth muscle cell growth and proliferation in an experimental blood vessel model by Wang et al. [20]. Gugutkov et al. [21] found a biologically active fibrinogen network to be a useful part of a 3D polymer scaffold, as they observed growth and adhesion patterns of human umbilical endothelial cells *in vitro*. A fibrinogen solution has been used successfully by Zhao and Wang as a part of a porous poly(D,L-lactic-co-glycolic acid) (PLGA) scaffold, manufactured using a rapid prototyping technique, in which cultured adipose-derived stem cells were able to grow well in the attached fibrin layer [22].

Table 1
Bioactive glass S53P4 in simulated body fluid − 7 days incubation with pH monitoring.

No	BG (g)	After 0 d SBF storage		After 1 d SBF storage		After 2 d SBF storage		After 3 d SBF storage		After 4 d SBF storage		After 7 d SBF storage	
		pH	t (°C)	pH	t (°C)	pH	t (°C)	pH	t (°C)	pH	t (°C)	pH	t (°C)
Ref	0	7.57	20.7	7.56	21.3	7.56	21.4	7.57	21.3	7.60	21.2	7.61	20.7
1	0.14			7.67	21.2	7.86	21.5	7.95	21	7.97	21.0	8.07	20.7
2	0.14			7.67	21.0	7.79	21.4	7.83	21	7.93	21.0	7.95	20.9
3	0.14			7.68	21.0	7.78	21.2	7.84	21.1	7.93	21.0	7.95	21.0
4	0.14			7.76	20.7	7.83	20.6	7.90	21.4	7.95	21.0	8.04	21.0
5	0.14			7.66	21.0	7.76	20.6	7.85	21.5	7.88	21.0	7.94	20.9
6	0.14			7.67	20.8	7.78	20.4	7.87	21.6	7.91	20.9	7.96	21.0
Av	0.14	7.6	21	7.7	21	7.8	21	7.9	21	7.9	21	8.0	21
SD	0.00			0.0	0.2	0.0	0.5	0.0	0.3	0.0	0.0	0.1	0.1
RSD	0.6			0.5	0.8	0.5	2.3	0.6	1.2	0.4	0.2	0.7	0.6

Table 2
Bioactive glass S53P4 and fibrin glue in simulated body fluid − 7 days incubation with pH monitoring.

| No	Fibrin glue (g)	BG (g)	After 0 d SBF storage		After 1 d SBF storage		After 2 d SBF storage		After 3 d SBF storage		After 4 d SBF storage		After 7 d SBF storage	
			pH	t (°C)	pH	t (°C)	pH	t (°C)	pH	t (°C)	pH	t (°C)	pH	t (°C)
Ref	0	0	7.48	20.9	7.49	21.5	7.47	21.5	7.48	21.7	7.49	21.9	7.54	20.9
1	0.1194	0.141			7.76	21.7	7.81	21.6	7.89	20.9	7.91	22.0	7.96	21.2
2	0.1026	0.141			7.74	21.7	7.78	21.7	7.88	21.4	7.89	22.0	7.94	21.2
3	0.1133	0.141			7.67	21.8	7.77	21.8	7.88	21.6	7.91	22.1	8.02	21.2
4	0.1113	0.14			7.75	21.7	7.81	21.8	7.88	21.3	7.89	22.1	7.99	21.1
5	0.1552	0.141			7.75	21.7	7.86	21.5	7.92	21.6	7.91	22.0	8.00	21.4
6	0.2039	0.141			7.77	21.8	7.83	21.6	7.88	21.8	7.90	22.1	8.00	21.5
Av	0.13	0.14	7.5	21	7.7	22	7.8	22	7.9	21	7.9	22	8.0	21
SD	0.04	0.00			0.0	0.1	0.0	0.1	0.0	0.3	0.0	0.1	0.0	0.2
RSD	28.8	0.2			0.5	0.2	0.4	0.6	0.2	1.5	0.1	0.2	0.4	0.7
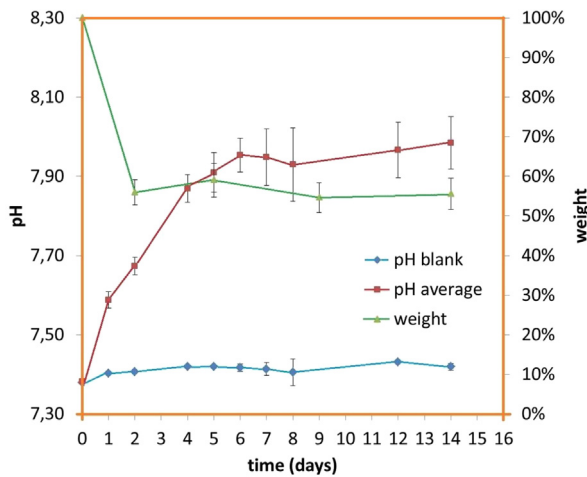
Fig. 2. Bioactive glass S53P4 and fibrin glue in simulated body fluid − 14 days incubation with pH monitoring and BG−fibrin glue-particle weight measurement.

