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Features of silicon– and titanium–polyethylene glycol precursors in sol–gel synthesis of new hydrogels

T. G. Khonina,*[a] A. P. Safronov,[bc] M. V. Ivanenko,[a] E. V. Shadrina[a] and O. N. Chupakhin[ac]

The formation of organic/inorganic hydrogels based on silicon and titanium polyethylene glycolates, new biocompatible water-soluble precursors in sol–gel processing, was investigated. The influence of different factors on the gelation process, such as excess of PEG, water molar content, pH of medium, electrolyte additives, was investigated in comparison with silicon– and titanium–glycerol precursors. The specific features of gelation for each type of precursor were revealed. It has been determined that titanium polyethylene glycolates synthesized and used in the excess of PEG formed transparent polymeric hydrogels resistant to syneresis under certain conditions. The titanium polyethylene glycolates synthesized without excess of PEG formed turbid heterogeneous colloidal gels. In the case of silicon polyethylene glycolates the hydrogels obtained were polymeric. Dynamic light scattering was used to confirm the polymeric or colloidal type of gelation. The solid and liquid phases of polymeric silicon– and titanium–polyethylene glycol hydrogels were separated by exhaustive extraction. The solid phase was characterized by combined thermal analysis with simultaneous quadruple mass spectrometry, XRD, IR spectroscopy, and liquid phase-atomic emission spectroscopy. The structural features of polymeric gels were investigated by SEM and TEM methods. The cross-linking density of polymeric hydrogels was evaluated using Flory–Rehner theory based on the mechanical properties of swollen networks of flexible polymeric chains.

Introduction

Sol–gel processing is widely used for obtaining various types of silica and titania materials. Alkoxy–silicon and alkoxy–titanium derivatives are conventional precursors for their production. Typically, gel formation takes place when alkoxy–silicon and alkoxy–titanium precursors interact with water providing hydrolysis and condensation reactions, which are governed by numerous factors such as pH, temperature, concentration of reactants, simple electrolytes, *etc.*[1–8]

In the last decade, biocompatible polyolate precursors, in particular silicon polyolates, are used to obtain materials for biomedical applications. Their advantage over typical alkoxy precursors based on monoatomic alcohols is that polyatomic alcohols, released in hydrolysis and condensation reactions, do not cause denaturation and/or precipitation of biomacromolecules.

For instance, silicon polyolate precursors (derivatives of glycerol, sorbitol, *etc.*) were used for the entrapment of enzymes into sol–gel derived silica.[9] It was shown that hydrolysis and condensation of polyol-modified silanes unlike alkoxysilanes led to the formation of optically clear monoliths under very mild processing conditions. Polyols trapped in the gel stabilized its structure against shrinkage but the excess of polyol (glycerol) in the system inhibited hydrolysis and subsequent condensation.

Silicon polyolates (derivatives of glycerol, ethylene glycol, and propane-1,2-diol) were synthesized to obtain mesoscopically organized silica monoliths with hierarchical porosity.[10] It was found that glycol-modified silanes showed an extraordinary condensation behavior with a very low gelation time under neutral conditions, which increased at pH 2 and decreased again in more acidic medium. Rapid gel formation under neutral conditions was explained by the high hydrolysis rate of glycol-modified silanes due to their high miscibility with water unlike alkoxysilanes.

A silicon–ethylene glycol precursor was used in the process of biomimetic mineralization of polysaccharides, proteins, and synthetic biopolymers.[11–13] The sol–gel process was carried out in neutral aqueous solutions under ambient conditions with no stage of colloidal particle formation.

[a] *Russian Academy of Sciences, Ural Branch, Postovsky Institute of Organic Synthesis, 22/20 S. Kovalevskoy/Akademicheskaya St., Ekaterinburg 620990, Russian Federation. E-mail: khonina@ios.uran.ru*

[b] *Russian Academy of Sciences, Ural Branch, Institute of Electrophysics, 106 Amundsena St., Ekaterinburg 620016, Russian Federation*

[c] *Ural Federal University, 19 Mira St., 620002, Ekaterinburg, Russian Federation*

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A titanium–glycerol precursor was used for the formation of the gel, which was further used as a support for bio-affinity chromatography due to the selective binding of phosphorylated proteins and peptides.[14] Glycerol was used in the titanium–glycerol sol–gel route as the chelating ligand, which decreased the hydrolysis/condensation rate by transesterification of the primary titanium precursor Ti(OiPr)$_4$, which gave less water-sensitive glycerol substituted precursor HOCH$_2$CH(OH)CH$_2$OTi(OiPr)$_3$.

The synthesis of a pharmacologically active titanium–glycerol hydrogel based on titanium glycerolates in the excess of glycerol was reported.[15] The gel showed dermatoprotective, transcutaneous properties and was used in medical practice.

Earlier we had reported the preparation of new pharmacologically active glycerohydrogels based on silicon glycerolates,[16] and combined silicon–titanium glycerolates[17] synthesized by transesterification of alkoxy derivatives in the excess of glycerol. The synthesized silicon–glycerol hydrogels were clear transparent monoliths, and combined silicon–titanium–glycerol hydrogels as well as titanium–glycerol hydrogels[15] were milky-white colloidal systems, deprived of fluidity. These gels are interesting due to their application as local and external pharmaceutical formulations and as the substrate for pharmaceutical compositions with wound-healing, regenerative and transcutaneous properties.[18,19] It was shown[20] that at any pH values gels based on silicon glycerolates unlike alkoxy–silicon derivatives were polymeric. Gels based on titanium glycerolates were mainly colloidal (at pH > 1.5).

Also we synthesized biologically active hydrogels based on silicon polyolates, which are the products of reactions of tetraethoxy– and methyltriethoxysilanes with polyols (propane-1,2-diol, polyethylene glycol, and glycerol)[21] and directed synthesis of new biologically active hydrogels based on combined silicon–titanium polyolates (glycerolates, polyethylene glycolates) was carried out.[22] Silicon and titanium polyethylene glycolates were not used as the precursors in sol–gel processing before. All synthesized gels were nontoxic and possessed wound-healing, regenerative, transcutaneous, and dermatoprotective properties of different degree.

Silicon and titanium polyethylene glycolates are flexible and promising precursors in sol–gel synthesis of hydrogels for medical applications. Thus, the presence of silicon in a biologically active and available form in the hydrogel is responsible for wound healing and regenerative properties, and the presence of titanium is responsible for dermatoprotective and antioxidant properties. The presence of polyethylene glycol in the gel results in increasing osmotic activity, which contributes to the removal of edema and inflammation in topical applications. Both silicon– and titanium–polyethylene glycol hydrogels can be used as separate medicines, in particular for the treatment of festering wounds in the exudation stage, and as a basis for various pharmaceutical formulations with active drug additives for the treatment of skin, soft tissues, and mucous membranes. Transcutaneous and transmucosal activity of polyethylene glycol hydrogels allows using minimum amounts of drug additives with maintaining their efficiency, and the corresponding gel structure permits one to prolong their release. Polyethylene glycol gels are

stable on storage; when dispersed the gels are readily converted to the ointment-like state and spread easily on skin and mucous membranes. These gels are drug candidates for local treatment, and they completely passed animal testing. The polyethylene glycol hydrogels expand the arsenal of available and effective medicines for the local treatment of diseases of the skin, soft tissues and mucous membranes of various etiologies.

