An Investigation of Bioactive Glass Powders by Sol-Gel Processing

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Bioactive glass powders, with a composition of SiO_2-CaO-P_2O_5, have been successfully synthesized via a sol-gel process at considerably lower temperatures than required for conventional melting methods. Bioactive glass powders made via conventional methods form an interfacial bond with bone when they are implanted. Bonding is correlated with the formation of a surface hydroxyapatite layer. This study examined the formation of a hydroxyapatite layer in Tris-buffered solution as a function of SiO_2 content of sol-gel derived powders. A FT-IRRS technique was used to monitor the formation of the hydroxyapatite on the surface of the powders. X-ray diffraction analysis and BET were also used to characterize the chemical and physical properties of the sol-gel derived bioactive powders. It was discovered that: (a) the rate of hydroxyapatite formation decreased with increasing SiO_2 content for powders whose SiO_2 content was less than 90 mol%; (b) a hydroxyapatite film does not form for the powders whose SiO_2 content is more than 90 mol%; (c) the SiO_2 limit, beyond which the powders lost their bioactivity, was much higher for bioactive glass powders made through sol-gel process (90%) than those made by conventional melting methods (60%). These results indicate that it is possible to significantly expand the bioactive composition range through microstructural control made possible by sol-gel processing techniques.

INTRODUCTION

It is now well established that certain compositions of silicate-based glasses and glass–ceramic implants can bond to bone.[1-4] A common characteristic of these compositions is the presence of CaO, P_2O_5, Na_2O, and SiO_2 in the material. The bonding to bone has been associated with the formation of a hydroxyapatite (HA) layer on the surface of the implant.

It has also been shown that an even narrower range of glass compositions can bond to soft tissues.[5,6] A characteristic of the soft-tissue bonding compositions is a very rapid rate of HA formation. This has been previously attributed to the presence of Na_2O or other alkali cations in the glass composition which increases the solution pH at the implant–tissue interface and thereby enhances the precipitation and crystallization of HA.[7] The rate of HA formation has also been shown to be very strongly dependent on the ratio of SiO_2, glass network former, to Na_2O, network modifier, in the glass.[8] When the glass composition contains 60% SiO_2, or more, bonding to tissues is no longer observed.

Up to the present time, bioactive glasses have been produced using conventional glass technology. The glass components in the form of grains of oxides or carbonates are mixed and then melted and homogenized at high temperatures, 1250–1400°C. The molten glass is then cast into steel or graphite molds to make bulk implants. A final grind and polish is often necessary to achieve required tolerances.

For some clinical applications, such as treatment of periodontal lesions[9] or urinary incontinence[10], powders of the bioactive glasses are required. With conventional glass processing, powders are made by pouring the molten glass into a liquid medium, such as water, fracturing the frozen glass into small fragments. Subsequent grinding and size separation steps are necessary to achieve powders with specific size ranges, such as 90–710 μm, required for periodontal treatment.

There are several disadvantages of these conventional glass processing methods for bioactive glasses:

(1) It is difficult to maintain the very high purity required for optimal bioactivity. This is primarily because of the high temperatures associated with melting and homogenization, but is also related to the low silica and high alkali content of the traditional bioactive glass compositions. These compositions are very reactive chemically and tend to dissolve even platinum and can easily pick up other multiple cations as impurities. Gross and Strunz[11] have shown how sensitive tissue bonding is to M^{3+}, M^{4+}, and M^{5+} impurity cations in bioactive glass–ceramics. Greenspan and Hench[12] have shown that a small amount of Al^{3+} can completely eliminate bone bonding for bioactive glasses. Recently Kitsugi and colleagues[13] and Kokubo and coworkers[14] have shown similar compo-

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sitional sensitivities in other bioactive glass and glass–ceramic systems.

(2) Process steps of grinding, polishing, fritting, sieving, etc., all expose a bioactive powder to potential contaminants and the negative effects on bioactivity described above.

(3) There is a compositional limitation imposed on bioactive glasses and glass–ceramics made by conventional high-temperature processes. This is due to the extremely high equilibrium liquidus temperature of SiO_2, 1713°C, and the extremely high viscosity of silicate melts with high SiO_2 content.

(4) High-temperature processing in platinum crucibles and multiple handling steps also increase production costs considerably. The additional costs are not only in energy, but also in capital equipment, labor, maintenance, quality assurance, quality control, etc. Lowering the processing temperature lowers such costs considerably.

Low-temperature sol-gel processing offers an alternative to conventional glass and glass–ceramic processing with the potential advantages indicated above.

The sol-gel process has become a widely spread research field during the last decade.[15–17] Basically, the process involves the synthesis of an inorganic network by mixing the metal alkoxides in solution, followed by hydrolysis, gelation, and low-temperature firing to produce a glass. Inherent in this process is the ability to modify the network structure through controlled hydrolysis and polycondensation reactions.[18,19] Thus, structural variation can be produced without compositional changes. Because the glasses can be prepared from gels by sintering at relatively low temperatures (600–700°C), most of the disadvantages of high-temperature processing can be eliminated with much higher control over purity. Also, sol-gel processing offers potential advantages of ease of powder production, a broader range of bioactivity, and a better control of bioactivity by changing either the composition or the microstructure through processing parameters.

Thus, the objectives of this work are: (a) synthesize bioactive gel powders through sol-gel processing by controlling the hydrolysis and polycondensation reactions; (b) eliminate Na_2O from the compositions by taking advantage of low-temperature mixing of CaO-P_2O_5-SiO_2 sols; (c) determine the compositional dependence (SiO_2 content variation) of the formation of hydroxyapatite; and (d) compare the bioactivity range of melt-derived bioactive glasses with the bioactive gel powders made through sol-gel processing.