Table 3
Bioactive glass S53P4 and fibrin glue in simulated body fluid − 14 days incubation with concentration of ions (mg l^{-1}).

Days	Ca	K	Mg	Na	P	Si
0	68	211	35	3239	20	<LOQ
2	150 ± 11	205 ± 10	36 ± 2	3456 ± 142	18 ± 9	39 ± 5
5	151 ± 42	180 ± 16	31 ± 2	3234 ± 202	2 ± 1	56 ± 5
9	86 ± 23	195 ± 6	31 ± 2	3392 ± 128	2 ± 1	67 ± 4
14	90 ± 28	191 ± 10	30 ± 1	3376 ± 146	4 ± 2	58 ± 4

As well as providing a suitable medium for cell growth, fibrin coating also increases the load bearing capability of a three-dimensional scaffold, as demonstrated by Gamboa-Martínez et al. [23]. It seems, generally speaking, that the presence of a fibrinogen layer as a part of a biocompatible polymer might be very beneficial as it not only directs the growth of adjacent cells but also improves mechanical strength.

When BG S53P4 particles are used clinically as a bone cavity filling material, the conventional method of choice is to moisten the particles with a physiological saline solution before application. Adhering BG particles partly in fibrin glue, on the other hand, results in a solid-like mixture that some surgeons find easier to control at the end of the surgery, when the BG-filled bone cavity is covered with an appropriate soft tissue.

When using BG S53P4 particles as an obliteration material for mastoid cavities, the required total volume of the particles can be up to 20 cm^3 [12]. In this study, the fibrin glue penetrated to a depth of a few Millimeters (4−6 mm) in the bed of the bioactive glass particles. Thus, if fibrin glue is applied on top of the particles after filling the cavity, the glue is likely to adhere to the surface layer only while the more distal particles are unaffected. From another perspective, the observation of uneven adherence of fibrin hydrogel was addressed by Zhao and Wang [22], who studied PLGA scaffolds with 1.35−1.55 mm pore size, rigid in comparison to BG granules. Consequently, when a stabilizing effect for BG particles via fibrin glue is pursued in bone cavity filling, it seems important to start

applying the glue with the tip of the application cannula deep inside the particle layer to ensure as thorough permeability as possible. Alternatively, applying BG granules and fibrin glue in a layer-by-layer fashion might be considered.

When BG S53P4 is used as a bone cavity filling material, a feature of particular importance is its extensive antibacterial effect, as demonstrated by Munukka et al. [8] and Leppäranta et al. [9] in vitro. In fact, even when an extremely challenging bacterial environment is encountered in vivo, such as in the surgical treatment of osteomyelitis, BG S53P4 seems to function very well in the operated area [24,25]. In addition, although bacterial biofilms are especially resistant to any therapeutic intervention, BG S53P4 was found to suppress the formation of S. aureus biofilm on titanium discs in a study done by Coraça-Huber et al. [26].

Since the rise in pH is thought to be an essential contributing factor when it comes to the antibacterial effect of BGs [18], it is important to know whether the use of fibrin glue in tandem with BG has any effect on the pH of the surrounding media. The release of sodium, calcium, phosphate and silicate ions from the BG surface, the subsequent elevation of pH and the osmotic pressure, and the following suppression of bacterial growth depends on the size of the particles in contact with the surrounding liquid environment [27,28]. The smaller the particles, the faster the ion release rate and the higher the antibacterial effect. Hence, any measure, such as adding fibrin glue into the bed of glass particles, reduces the available responsive BG surface area and might thus be counter-productive. Yet from the clinical standpoint discussed above, it might be beneficial to use fibrin glue together with BG particles, if the glue does not change the anticipated rise of the pH of the surrounding solution and thus possibly reduce the antibacterial effect of the BG particles.