Despite the practical importance of the obtained products and specific features of gelation of silicon– and titanium–polyethylene glycol precursors, the structure and properties of formed hydrogels have been studied insufficiently. The nature of networking in silicon– and titanium–polyethylene glycolate gels might differ from that known for corresponding glycerolate gels.[20] The gelation clearly depends on the chemical nature of the precursors, water content, pH, the presence of catalysts, and temperature, but the details of this process are still unclear.

The objective of the present study was to investigate the gelation process and structural networking of hydrogels formed from silicon and titanium polyethylene glycolates. We intended to study the influence of different factors on the gelation process such as polyethylene glycol and water molar content, pH of medium, and electrolyte additives in comparison with corresponding glycerol precursors, to compare the reactivity of these precursors in sol–gel processing, and to analyze the physical basis of the structural features of the obtained gels.

Materials and methods

Materials

Tetraethoxysilane (TEOS) or Si(OEt)$_4$ (cp grade, Russia) was distilled under atmospheric pressure; glycerol (Gl) or HOCH$_2$CH(OH)CH$_2$OH (analytical grade, Russia) and tetrabutoxytitanium (TBOT) or Ti(OBu)$_4$ (p grade, Russia) were distilled in vacuo. Polyethylene glycol (PEG) or HO[CH$_2$CH$_2$O]$_9$H (average MW 400) was purchased from Acros Organics (purity ≥99.5%). PEG was dehydrated in vacuo before usage similar to the method described in ref. 23.

Synthesis of silicon– and titanium–polyol precursors

All silicon– and titanium–polyol precursors were synthesized without solvent and catalyst in a dry atmosphere by transesterification of TEOS or TBOT using polyols (PEG-400 or Gl) at different molar ratios followed by the removal of ethanol or butanol under atmospheric pressure and/or in vacuo. Alkoxy groups were completely replaced and monitored by ^{1}H NMR (D$_2$O). The compositions of the reaction mixture and the precursor characteristics are given in Table 1. The chemical composition of all precursors was studied by elemental analysis, refractometry, and IR spectroscopy. All the liquid precursors retained constant viscosity when stored for several months.

Syntheses of silicon tetra(polyethylene glycolate) or STP$_{EG}$ (tetrakis(ω-hydroxypolyethyleneglycoxy)orthosilicate),[24] titanium tetra(polyethylene glycolate) or TTP$_{EG}$ (tetrakis(ω-hydroxypolyethyleneglycoxy)orthotitanate), and titanium tetra(polyethylene

Table 1 Silicon– and titanium–polyol precursors

| Precursor compositions | Molar ratio of reagents in the precursor synthesis | | | | Precursor characteristics | Dynamic viscosity of precursors (Pa s) |
| | TEOS/TBOT : PEG/Gl | | | | | |
	TEOS	TBOT	PEG	Gl		
H[OH$_2$CH$_2$C]$_9$O O[CH$_2$CH$_2$O]$_9$H Si H[OH$_2$CH$_2$C]$_9$O O[CH$_2$CH$_2$O]$_9$H (STP$_{EG}$)	1.0	—	4.0	—	Colorless transparent viscous liquid	6.0
HO OH HOH$_2$CHCH$_2$CO OCH$_2$CHCH$_2$OH Si HOH$_2$CHCH$_2$CO OCH$_2$CHCH$_2$OH HO OH (STG)	1.0	—	—	4.0	Semi-transparent colorless solid	—
HO OH HOH$_2$CHCH$_2$CO OCH$_2$CHCH$_2$OH Si HOH$_2$CHCH$_2$CO OCH$_2$CHCH$_2$OH · HO OH · 6 HOCH$_2$CH(OH)CH$_2$OH (STG · 6Gl)	1.0	—	—	10.0	Colorless transparent viscous liquid	18.3
H[OH$_2$CH$_2$C]$_9$O O[CH$_2$CH$_2$O]$_9$H Ti H[OH$_2$CH$_2$C]$_9$O O[CH$_2$CH$_2$O]$_9$H (TTP$_{EG}$)	—	1.0	4.0	—	Yellow transparent viscous liquid	4.0
H[OH$_2$CH$_2$C]$_9$O O[CH$_2$CH$_2$O]$_9$H Ti H[OH$_2$CH$_2$C]$_9$O O[CH$_2$CH$_2$O]$_9$H · · 10 HO[CH$_2$CH$_2$O]$_9$H (TTP$_{EG}$ · 10PEG)	—	1.0	14.0	—	Light yellow transparent viscous liquid	1.9
HO OH HOH$_2$CHCH$_2$CO OCH$_2$CHCH$_2$OH Ti HOH$_2$CHCH$_2$CO OCH$_2$CHCH$_2$OH · HO OH · 10 HOCH$_2$CH(OH)CH$_2$OH (TTG · 10Gl)	—	1.0	—	14.0	Viscous milky-white colloidal suspension	72.4

glycolate) in the excess of polyethylene glycol or TTP$_{EG}$·10PEG (PEG solution) were described below.

Silicon tetra(polyethylene glycolate), STP$_{EG}$. PEG-400 (98.58 g, 237.80 mM), was placed in a one-neck round-bottom flask equipped with a three-neck adapter connected to a mechanical stirrer, a reflux condenser, and a dropping funnel, and then TEOS (12.39 g, 59.45 mM) was added. The reaction mixture was stirred for 15 h at 90 °C, then ethanol was removed first under atmospheric pressure and then in a rotary evaporator at 2–5 mm Hg and 90 °C to a constant weight of the reaction mixture (which corresponded to the removal of the theoretical amount of ethanol); the yield of STP$_{EG}$ was 99.00 g (99%). The product was a colorless transparent viscous liquid with a dynamic viscosity of 6.0 Pa s (20 ± 0.5 °C) and an n_D^{20} of 1.4658, readily soluble in water and liquid PEG. Found (%): C, 51.03; H, 8.92; Si, 1.70. C$_{72}$H$_{148}$O$_{40}$Si. Calculated (%): C, 51.41; H, 8.87; Si, 1.67. IR, ν/cm^{-1}: 3337 (OH); 2870 (C–H); 1107 (C–O–C); 1023 (Si–O–C) (cf.:[24] n_D^{20} 1.4705; Si 1.41, 1.46; MW 1520).