EXPERIMENTAL PROCEDURE

Table I shows the compositions of CaO-P_2O_5-SiO_2 gel powders investigated in the present studies. The samples

TABLE I. Compositions of Gel Powders (mol%)

Sample	SiO_2	P_2O_5	CaO
49S	50	4	46
54S	55	4	41
58S	60	4	36
63S	65	4	31
68S	70	4	26
72S	75	4	21
77S	80	4	16
81S	85	4	11
86S	90	4	6
90S	95	4	1

were prepared from tetraethyoxysilane (TEOS), triethyl phosphate [$OP(OEt)_3$], and calcium nitrate [$Ca(NO_3)_2 \cdot 4H_2O$]. Nitric acid was added to accelerate the hydrolysis reaction of TEOS. After mixing the components, the sol was cast into a polyethylene container and placed inside an oven at 60–180°C where the sol was gelled, aged, and dried. The dried gels were heated in a silica crucible at a temperature range of 600–700°C for several hours in a nitrogen atmosphere. The material then was ground into powders with a particle size range of 100–700 μm.

Previous studies indicate that the essential condition for a material to bond with bone is the formation of the surface hydroxyapatite layer in the body environment. Therefore, the powders made as described above were subjected to an *in vitro* solution test to evaluate the potential bioactivity of the material. In the *in vitro* test procedure, the gel powders were reacted with a Tris-buffered solution (pH = 7.2 ± 0.1) at 37°C for various times. The resultant reacted powders were then examined by Fourier Transform Infrared Reflection (FTIR) Spectroscopy on a Nicolet 20SXB Spectrometer with a diffuse reflectance stage between 1400 and 400 cm^{-1}. Also, to ensure that the gel powders did not undergo any reaction prior to the *in vitro* testing, unreacted powders were tested by FTIR.

There are several solution test procedures which can be used for powders.[20] The one which gave a more reliable and reproducible result for the bioactive gel powders is dynamic rather than static. In this study, powders were poured directly into the Tris-buffered solution in a Nalgene container and agitated in an incubator shaker for the reaction times indicated. This shaker is designed to deliver orbital motion in a controlled temperature environment. The operating temperature remained at 37°C ± 1°C and the spinning rate was 220 rpm. This dynamic test procedure allowed the reacting solution to surround and react with the powders continuously.

X-ray diffraction (XRD) was used to study the powders after heating between 600 and 700°C and after reaction in the *in vitro* test solution. The XRD range was from 5° to 85° 2θ at a rate of 3°/min, using Cu-K_α radiation at 40 KV. A Quanta Chrome Autosorb-6 was employed to measure the surface area and pore size distributions of the samples using N_2 as an absorbent.

RESULTS

Conventionally produced bioactive glasses, such as 45S5 Bioglass® (Copyrights, University of Florida, Gainesville, FL 32611) contain sodium oxide as one of the components necessary to develop bioactivity. With the glasses derived by sol-gel method, bioactivity could be achieved with sodium absent from the composition, reducing the glass from a four to a three component system.

Figure 1 shows the x-ray diffraction spectra of the gel powders after the dried gels had been heated between 600 and 700°C for 3 h. The x-ray diffraction spectrum of a standard bioactive glass (45S5 Bioglass®) is also shown in Figure 1 for comparison. The melt-derived glass shows no x-ray diffraction lines, only a very broad peak characteristic of an amorphous solid. The 49S, 54S, and 58S sol-gel derived powders show a very small amount of crystallinity. All the other sol-gel compositions show complete amorphous x-ray spectra. Figure 2 shows the FTIR spectrum of gel powders before the reaction *in vitro*. Figures 3 and 4 show the diffuse reflectance spectra of the various sol-gel derived powders at early stages of the *in vitro* reaction (1 and 8 h, respectively).

The peak at 1095 cm^{-1} in the FTIR spectra is assigned as a Si-O-Si stretching vibration.[21,22] The peak at 482 cm^{-1} is assigned as a Si-O-Si bending mode. The peaks at