In this study, BG S53P4 particles at 4 mg/ml were used without added fibrin glue. This increased the pH of SBF by 0.4 units during a 7-day incubation period. When these results are compared to those of other studies, it seems evident that an increase in BG concentration results in higher pH in SBF. By comparison, Massera and Hupa used lower BG S53P4 particle concentration of 1.5 mg/ml
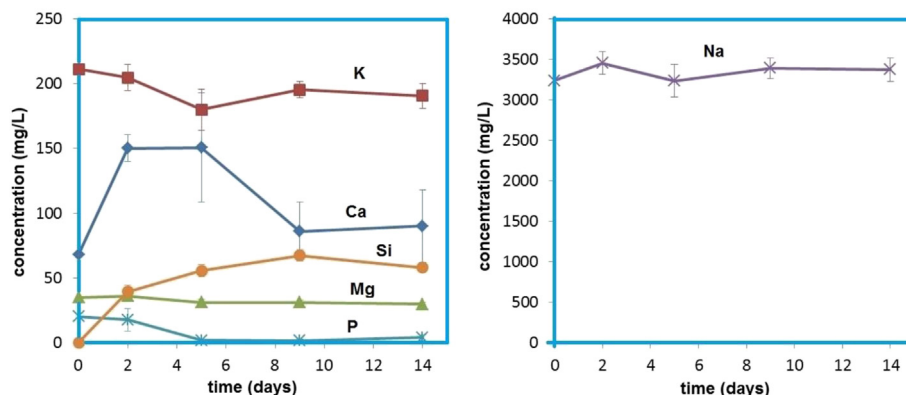

Fig. 3. Bioactive glass S53P4 and fibrin glue in simulated body fluid − 14 days incubation with concentration of ions (mg l^{-1}).

yielding a 0.15 unit pH increment to a final pH of 7.65 after a 7-day incubation period [28]. When immersing plates of BG S53P4 and 45S5 Bioglass® using the surface area to volume solution ratio Sa/V = 0.4 cm^{-1}, the pH of SBF after one week increased by 0.6 units and 1.2 units, respectively [29]. When immersing particles of Bioglass® 45S5 (100 mg/ml) in SBF containing also glass fiber reinforced biostable composites, the pH of the solution increased 1 ± 0.2 units from the initial value after one week of incubation in SBF [30]. Bioglass® 45S5 consists of the same oxides as BG S53P4 but the mutual contents of the oxides are different. In general, 45S5 containing a lower amount of SiO$_2$ shows a more rapid dissolution and bioactivity than S53P4 [31].

Along with BG concentration, a major contributing factor in the anticipated pH changes in SBF is the available reactive BG surface area, as mentioned above. By way of decreasing BG particle size, for example, a more pronounced pH increase in SBF can be expected, as demonstrated tangibly by Zhang et al. using seven different BG particle sizes in their work [27]. Compared to small BG granules or particles, BG plates have a much smaller reactive surface area per weight unit, and therefore using BG plates, a more modest pH increase is to be expected relative to actual BG concentration in the solution [29].

Does fibrin glue suppress or retard the increase in the pH of SBF when used in tandem with BG S53P4 particles, by decreasing, for instance, the available reactive surface area? Based on the results in this study, it seems that coagulated fibrin glue particles alone don't affect the pH of SBF after seven days of incubation. When fibrin glue was used simultaneously with BG particles in the 7-day test protocol, a pH increase of 0.5 units was noticed and this slightly greater pH increment pattern in BG–fibrin glue-group, compared to several time points to that of the BG-alone-group, was statistically significant (p = 0.008). For the purposes of a dissolution test, a 14-day test protocol with BG and fibrin glue was also carried out, now with a BG concentration of 25 mg/ml, and a further 0.6 unit pH increase was noted at the end of a two week incubation period.