Titanium tetra(polyethylene glycolate), TTP$_{EG}$. PEG-400 (97.43 g, 235.04 mM), was placed in a one-neck round-bottom flask equipped with a three-neck adapter connected to a mechanical stirrer, a reflux condenser, and a dropping funnel, and then TBOT

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(20.00 g, 58.76 mM) was added. The reaction mixture was stirred for 25 h at 80 °C, then butanol was removed in a rotary evaporator at 2–5 mm Hg and 80 °C to a constant weight of the reaction mixture (which corresponded to the removal of the theoretical amount of butanol); the yield of TTP$_{EG}$ was 99.00 g (99%). The product was a yellow transparent viscous liquid with a dynamic viscosity of 4.0 Pa s (20 ± 0.5 °C) and an n_D^{20} of 1.4750, readily soluble in water and liquid PEG. Found (%): C, 51.00; H, 8.90; Ti, 2.72. C$_{72}$H$_{148}$O$_{40}$Ti. Calculated (%): C, 50.82; H, 8.77; Ti, 2.82. IR, ν/cm^{-1}: 3335 (OH); 2869 (C–H); 1110 (C–O–C); 950, 1110, 1249 (Ti–O–C).

Titanium tetra(polyethylene glycolate) in 10 mol excess of polyethylene glycol, TTP$_{EG}$·10PEG, was synthesized by a similar procedure in 99% yield. The product was a light yellow transparent viscous liquid with a dynamic viscosity of 1.9 Pa s (20 ± 0.5 °C) and an n_D^{20} of 1.4720, readily soluble in water. Found (%): C, 52.06; H, 9.25; Ti, 0.71. C$_{252}$H$_{528}$O$_{140}$Ti. Calculated (%): C, 51.77; H, 9.10; Ti, 0.82. IR, ν/cm^{-1}: 3338 (OH); 2870 (C–H); 1110 (C–O–C); 951, 1110, 1249 (Ti–O–C).

Synthesis of silicon tetraglycerolate or STG (tetrakis-(2,3-dihydroxypropyl)orthosilicate) (solid),[9,10] silicon tetraglycerolate in the excess of glycerol or STG·6Gl (glycerol solution with a dynamic viscosity of 18.3 Pa s (20 ± 0.5 °C)), and titanium tetraglycerolate (tetrakis(2,3-dihydroxypropyl)orthotitanate) in the excess of glycerol or TTG·10Gl (colloidal suspension with a dynamic viscosity of 72.4 Pa s (20 ± 0.5 °C)) was carried out according to the similar procedures described previously.[20] The heterogeneity of the TTG precursor is consistent with the literature data[25] and stems from the formation of hydrophobic chelate complexes insoluble in glycerol and water.

Published data indicate that the interaction products of TEOS and TBOT with glycerol at 1:4 molar ratio are not individual substances (^{13}C, ^{29}Si NMR[9,10] and ^{13}C NMR[25]). It was noted that silicon polyolates because of polyfunctionality were susceptible to equilibrium intermolecular condensation reaction with releasing of polyol and formation of oligomeric condensation products.[10] In the paper reported as ref. 23, titanium polyethylene glycolates were obtained by the interaction of TBOT with PEG-400 at 1:2 molar ratio at 120 °C. The products were spirocycles, which were stable alternatives of networks.

We have mainly used the silicon and titanium polyolates synthesized in the excess of the corresponding polyol. Excess of polyol prevents condensation of the precursor and has a significant impact on gelation (see below). All synthesized precursors were used without further purification similar to those described in ref. 9, and 10.

Hydrogel synthesis and characterization

A precursor was placed in a 10 mL tightly sealed probe tube, and distilled water or solution of electrolyte (hydrochloric acid or salts) was added to the precursor at a different molar ratio (see below), and then the reaction mixture was stirred. The probe tube was kept in a thermostat at 25 or 80 °C. The gelation time was determined visually by the loss of the fluidity of the system with 1 min accuracy. The precursor to water molar ratio in the gel is indicated in the following way: e.g. TTP$_{EG}$·10PEG·40H$_2$O stands for the gel prepared from TTP$_{EG}$·10PEG at 1:40

precursor to water ratio. Gels were characterized by elemental analysis, refractometry, and IR spectroscopy (see below).

Hydrogel STP$_{EG}$·H$_2$O: STP$_{EG}$ (9.89 g, 5.88 mM) and distilled water (0.11 g, 5.88 mM) were kept at 80 °C for 120 min to give a transparent colorless monolith (10.00 g, 100%). n_D^{20}, 1.4645. Found (%): C, 50.53; H, 8.95; Si, 1.59. C$_{72}$H$_{150}$O$_{41}$Si. Calculated (%): C, 50.87; H, 8.89; Si, 1.65. IR, ν_{max}/cm^{-1}: 3340 (OH); 2871 (C–H); 1643 (H–O–H); 1111 (C–O–C); 1024 (Si–O–C).

Hydrogel STP$_{EG}$·2H$_2$O: STP$_{EG}$ (9.79 g, 5.82 mM) and 0.15 M solution of KF (0.21 g, 11.64 mM H$_2$O) were kept at 80 °C for 30 min to give a transparent colorless monolith (10.00 g, 100%). n_D^{20}, 1.4640. Found (%): C, 50.05; H, 9.03; Si, 1.60. C$_{72}$H$_{152}$O$_{42}$Si. Calculated (%): C, 50.34; H, 8.92; Si, 1.64. IR, ν_{max}/cm^{-1}: 3342 (OH); 2873 (C–H); 1640 (H–O–H); 1110 (C–O–C); 1028 (Si–O–C).

Hydrogel TTP$_{EG}$·10PEG·40H$_2$O: TTP$_{EG}$·10PEG (8.89 g, 1.52 mM) and distilled water (1.10 g, 60.80 mM) were kept at 25 °C for 35 min to give a transparent light-yellow monolith (10.00 g, 100%). n_D^{20}, 1.4430. Found (%): C, 46.71; H, 9.48; Ti, 0.60. C$_{252}$H$_{608}$O$_{180}$Ti. Calculated (%): C, 46.09; H, 9.33; Ti, 0.73. IR, ν_{max}/cm^{-1}: 3466 (OH); 2875 (C–H); 1643 (H–O–H); 1103 (C–O–C); 949, 1103, 1250 (Ti–O–C).

Gels synthesized under appropriate conditions at an optimal water to precursor molar ratio were resistant to syneresis. The gels have been stable for 2 years. As-prepared gels were clear and transparent except for the gels based on TTG·10Gl precursors, which were milky-white at pH > 1.5 and transparent at lower pH values.[20] When dispersed, the gels readily convert to the ointment-like state.

The chemical composition of solid phases of silicon– and titanium–polyethylene glycol hydrogels was determined for the following samples STP$_{EG}$·H$_2$O and TTP$_{EG}$·10PEG·40H$_2$O. The solid phase was separated by exhaustive cold extraction in absolute ethanol. The gel sample (5.00 g) was dispersed in absolute ethanol (10 mL) in a 50 mL beaker by stirring for 15 min. The precipitate was filtered, washed repeatedly with ethanol (5 mL portions) and dried at room temperature in vacuo 2–5 mm Hg for 2 h. The transparent filtrate was evaporated at 10 mm Hg for 2 h and then analyzed by atomic emission spectroscopy. The solid samples obtained after extraction were analyzed by combined thermal analysis coupled with simultaneous quadruple mass spectrometry (QMS), XRD analysis, IR spectroscopy and scanning electron microscopy (SEM).

Fig. 1 shows the photograph of the synthesized hydrogels based on titanium polyethylene glycolates (a), silicon polyethylene glycolates (b), and titanium glycerolates (c) for comparison.