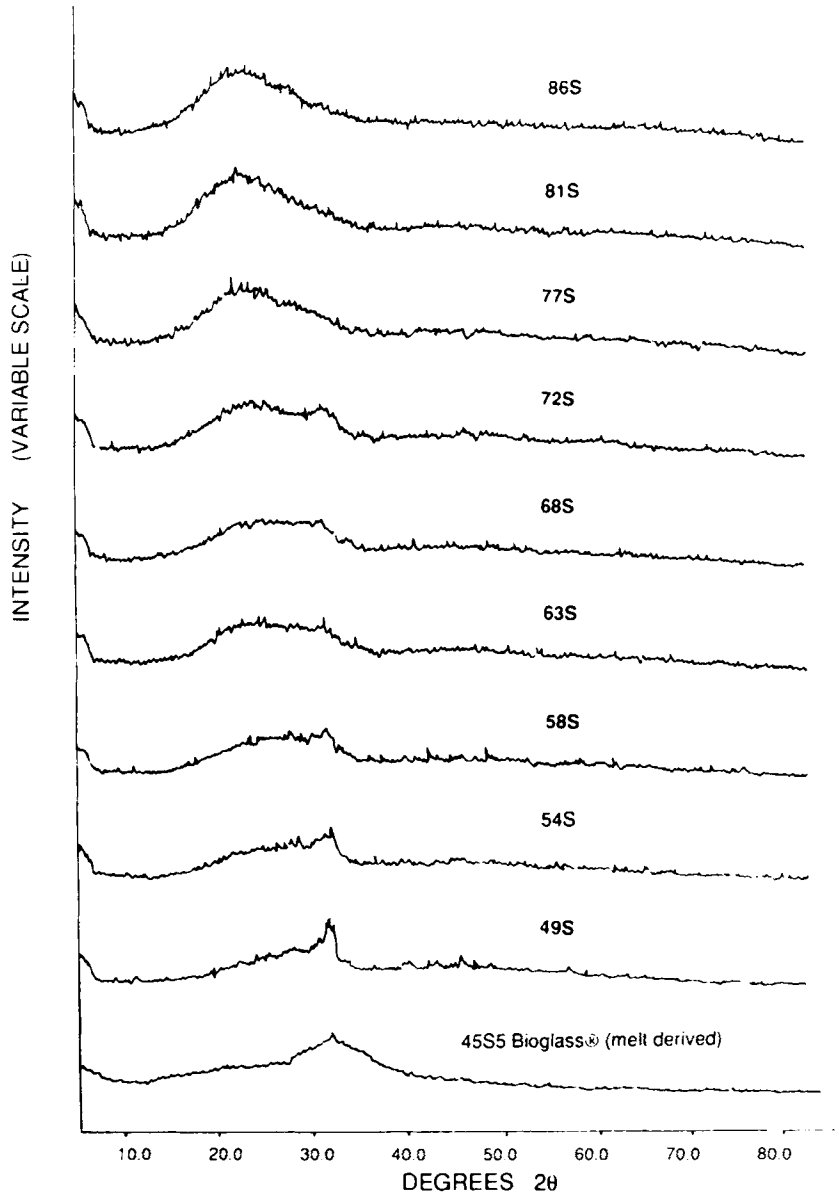

Figure 1. The comparison of x-ray diffraction data of the bioactive gel powders listed in Table I after heating to 600°C and 45S5 Bioglass® by standard melting and casting.

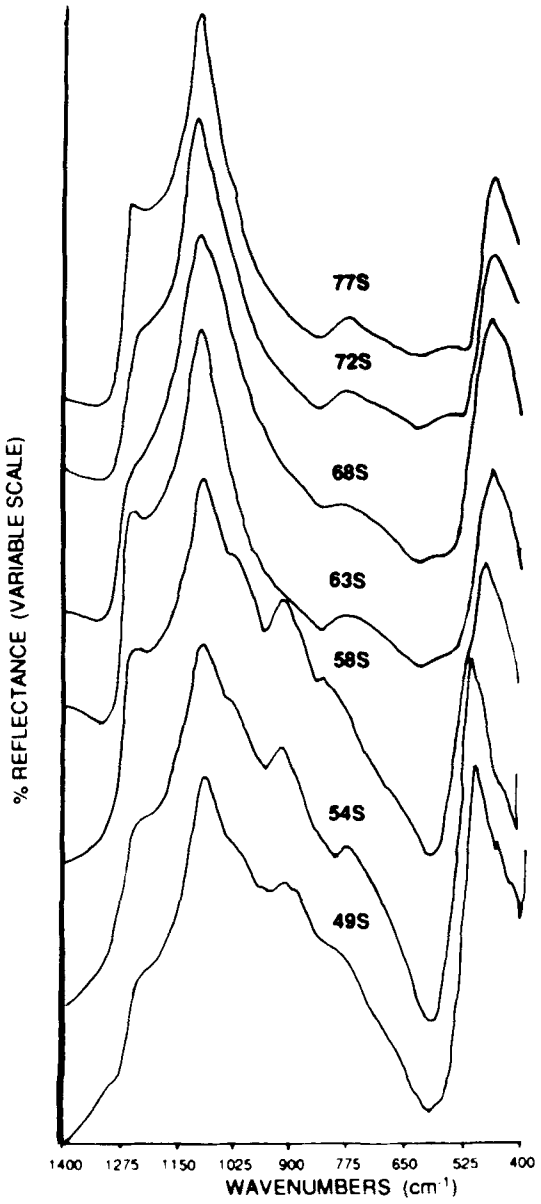

Figure 2. FT-IRRS spectra of gel powders with various composition before reaction.