Based on these findings, it would seem that the use of fibrin glue with BG will not diminish the expected pH increase of SBF, but rather seems to strengthen the pH increase, thus possibly increasing the bioactivity of the product. To some extent, this finding conflicts with the results from ion dissolution tests discussed later. Whether the observed pH increment pattern difference between BG- and BG–fibrin glue-groups is also perceptible with other concentrations and incubation periods, not to mention relevant *in vivo*, remains to be answered with further studies. In addition, further research is needed in order to comprehend the influence of enzymatic activity *in vivo* with the interaction of fibrin glue and BG.

From the SBF ion concentration measurements of the 14-day test protocol with BG–fibrin glue-samples, a rapid Ca-ion concentration increase can be seen, an observation comparable to several previous studies [29,30,32], representing the early Ca-ion dissolution from the BG surface. In general, this increase is followed by a decline in SBF Ca-ion concentration, when CaP layer is growing on BG surface [29]. Massera and Hupa [28] observed with BG S53P4 particles incubated in SBF with a concentration of 1.5 mg/ml, a steep early increase in Ca-ion concentration reaching its maximum after 30 h, followed by a Ca-ion concentration decline, reaching a relatively steady state after 70 h. In contrast, in this study with BG–fibrin glue-combinations at a concentration of 25 mg/ml, a slightly slower increase with a prolonged Ca-ion concentration increment was found, which only started to decrease from peak levels after 5 days reaching eventually stable levels after 9 days. An explanation for such a difference between these two studies might be the fibrin glue's ability to adhere to BG, thus forming a diffusion barrier between the glass and the solution. Accordingly, at least some of the particle surfaces are less prone to react and release ions in the solution during the early phase of incubation. This slows down the CaP layer formation, thus prolonging the process of Ca-ion consumption from SBF in later phase. The changes in the sample mass as a function of time suggest further that already after two days of incubation most of the fibrin glue has dissolved making the surfaces of all particles available for reactions *in vitro*.

The concentration of Si in the BG–fibrin glue-protocol increased, reaching its highest levels after 9 days of incubation. The observed value is typical for a test done in static solutions and suggests that the solution is saturated with respect to Si. In the same fashion as discussed above, this took again considerably more time compared to earlier work using only BG S53P4 particles without fibrin glue [28]. P-ion levels declined, whereas other measured ion concentrations, namely K, Mg and Na, stayed on a relatively constant level. The slight decreases in the concentrations of these ions suggest that they are incorporated into the CaP layer. Previous studies have shown comparable characteristics in ion concentration behavior [28,30]. The results further suggest that the dissolution of phosphate from the glass is a rate determining step for the CaP formation. *In vivo*, the continuous flow of fluids is likely to enhance the dissolution reactions. However, considering that the fibrin glue partly occupies free spaces between the particles, the pH of the solution around some glass particles can increase locally. This may affect the dissolution rate of the glass.

Possible error sources in our study include the encountered difficulties in measuring the exact amount of applied fibrin glue, as opposed to more accurate weighing of BG particles. Likewise, when some partly dissolved BG–fibrin glue-combinations were weighed during incubation in order to determine the weight loss, the acquired weight measurements should be considered somewhat rough estimates, as BG particles became increasingly detached and thus weren't a single, clearly defined solid unit. Expectedly for each test protocol, the starting pH of SBF varied between 7.4 and 7.6, which reflects the difficulty in getting absolute constant test conditions for each test series owing to the slight differences between SBF batches. Hence, more emphasis should be put on the observed pH changes than merely on the final pH values at the end of the experiments.

5. Conclusions

Degradation of fibrin glue (Tisseel) does not seem to have any significant effect on the pH of SBF when used at low concentrations. When BG S53P4 particles were partly covered by fibrin glue, a slightly greater rise in the pH after 7 days of incubation was observed compared to the rise induced by BG particles alone. Thus, the concomitant use of fibrin glue with BG S53P4 particles is unlikely to diminish the pH-rise-dependent antibacterial effects when compared to those of BG particles alone, suggesting these two bioactive materials can well be used simultaneously. However, our results from dissolution measurements suggest delayed ion concentration changes of BG–fibrin glue-samples in SBF, compared to previous studies using BG individually, an effect probably mediated by early fibrin glue adherence on BG surface. When fibrin glue is used in tandem with BG particles, there seems to be the noticeable glue penetration with adherence, making BG particles easier to use. However, one should consider starting the application of the glue deep inside the particle layer to have a thorough permeability, if desired.

Declaration of conflicting interests

None declared.

Acknowledgements

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