Methods

Elemental analysis (C, H, and Si) was carried out using a Perkin Elmer PE 2400 elemental analyzer (series II CHNS–O EA 1108). IR spectra were recorded using a Spectrum One Perkin Elmer FT-IR spectrometer at 400–4000 cm^{-1}. Atomic emission spectroscopy was carried out using an iCAP 6300 Duo Thermo Scientific optical emission spectrometer. XRD analysis was carried out using a Bruker D8 ADVANCE X-ray diffractometer. ^{1}H NMR spectra were recorded at room temperature on a Bruker ADVANCE DRX-400 spectrometer. The dynamic viscosity
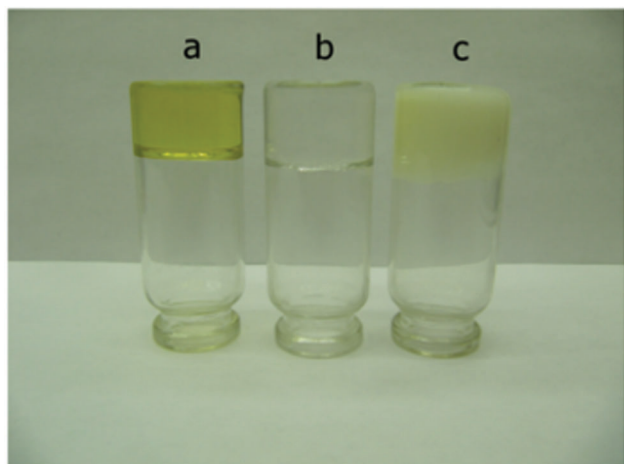
Fig. 1 Photograph of the synthesized hydrogels: (a) $TTP_{EG} \cdot 10PEG \cdot 40H_2O$, (b) $STP_{EG} \cdot H_2O$, and (c) $TTG \cdot 10Gl \cdot 40H_2O$ (for comparison).

Fig. 2 Dependence of gelation time on water molar content (y) in the titanium–polyol gels at 80 °C.

was measured on a HAAKE VISKOTESTER 550 (Thermo Scientific) viscometer with the measurement error of $\pm6\%$. Combined thermal analysis with simultaneous QMS was carried out using a NETZSCH STA409 thermal analyzer.

The sample morphology was observed using a Quanta 200 FEI SEM with a Pegasus elemental analysis system operating at 300 kV with a resolution of more than 5 nm. Transmission electron microscopy (TEM) observation was performed using a sample prepared by drying a putted drop of ethanol with an ultrasonically dispersed piece of the gel on a copper grid *in vacuo* at room temperature. Pictures were taken using a Jeol Jem 2100 high resolution transmission electron microscope with a digital camera Olympus Cantaga G2 and a prefix for microanalysis Oxford Inca EnergyTEM 250 at an acceleration voltage of 200 kV and an amperage of 105 mA.

Measurements of the particle size were carried out using a Brookhaven Zeta Plus universal analyzer by a dynamic light scattering method.[26] PS latex PSL with a particle size of 40 nm was used as a standard sample for the instrument validation. The standard deviation of manufacturer values did not increase to 2%. All measurements were carried out at 25 °C.

Mechanical deformation of gels was studied using a laboratory setup. Gel samples were placed under a load of 0.0–4.7 KPa, and the change in their height was measured using an optical cathetometer with 100 μm resolution.

Results and discussion

All synthesized silicon and titanium polyolates were used as precursors in sol–gel processing. Silicon– and titanium–glycerolate precursors STG, STG·6Gl, and TTG·10Gl investigated earlier by us[20] were used for comparison.

Influence of PEG excess and water content on gelation

Silicon– and titanium–polyethylene glycol precursors STP_{EG} and TTP_{EG} differed significantly in reactivity with water as well as silicon– and titanium–glycerol precursors.[20] Titanium–polyethylene glycol precursor TTP_{EG} showed higher reactivity than corresponding silicon precursor STP_{EG}. The addition of water to TTP_{EG} as a rule resulted in the formation of unstable opaque gels and/or titania precipitation. To attenuate the reactivity of the precursor and to obtain the transparent monolithic titanium–polyethylene glycol gels resistant to syneresis we used 10-fold molar excess of PEG in precursor composition $TTP_{EG} \cdot 10PEG$. The reactivity of the STP_{EG} precursor was much lower and the excess of PEG in the precursor composition completely prevented gelation in water.
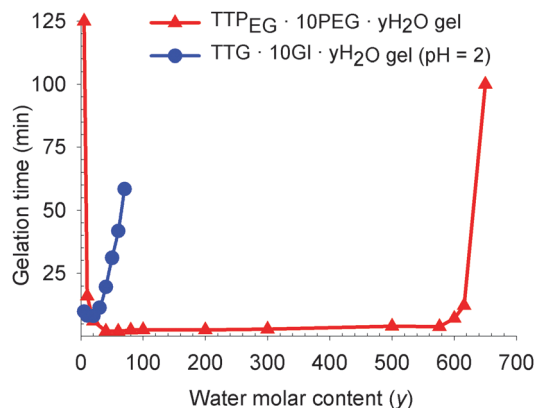
Fig. 2 shows the dependence of the gelation time on the water to precursor molar ratio (y) for the $TTP_{EG} \cdot 10PEG$ precursor in comparison with glycerol precursor $TTG \cdot 10Gl$. The gels were obtained correspondingly in neutral and acidic medium (pH = 2) at 80 °C.

As shown in Fig. 2, the gelation time of the $TTP_{EG} \cdot 10PEG$ precursor remains low (around 3 min) and almost constant over the broad range of water to precursor molar contents ($20 \leq y \leq 600$). All the synthesized gels were transparent light-yellow monoliths with no syneresis observed. However, the obtained gels differed in their elasticity. The optimum molar water content for the synthesis of transparent monoliths was $20 \leq y \leq 100$. At $y < 20$ the obtained gels were stiff; at $y > 100$ the obtained gels were very soft.

At low water content ($y < 20$) the gelation time rapidly increases likely due to the insufficient water content to accomplish hydrolysis of precursors. At high water content ($y > 600$) the precursor concentration becomes very low and the probability of condensation in the gel network decreases. At large water content ($y \gg 1000$) the opacity of the reaction mixture and precipitation of TiO_2 took place.