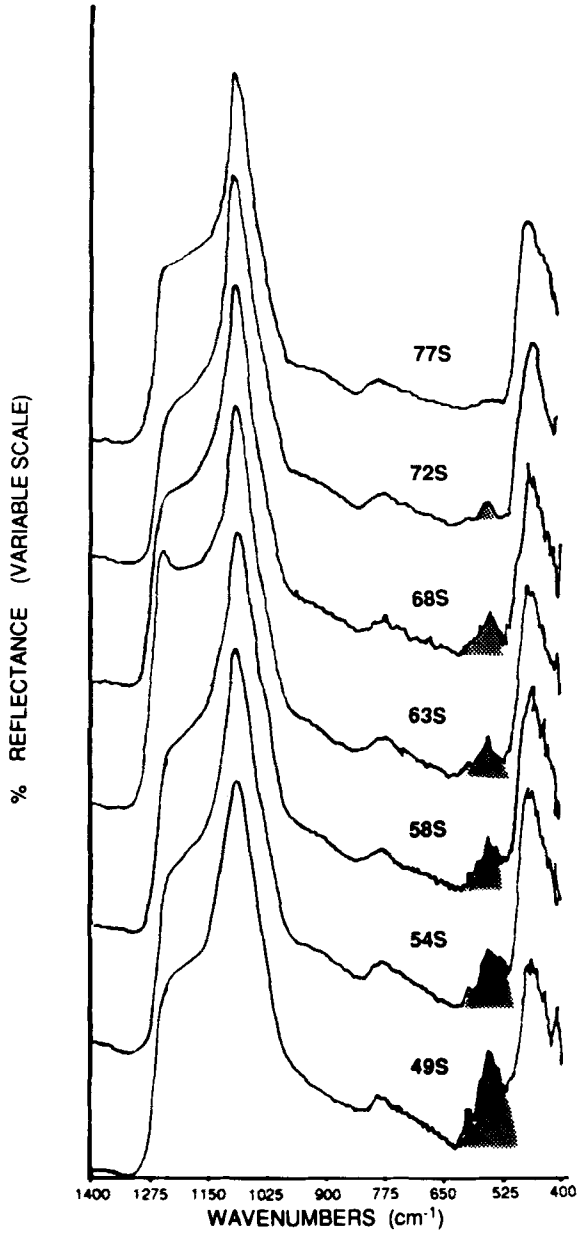

Figure 3. FT-IRRS spectra of gel powders with various composition after 1 h.

598 cm^{-1} and 566 cm^{-1} are assigned as P–O bending vibrations in $[PO_4]$ tetrahedra.[23] These two peaks are characteristic of a hydroxyapatite crystalline phase.

Figure 5 shows the time-dependent increase in intensity of the spectra of hydroxyapatite peaks for 58S composition. Figure 6 compares the FTIR spectra of two melt-derived glass powders, 45S and 60S after 20 h *in vitro* reaction and Figure 7 is the comparison of the x-ray diffraction spectra of 58S bioactive gel powders and 45S5 Bioglass® after different reaction times.

DISCUSSION

Conventional bioactive glasses contain less than 60 mol% SiO_2, have high Na_2O and CaO content and a high Ca/P ratio, e.g., 45S5 Bioglass® contains 24.5% Na_2O, 24.5% CaO (in weight %), and a Ca/P ratio of 5.2. When bioactive glass is exposed to water or body fluids several key reactions occur. There is a cation exchange of Na^{+1} and Ca^{+2} cations from the glass for protons in the solution, producing hydrolysis of the surface silica group (silanols). The cation exchange also increases the hydroxyl concentration of the solution which leads to attack of the silica glass network producing additional silanol formation and controlled interfacial dissolution. As the interfacial pH becomes more alkaline, the hydrolyzed surface silanol groups repolymerize, producing a silica-rich surface layer. Another consequence of the alkaline pH at the glass solution interface is that CaO and P_2O_5,

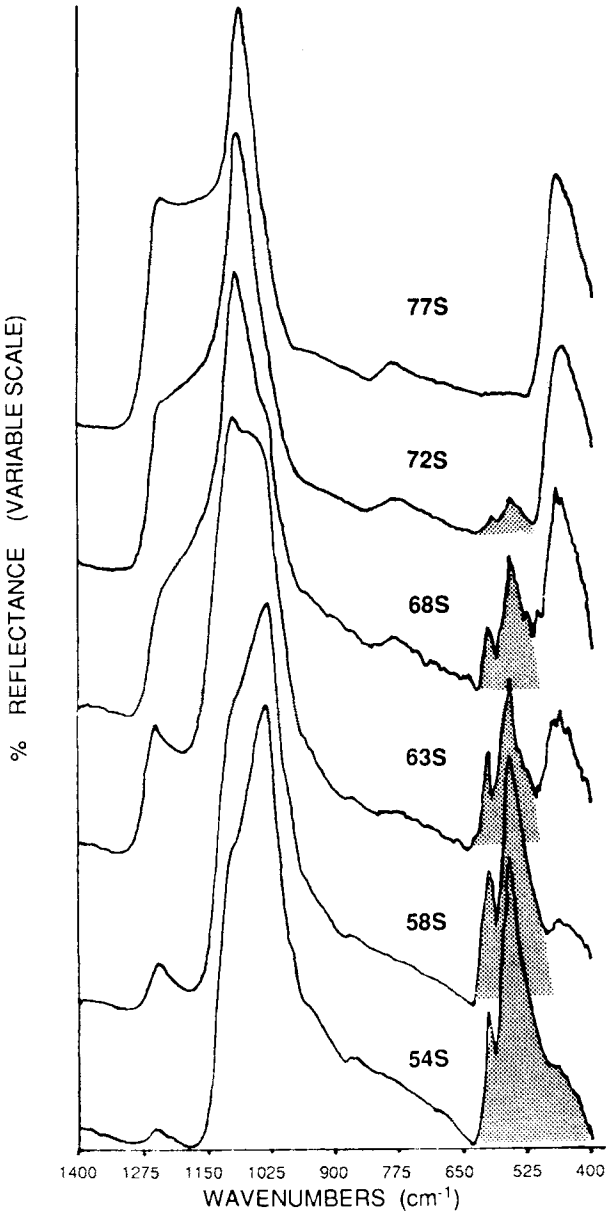

Figure 4. FT-IRRS spectra of gel powders with various composition after 8 h.

which have been released into solution during network dissolution, crystallize into a mixed hydroxy-carbonate apatite on the surface.[8] The crystallites of the HCA phase are proposed to bond to interfacial metabolites such as mucopolysaccharides and collagen. It is hypothesized that this incorporation of organic biological constituents within the growing HCA- and SiO_2-rich layers appears to be the initial step in establishing bioactivity and bonding to tissues.[8]