The titanium–polyethylene glycol precursor is much more reactive than the titanium–glycerol precursor. Earlier[20] it was shown that the $TTG \cdot 10Gl$ precursor does not gelate under all neutral conditions and hydrogels can be prepared only at $0.5 \leq pH \leq 2.5$. Fig. 2 shows the dependence of the gelation time on the water to precursor molar ratio (y) for $TTG \cdot 10Gl$ at pH = 2. The gelation time remains low in the narrow range of
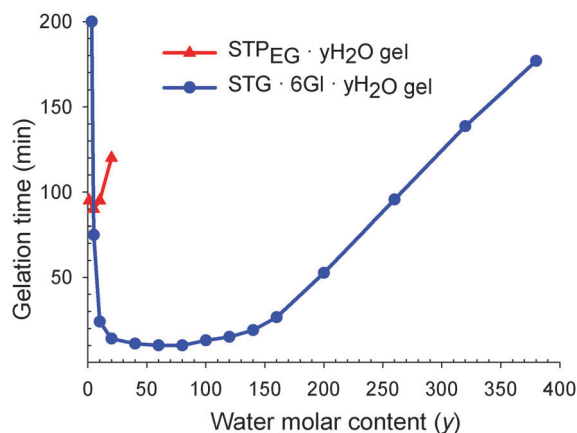
Fig. 3 Dependence of gelation time on water molar content (y) in the silicon–polyol gels at 80 °C.

water content ($10 \leq y \leq 30$). Apparently, low reactivity of the TTG·10Gl precursor stems from its heterogeneity due to the formation of titanium chelate complexes with glycerol. Meanwhile, TTP$_{EG}$·10PEG is completely soluble in water and can be readily involved in hydrolytic polycondensation.

Fig. 3 presents the dependence of the gelation time on the water to precursor molar ratio (y) for silicon precursors STP$_{EG}$ and STG·6Gl, both of which gelate under neutral conditions at 80 °C.

Unlike TTP$_{EG}$, silicon–polyethylene glycol precursor STP$_{EG}$ exhibits low reactivity with water. Resistant to syneresis the transparent monolithic gel was obtained only at a low water molar content (at $y = 1$). Although in the water content range $2 \leq y \leq 20$ transparent gels were still obtained, they were very soft, and subjected to syneresis. At water content $y > 20$ no gel network structure was obtained and the reaction medium was the transparent viscous liquid.

As in the case of the titanium–polyethylene glycol precursor (Fig. 2), at high concentration of the silicon–glycerol precursor the gelation time decreased with increasing molar water content probably due to the growth of hydrolysis rates. When the precursor concentration decreased (at $y > 80$, and especially at $y > 150$), the gelation time increased notably due to the deceleration of silanol condensation.

As seen from Fig. 3, silicon–polyethylene glycol precursor STP$_{EG}$ is less reactive than silicon–glycerol precursor STG·6Gl. The latter gelates in the broad range of water molar content, and the optimum molar water content for the production of resistant to syneresis transparent monoliths was $20 \leq y \leq 40$. Glycerol residues are more electronegative and hydrophilic than PEG ones and it results in higher hydrolysis and subsequent condensation rates of STG·6Gl. Although at water content $40 < y < 400$ transparent gels were also obtained, they were unstable to syneresis. At water content $y \geq 400$ no gel network structure was obtained but the reaction medium was transparent.

Influence of pH on gelation

The dependence of the gelation time on H (the accuracy of measurements was 0.1) of the initial aqueous solution of

titanium–polyethylene glycol precursor TTP$_{EG}$·10PEG (at $y = 40$) in comparison with titanium–glycerol precursor TTG·10Gl (at $y = 40$) at 80 °C is shown in Fig. 4.

The obtained dependence for the titanium–polyethylene glycol precursor significantly differs from that for the titanium–glycerol precursor.[20] As seen in Fig. 4, under neutral and slightly acidic conditions titanium–polyethylene glycol gels are formed very rapidly, the obtained transparent light yellow monoliths being stable to syneresis. The gelation time remains practically constant at $2 < \mathrm{pH} < 6.5$. At lower pH the gelation time gradually increases; at a pH value below 1.5 no gelation takes place, but the solution remains transparent.

The dependence of the gelation time on pH for the TTG·10Gl precursor was explained by the coagulation–condensation mechanism of sol–gel transformation.[20] Gels from titanium–glycerol precursor are not formed under neutral conditions. It is probably due to the insolubility of titanium chelate complexes in glycerol, which prevents the hydrolysis and condensation reactions. The maximum gelation rate (the lowest gelation time) was observed in a pH range 1–2, which was close to the isoelectric point (IEP) of colloid dispersion. In the pH range near IEP electrostatic repulsion between TTG particles diminishes and they coagulate. Coagulation is necessarily followed by chemical reactions of hydrolysis and condensation, which bind particles together and lead to the network formed by chemically bound particles. At pH < 1.5 the gelation time increases likely due to formation of water-soluble hydroxytitanium chlorides and under strongly acidic conditions no gelation takes place.

The dependence of the gelation time on pH of the initial aqueous solution of silicon–polyethylene glycol precursor STP$_{EG}$ ($y = 3$) in comparison with silicon–glycerol precursor STG ($y = 10$) at 80 °C is shown in Fig. 5.

The dependence for silicon–polyethylene glycol precursor STP$_{EG}$ is in general similar to that for the titanium–polyethylene glycol precursor (Fig. 4); herein observed differences can be explained by the different reactivity of these precursors. Low reactivity of the STP$_{EG}$ precursor and low water content essentially slow down the gelation at pH < 6 and at pH < 4 gels are not formed.

The curve type of gelation for the STG precursor[20] is in principle similar to that given in the literature for the inorganic
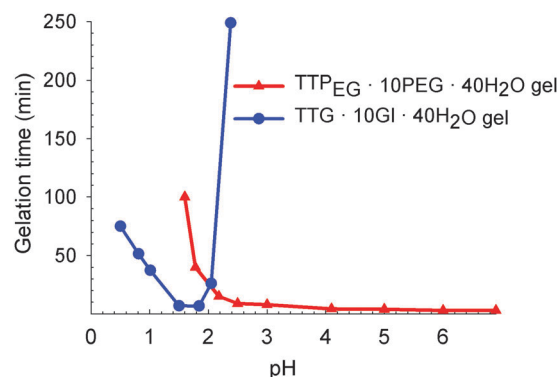

Fig. 4 Dependence of gelation time on H of the initial aqueous solution of TTP$_{EG}$·10PEG precursor in comparison with TTG·10Gl at 80 °C.

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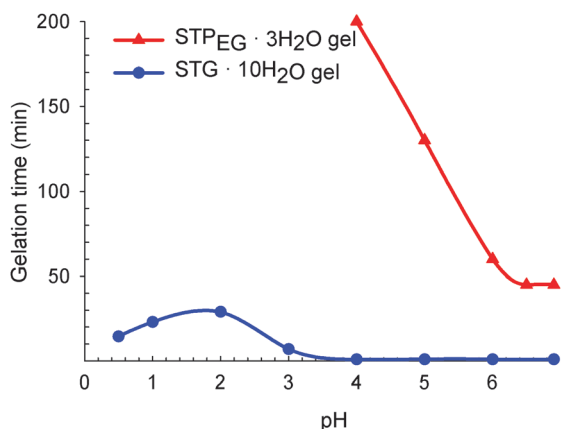J. Mater. Chem. B, 2015, **3**, 5490–5500 | **5495**

Fig. 5 Dependence of gelation time on H of the initial solution of the STP_{EG} precursor in comparison with STG at 80 °C.

silica gel formation from alkoxy-precursors.[3,4,27] It is based on the formation of transition states by nucleophilic or electrophilic attacks that depend on pH and the partial charge as well as the electronegativity of each atom in this transition state. Gelation of the STG precursor is, however, different from the gelation of TTG as it stems from the comparison of Fig. 4 and 5.

In general, according to the data presented in Fig. 4 and 5, the titanium–polyethylene glycol precursor (except for in the strongly acidic medium) is more reactive in gelation than the titanium–glycerol precursor. At all pH values the silicon–polyethylene glycol precursor is less active than the silicon–glycerol precursor.

The specific features of the gelation for polyethylene glycolate precursors

According to ref. 3, 4 and 27–31 for silicon– and titanium–organic precursors it is conventional to distinguish colloidal and polymeric gelation (the colloidal sol–gel route and the polymeric sol–gel route), and colloidal and polymeric gels, respectively. Colloidal gels are formed from sols, which are the products of hydrolysis and condensation reactions of precursors in sol–gel processing; polymeric gels are formed always from clear transparent solutions of precursors, where hydrolysis and condensation reactions also take place, but no colloidal particles can be observed.[3,4] Hydrolysis and condensation reactions occur simultaneously and reaction rates depend on the type of precursor as well as reaction conditions. The dominating gelation type stems from the relative rates of hydrolysis and condensation reactions, which are basically governed by pH of medium and hydrolysis water content. In colloidal gelation a faster hydrolysis rate is obtained by using a precursor with a fast hydrolysis rate, as a rule in the excess water and is favored by strongly acidic conditions that provide a fully hydrolyzed alkoxide. In polymeric gelation the hydrolysis rate is kept low by adding successively small amounts of water and by choosing a precursor which hydrolyzes relatively slowly, resulting in partial hydrolysis of the alkoxide. The final stage of this process is a three dimensional polymeric network with a structure different from that obtained from a colloidal route.[8,30–32]

Silicon systems can be controlled very well and both colloidal and polymeric sol–gel routes can be realized. Alkoxy–titanium precursors exhibit dramatically higher reactivity than alkoxysilanes with water, which generally leads to the precipitation of titania rather than the formation of colloidal or polymeric gels.[14] Typically in the sol–gel processes with alkoxy–titanium derivatives the formation of titania colloidal particles is dominant, and most of the obtained titania gels are turbid colloidal systems. Transparent colloidal titania solutions with a small TiO_2 species and transparent colloidal gels on their bases were obtained under strongly acidic conditions.[32–34] However, some papers report the formation of transparent polymeric gels based on alkoxy–titanium precursors.[30,31,35] In these cases the necessary condition for polymeric gelation is the low water content.

Let us consider in detail the features of the formation of transparent monolithic hydrogels from silicon and titanium polyethylene glycolates.

In the case of the TTP_{EG}·10PEG precursor gelation was investigated by dynamic light scattering (DLS). The dependencies of the hydrodynamic diameter (D_{hd}) of particles of titanium–polyethylene glycol precursors at low ($y = 40$) and excessive ($y \gg 1000$) molar water content are presented in Fig. 6. For the first 2 min no measurements were made as the mixture was stirred. Then consequent DLS measurements of D_{hd} of particles were performed.

In the case of the water to precursor molar ratio $y = 40$ at the 2nd min the mean D_{hd} of particles was 680 nm. The extrapolation of the regression curve gives *ca.* 600 nm diameter of the particles in the solution at the start of mixing. According to MM2 computer modeling,[36] the geometric diameter of TTP_{EG} molecules does not exceed 6.5 nm. It means that TTP_{EG} molecules are aggregated even in the initial precursor. It can be suggested that the aggregation is caused by intermolecular condensation of starting molecules of the precursor and by solvation as well. The D_{hd} of aggregates increased up to 1500 nm after 30 min when the solution lost its fluidity and the gelation was accomplished. In the course of gelation the reaction mixture remained transparent. The resulting gel is a transparent light-yellow monolith (Fig. 1a), which does not convert to the sol upon its disaggregation.

In the case of large excess of water ($y \gg 1000$) the first DLS measurement after 2 min gave 230 nm of D_{hd}, which is three times lower than the initial value in the case of $y = 40$. The regression curve can be extrapolated fairly well to the zero value of D_{hd}, which leads to disintegration of titanium–polyethylene glycol aggregates. Although hydrolysis of titanium–polyethylene glycol precursors in large excess of water began at a lower D_{hd}, it increased much more rapidly and after 7 min the D_{hd} reached 3800 nm. During the process the opacity of the reaction mixture gradually increased but the mixture remained fluid. It looks reasonable that the rapid hydrolysis of precursors in the large excess of water corresponds to the formation and growth of TiO_2 particles, which finally precipitate.

Thus, according to DLS the hydrolysis and subsequent condensation of TTP_{EG} precursors apparently may follow different
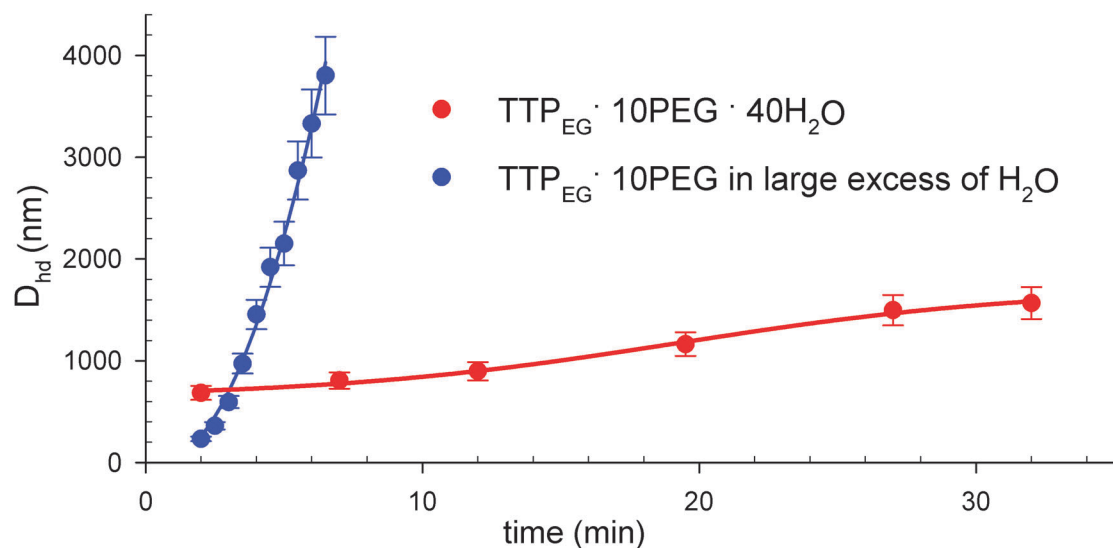
Fig. 6 Dependence of the hydrodynamic diameter (D_{hd}) of titanium–polyethylene glycol aggregates $TTP_{EG}\cdot10PEG$ in 40-fold molar excess of water and in large excess of water at the time of hydrolytic condensation at 25 °C.

sol–gel routes depending on water content. At relatively low water content due to the high concentration of $TTP_{EG}\cdot10PEG$ in the reaction mixture, the excess of PEG (as well as glycerol) retards the hydrolysis and condensation reactions similar to that described in ref. 14. It can be assumed that it results in a partially hydrolyzed precursor and provides the formation of polymeric gels with cross-linked organic/inorganic subchain networks swollen in water/PEG medium. At high water content the hydrolysis and condensation reactions are very fast. It results in the formation of colloidal titania particles, which finally precipitate.