Studies have shown that there is a minimum rate of hydroxyapatite formation which is necessary to achieve bonding with hard tissues.[24] Both the glass composition and the microstructure exert an influence on the development and growth of the HCA phase. As the SiO_2 content of the standard melt-derived bioactive glasses approaches and exceeds 60 mol%, the rates of network dissolution and hydroxyapatite crystallization are retarded and the bioactivity is reduced and eventually eliminated. After reaction, Figure 6 shows that a pair of hydroxyapatite peaks is present for the FTIR spectrum from the 45S5 glass surface. These peaks grow as the broad Si-O-Na and Si-O-Ca peak, shown for 45S5 before reaction, disappears. The 45S5 Bioglass® (45 wt% SiO_2) is very bioactive and bonds to both hard and soft tissues. In contrast, the 60S melt-derived composition (60 wt% SiO_2) does not develop an apatite layer, even after several weeks in solution. This composition is not bioactive and does not bond to bone or soft tissues. Therefore, the maximum SiO_2 content of bioactive melt-derived glasses is 60 mol%.

The gel powders made by sol-gel process contain no Na_2O. The spectra of unreacted samples show that there are only silica and silica plus alkaline earth vibrational peaks from 1400 to 400 cm^{-1} before reaction in the solution (Fig. 2). With a reaction time of only 1 h, the peaks at 598 cm^{-1} and 566 cm^{-1} increase their intensities for most compositions, indicative of the formation of an HA phase on the surface. No hydroxyapatite crystal is found for 77S within 1 h. The intensities of the characteristic hydroxyapatite peaks decrease with increasing SiO_2 content in the one hour test (Fig. 3).

The Si-O-Si rocking vibration peak at 482 cm^{-1} is diminished in the 54S and 58S samples after 8 h reaction in the solution (Figure 4). Because of the very small penetration depth of the IR beam (<1 μm), the hydroxyapatite peaks developed on the gel–glasses (Figs. 3–5) must be due to a surface layer of HA formed on the powders. This is confirmed by XRD (Fig. 7). The 58S gel powders show strong x-ray diffraction peaks which index as hydroxyapatite after only 8 h reaction *in vitro*, whereas the melt-derived 45S5 bioactive glass requires more than 100 h to demonstrate sharp HA lines. Other instrumental techniques have confirmed this interpretation both *in vitro* and *in vivo*.[3] In Figure 8, the rate of formation of the hydroxyapatite layer is compared for different compositions of the gel–glass powders. The comparison is made by obtaining a ratio of peak intensities of FT-IRRS spectra. The intensity of each peak was measured relative to the intensity between 470 and 610 cm^{-1}. I_1 refers to the intensity of P–O bending vibration at about 566 cm^{-1} and I_2 refers to Si–O–Si bending vibration at about 482 cm^{-1}. A ratio was calculated of the apatite peak intensity divided by the silica peak intensity, I_1/I_2. The plot of I_1/I_2 as a function of time shows that HA formation is delayed with the increasing of SiO_2 content at early stages. The data of Figure 8 suggest that the compositional limit of formation of HA on the gel–glasses is approximately 72% SiO_2. However, if the exposure time is increased to 7 days, HA formation is demonstrated for the gel powder with up to 90 mol% silica (86S) (Fig. 9). It should be noted that while the silica compositional limit for HA formation is extended, the

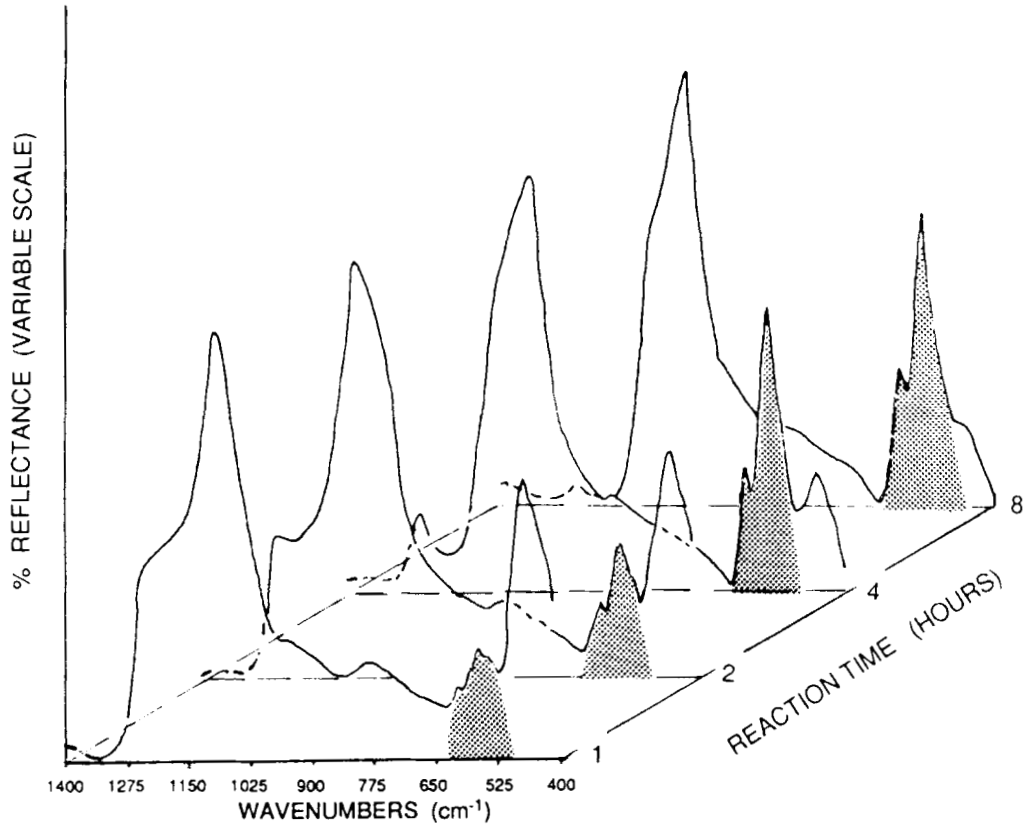

Figure 5. FT-IRRS spectra of 54S gel powders with various reaction times.