Solid phases of $STP_{EG}\cdot H_2O$ and $TTP_{EG}\cdot10PEG\cdot40H_2O$ gels were separated by exhaustive cold extraction in absolute ethanol. Fig. 7 presents the results of XRD and thermal analysis of the solid phase of the $TTP_{EG}\cdot10PEG\cdot40H_2O$ gel.

The weight loss in the thermal decomposition of the solid phase is 80%, and according to QMS plots the evolving gases contain large concentration of CO_2. It means that up to 80% in the solid phase of the $TTP_{EG}\cdot10PEG\cdot40H_2O$ gel corresponds to organic moieties, which are likely PEG residues. The XRD plot reveals no crystallinity in the solid phase of the gel. The similar results were obtained for the $STP_{EG}\cdot H_2O$ gel.

Further evidence of the polymeric type of gelation in these gels is given by IR spectra. Solid phases of hydrogels contain residues of polyethylene glycol molecules covalently bonded to silicon or titanium atoms with the following IR absorption bands (ν_{max}, cm^{-1}): 3300 (O–H); 2880, 1460, 1350 (C–H in –CH$_2$–); 1060 (Si–O in Si–O–C and Ti–O in Ti–O–C). The polycondensation mechanism of gelation is confirmed by the presence of IR absorption bands (ν_{max}, cm^{-1}): 1060 (Si–O–Si) and 400–700 (Ti–O–Ti).

The liquid phases separated in the cold extraction were transparent viscous solutions. Using the atomic emission spectroscopy it was shown that in the case of the $STP_{EG}\cdot H_2O$ gel the silicon distribution between solid and liquid phases

was 1 : 2, whereas in the case of the $TTP_{EG}\cdot10PEG\cdot40H_2O$ gel the titanium distribution was 1 : 0.1. The data obtained correlate with the reactivity of silicon– and titanium–polyethylene glycol precursors. A high reactivity of the titanium–polyethylene glycol precursor in hydrolysis and condensation reactions leads to more complete incorporation of titanium in the polymeric phase, whereas the silicon–polyethylene glycol precursor is considerably less active, therefore the most part of silicon remains in the liquid phase.

The structural features of the $TTP_{EG}\cdot10PEG\cdot40H_2O$ gel were investigated by SEM and TEM methods. Fig. 8 presents the SEM image of the solid phase of the gel after extraction.

According to the SEM image, the size of agglomerated amorphous particles is 10–100 μm. Elemental analysis data received by the system Pegasus indicate the absence of TiO_2-particles in the analyzed areas of the solid phase sample.

Fig. 9 presents the TEM micrographs of the sample produced by drying a suspension of the $TTP_{EG}\cdot10PEG\cdot40H_2O$ gel in ethanol on the copper grid.

Fig. 9 shows the gel amorphous structure and the absence of point and ring reflexes, which are characteristic for crystalline titania. The SEM and TEM results obtained also confirm a polymeric nature of the transparent monolithic $TTP_{EG}\cdot10PEG\cdot40H_2O$ gel.

Thus, based on the concept of the relative rates of hydrolysis and condensation reactions[3,4,27] we may assume that in the case of $STP_{EG}\cdot H_2O$ and $TTP_{EG}\cdot10PEG\cdot40H_2O$ gels hydrolysis of precursors dominates over condensation as well as in the case of silicon glycerolates.[20] The hydrolytic polycondensation processes result in the formation of a three-dimensional network of the irreversible polymeric gel, wherein the excess of PEG prevents the complete precursor hydrolysis and formation of colloidal gels or TiO_2 precipitation. In the gel structure PEG also prevents the syneresis and acts as a plasticizer.
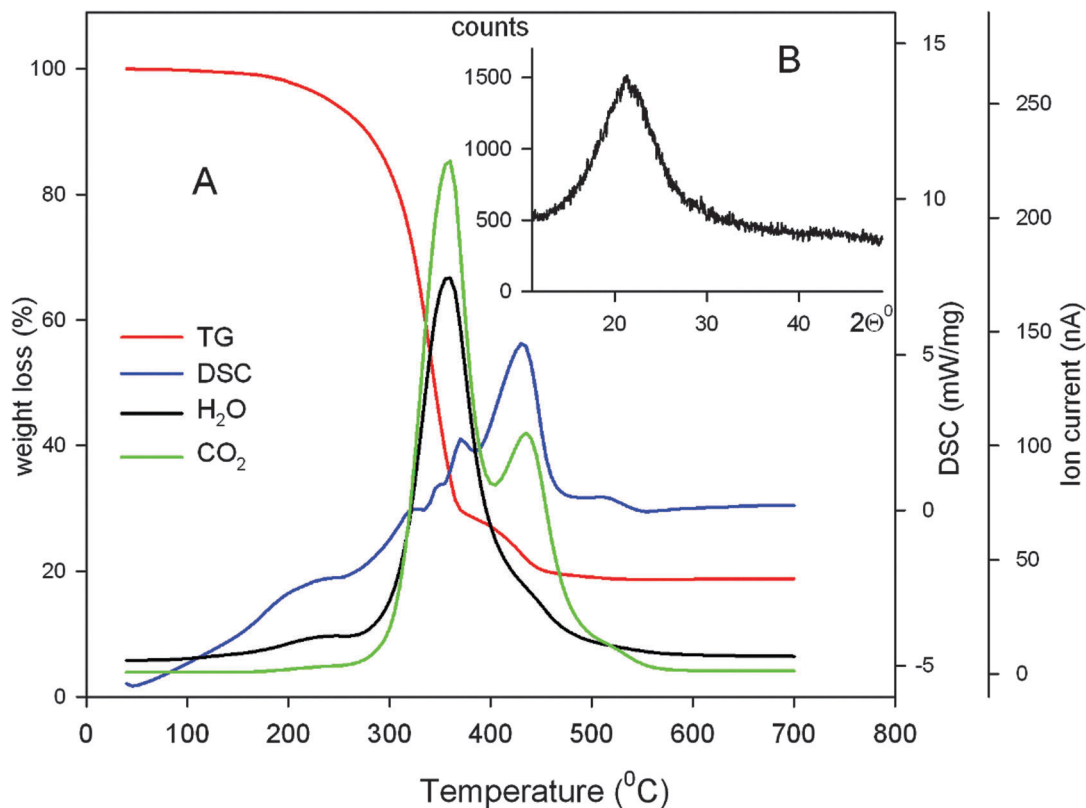
Fig. 7 Thermal analysis (A) and XRD (B) plots for the solid phase of the TTP$_{EG}$·10PEG·40H$_2$O gel.
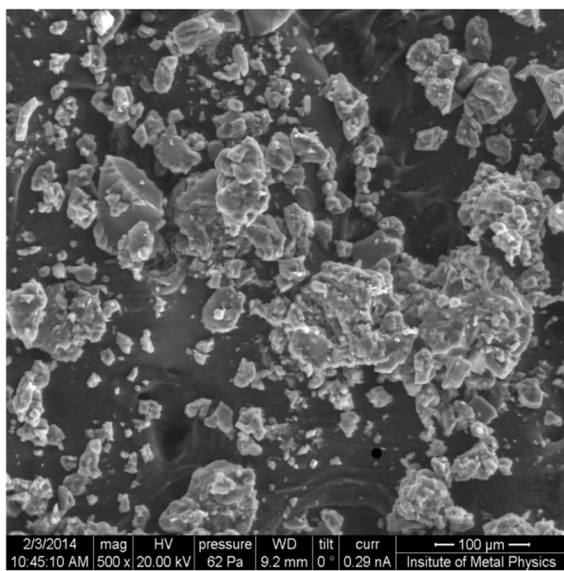
Fig. 8 SEM image of the solid phase of the titanium–polyethylene glycol gel.
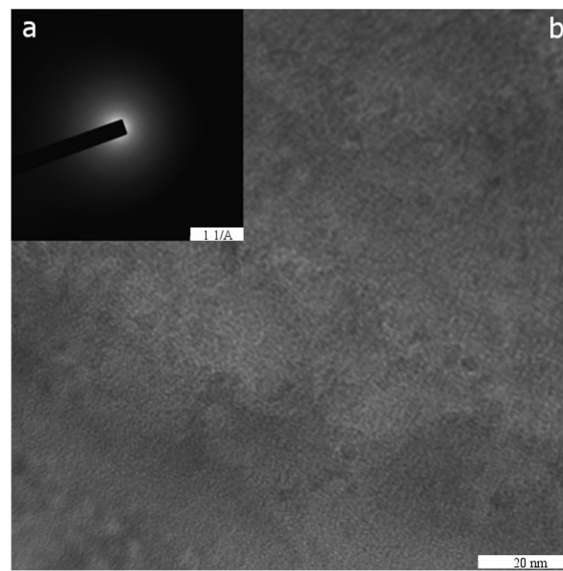
Fig. 9 TEM micrographs of the dried titanium–polyethylene glycol gel on the copper grid: (a) electron diffraction area; and (b) high resolution TEM image.