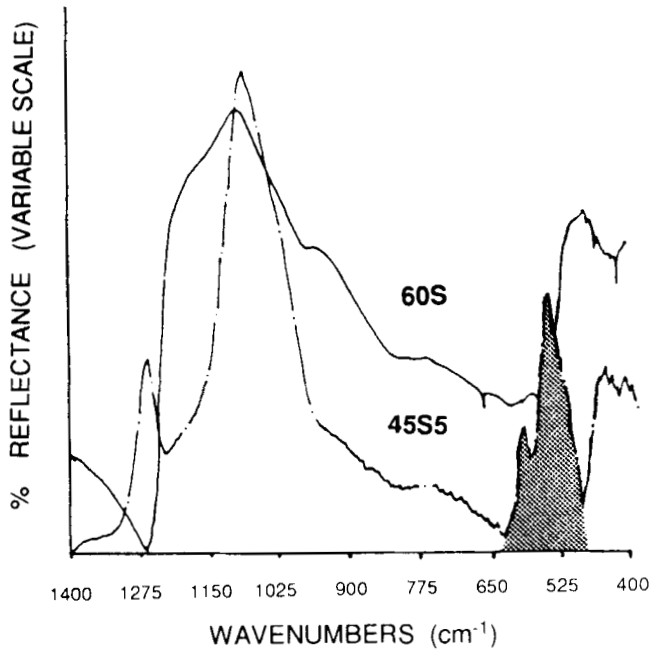

Figure 6. FT-IRRS spectra for 45S5 Bioglass® and 60S by melting method, after 20 h reaction.

kinetics of HA formation are retarded as the CaO and P_2O_5 content of the gel–glasses is varied. These results indicate that it is possible to extend the compositional boundary for bioactivity up to 90 mol% SiO_2 by making use of sol-gel processing.

A possible explanation for the extension of the compositional boundary for bioactivity is the presence of very small pores and large surface areas of the sol-gel derived powders (Table II). The surface area of all the sol-gel derived compositions range from 200 to 650 m^2/g and the total pore volume range between 0.3 and 0.6 cm^3/g as determined by Autosorb-6 analysis. These ultrastructural features may give rise to an increased density of potential nucleation sites that result in the formation of the hydroxyapatite layer on the surface of the gel-derived powders. Previous investigations[25] of melt-derived Bioglasses® show that bonding with bone *in vivo* occurs within 10 to 30 days if the surface area developed in simulated test solutions is the range of 200–500 m^2/g. In contrast, compositions of glass that do not bond to bone and

TABLE II. BET Data of Bioactive Gel Powders

	Surface Area (m^2/g)	Total Pore Volume (cm^3/g)	Average Pore Size (Å)
49S	203	0.57	57
54S	213	0.53	50
58S	289	0.49	34
63S	324	0.44	27
68S	326	0.41	25
72S	380	0.38	20
77S	431	0.32	15
81S	547	0.37	14
86S	627	0.45	14

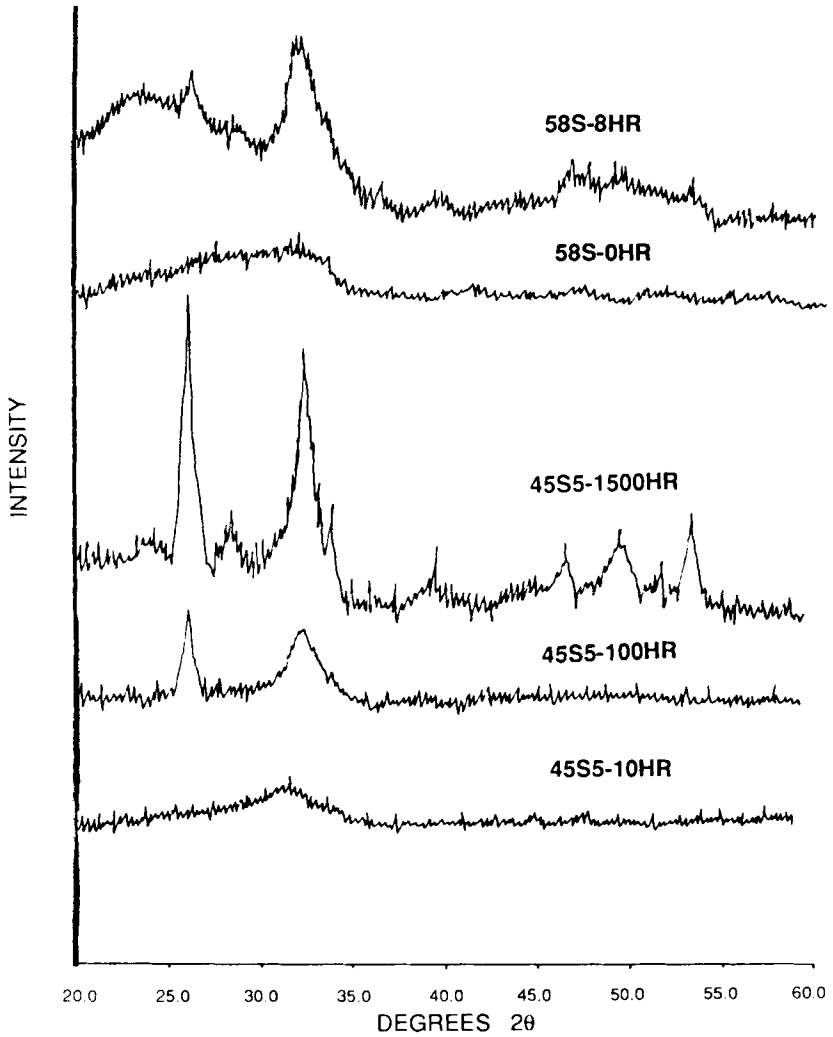

Figure 7. The comparison of x-ray diffraction data of the 58S bioactive gel powders and 45S5 Bioglass® by standard melting after different reaction times.

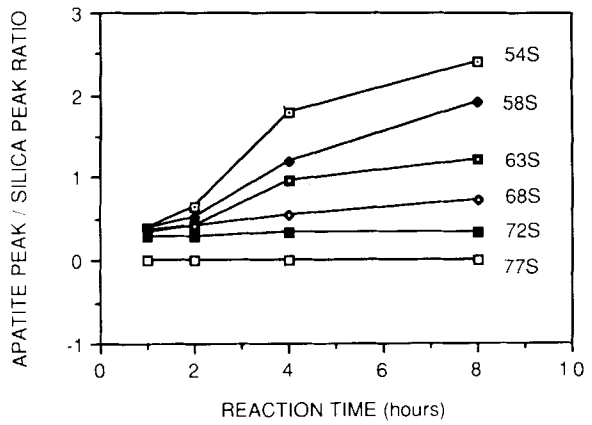

Figure 8. Rate of formation of hydroxyapatite at early stage for some bioactive gel powders.

are not bioactive develop less than 0.1 m^2/g surface area when exposed to simulated test solutions. Consequently, it is concluded the sol-gel derived $CaO-P_2O_5-SiO_2$ gel powders will be highly bioactive since their initial surface areas are high. The exposure to the Tris-buffered solution increases the surface area even more. Thus the compositional range of bioactivity has been extended significantly through sol-gel-derived gels. This extended compositional range of HA formation and presumably bioactive bonding is summarized on Figure 10.

CONCLUSION

(1) Alkali-free bioactive $CaO-P_2O_5-SiO_2$ gel powders which can form a hydroxyapatite layer when exposed to Tris-buffered solution have been synthesized using low temperature sol-gel processing.

(2) The rate of formation of hydroxyapatite, which is an indicator of bioactivity, varies with the composition of the gel powders. Gel powders, which have lower SiO_2 content and higher CaO and P_2O_5 content, exhibit higher rates of HA formation.

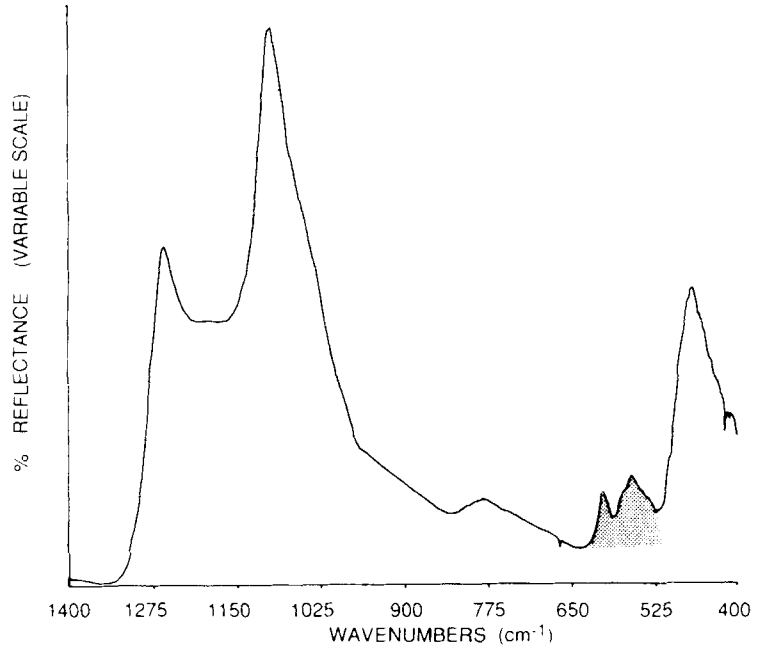

Figure 9. FT-IRRS spectrum for 86S bioactive gel powder after 7 days reaction in simulated *in vivo* solution.

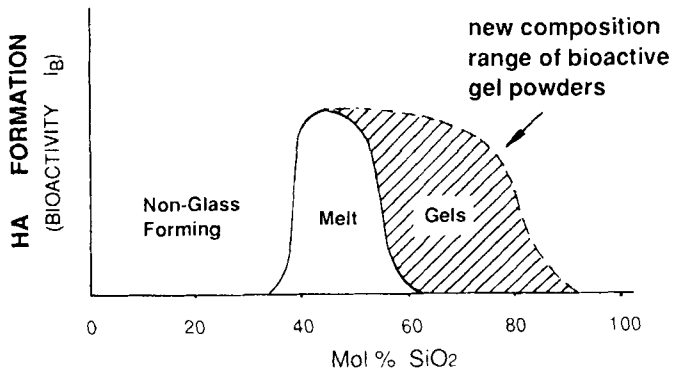

Figure 10. The difference in range of bioactivity for the bioactive gel vs. melt-derived Bioglasses®.

(3) The compositional boundary of HA formation has been significantly extended through sol-gel derived bioactive gel powders over the melt-derived Bioglass® powders. The upper limit is approximately 90 mol% SiO_2.

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REFERENCES

1. Hench, L.L.; Splinter, R.J.; Greenlee, T.K.; Allen, W.C. Bonding mechanisms at the interface of ceramic prosthetic materials. J. Biomed. Mater. Res. 2:117; 1971.
2. Hench, L.L.; Ethridige, E.C. Biomaterials—An Interfacial Approach. New York: Academic Press; 1982.
3. Hench, L.L.; Clark, A.E. Biocompatibility of Orthopedic Implants. Williams, D.F. ed., Boca Raton:CRC Press; 1982:Vol. 2, Chap. 6.
4. Hench, L.L. Fundamental Aspects of Biocompatibility. Williams, D.F. ed. Boca Raton:CRC Press; 1982; Vol. 1, Chap. 4.
5. Wilson, J.; Pigott, G.H.; Schoen, F.J.; Hench, L.L. Toxicology and biocompatibility of bioglasses®. J. Biomed. Maters. Res. 15:805; 1981.
6. Wilson, J.; Merwin, G.E.; Rodgers, L.W.; Martin, R.G.; Spilman, D. Facial bone augmentation using Bioglass in dogs. Biological and Biomechanical Performance of Biomaterials, Christel, P.; Meunier, A; Lee, A.J.C. eds. Amsterdam: Elsevier; 1963:93.
7. Clark, A.E. Solubility and biocompatibility of glass, Gainesville:Univ. Florida; 1974. Dissertation.
8. Hench, L.L. Bioactive ceramics. Bioceramics: Material Characteristics Versus In Vivo Behavior, Ducheyne, P.; Lemons, J.E. eds. New York:The New York Academy of Sciences; 1988:54.
9. Wilson, J.; Low, S.; Fetner, A.; Hench, L.L. Bioactive Materials for Periodontal Treatment—A Comparative Study in Biomaterials Clinical Applications. Pizzoferrato, A.; Marchetti, P.G.; Ravaglioli, A.; Lee, A.J.C. eds. Amsterdam:Elsevier. 1987:223.
10. Ramer, M. Bioglass®—hylan suspension for treatment of urinary incontinence. Gainesville: Univ. Florida; 1990. MS Thesis.
11. Gross, U.M.; Strunz, V. The anchoring of glass ceramics of different solubility in the femur of the rat. J. Biomed. Mater. Res. 14:607; 1980.
12. Greenspan, D; Hench, L.L. Chemical & mechanical behavior of Bioglass coated alumina. J. Biomed. Mater. Res. 10:503; 1976.
13. Kitsugi, T.; Yamamuro, T.; Nakamura, T.; Kotani, S.; Kokubo, T.; Effects of varying amounts of Al_2O_3 on the bond between A-W glass ceramics and bone. Oonishi, H.; Aoki, H.; Sawai, K. eds. Bioceramics, Vol. 1. Ishiyaku Euro America Inc.; 1989.
14. Kokubo, T.; Ito, S.; Huang, Z.T.; Hayashi, T.; Sakka, S.; Kitsugi, T.; and Yamamuro, T. Ca, P-rich layer formed on high-strength bioactive glass-ceramic A-W. J. Biomed. Mater. Res. 24:331; 1990.

15. Sakka, S. Glasses and glass-ceramics from gels, J. Non-Cryst. Solids 73:651; 1985.
16. Zarcycki, J. Processing of gel glasses. Uhlman, D. R., Kreidl, N. J. eds. Glass Science and Technology. Vol. 2, 209.
17. Orgaz-Orgaz, F. Gel to glass conversion: Densification kinetics and controlling mechanisms. J. Non-Cryst. Solids 100:115; 1988.
18. Brinker, C. J.; Scherer, G.W. Sol-gel glass: I. Gelation and gel structure. J. Non-Cryst. Solids 70:301; 1985.
19. Pope, E. J. A.; Mackenzie, J. D.; Sol-gel processing of silica. II. The role of the catalyst. J. Non-Cryst. Solids 87:185; 1986.
20. Warren, L.; Clark, A. E.; Hench, L. L. Quality assurance of Bioglass powders. J. Biomed. Mater. Res. Appl. Biomater. 23(A2):201; 1989.
21. Bell, R. J.; Dean, P. Atomic vibrations in vitreous silica. in Discuss. Faraday Soc. 50:55; 1970.
22. Gaskell, P. H. Vibrational spectra of simple silicate glasses. Discuss. Faraday Soc. 50:82; 1970.
23. Fowler, B. O. Infrared studies of apatites, I. Vibrational assignments for calcium, strontium and barium hydroxyapatites utilizing isotopic substitution. Inorg. Chem. 13:194; 1974.
24. Ogino, M.; Hench, L. L. Compositional dependence of the formation of calcium phosphate films on Bioglass™. J. Biomed. Mater. Res. 14:55; 1980.
25. Walker, M. M. An investigation into the bonding mechanisms of Bioglass™. Gainesville: Univ. Florida; 1977. MS Thesis.

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