Influence of salt–electrolytes on gelation

Previously we have found the different influence of salt–electrolytes on the gelation of silicon and titanium glycerolates.[20] In the present study the influence of 0.15 M salt solutions (KF, (NH$_4$)$_3$PO$_4$, (NH$_4$)$_2$SO$_4$, NH$_4$Cl, NaCl, ZnSO$_4$, CaCl$_2$, AlCl$_3$, Al(NO$_3$)$_3$, and Al$_2$(SO$_4$)$_3$) on the formation time

of STP$_{EG}$·2H$_2$O and TTP$_{EG}$·10PEG·40H$_2$O gels was investigated in comparison with glycerolate gel formation. In general, the influence of salts on the formation of the silicon–polyethylene glycol hydrogel was similar to the gelation of the silicon–glycerol precursor: as a rule all salts accelerated gelation except for aluminium salts.

Table 2 Parameters of the network structure of silicon– and titanium–polyol polymeric hydrogels

Gel	ρ (g cm^{-3})	$E \times 10^{-3}$ (Pa)	φ	M_c (g mol^{-1})
TTP$_{EG}$·10PEG·40H$_2$O[a]	1.57	2.0	0.012	4×10^5
STP$_{EG}$·2H$_2$O[b]	1.33	24.4	0.047	4×10^4
STG·6Gl·12H$_2$O[a]	1.22	147.0	0.151	9×10^3
STG·6Gl·30H$_2$O[a]	1.22	31.1	0.109	4×10^4

[a] Obtained in neutral medium. [b] Obtained in 0.15 M KF solution.

In the case of the titanium–polyethylene glycol precursor all used salts promoted the gelation, whereas in the case of titanium–glycerol precursor gelation took place only in aluminium salts solutions.

Parameters of the network structure of silicon– and titanium–polyol polymeric hydrogels

The network structure of polymeric gels was characterized by a Flory–Rehner approach based on the mechanical properties of the swollen network of flexible polymeric chains.[37]

The average molar weight of the subchains M_c in the elastic network was calculated using the Flory–Rehner equation:[37,38]

$$M_c = \frac{\rho RT}{E} \left(\varphi^{\frac{1}{3}} - \frac{2\varphi}{f} \right) \times 10^6 \tag{1}$$

where E – initial modulus of elasticity (Pa); ρ – density of the polymeric phase in gel (g cm^{-3}); T – temperature (298 K); R = 8.314 Joule K^{-1} mol^{-1}; φ – relative volume fraction of the polymeric phase in gels; and f (= 4) – network functionality. The density of the polymeric phase in gels and the relative volume fraction of polymers in the network were calculated using Van der Waals increments of atomic and group volumes estimated by means of CAChe 7.5 molecular modeling software.[36] The experimental values of E and the calculated values of ρ, φ and M_c are given in Table 2 for silicon– and titanium–polyethylene glycol hydrogels in comparison with silicon–glycerol hydrogels.[20]

The values of M_c given in Table 2 indicate that the subchains in the network have a considerable length, which provides their conformational flexibility and the elastic deformation of the gel. The highest value of M_c, which corresponds to the lowest network density, was obtained for the TTP$_{EG}$·10PEG·40H$_2$O gel. This gel had the lowest initial modulus of elasticity. The network density of the STP$_{EG}$·2H$_2$O gel is higher, but this increase is provided mostly due to the lower volume fraction of the solvent in the gel. Nearly the same value of the network density of silicon– glycerol gels can be obtained at considerably higher solvent content. In general, it means that in the case of polymeric silicon–polyol hydrogels glycerol residues provide more effective cross-linking of gel structures than polyethylene glycol residues. This result correlates well with the relative reactivity of STP$_{EG}$ and STG precursors.

Conclusions

Silicon and titanium polyolates are new biocompatible water-soluble precursors in the sol–gel synthesis of silicon– and titanium–polyol hydrogels for medical applications.

In the present study we have compared silicon and titanium polyolates based on polyethylene glycol (PEG-400) and glycerol. Titanium tetra(polyethylene glycolate) (TTP$_{EG}$) shows a much greater reactivity with water than silicon tetra(polyethylene glycolate) (STP$_{EG}$) as well as in the case of silicon– and titanium–alkoxy precursors. To obtain transparent monolithic hydrogels rather than colloidal gels or titania precipitates one has to use excess of PEG in the precursor composition TTP$_{EG}$·10PEG (solution TTP$_{EG}$ in PEG).

In general, the titanium–polyethylene glycol precursor TTP$_{EG}$·10PEG is more active than the corresponding titanium–glycerol precursor. At any pH of medium and molar water content silicon–polyethylene glycol precursor STP$_{EG}$ is considerably less active in gelation than the STG precursor. Electrolyte additives as a rule promote the formation of silicon– and titanium–polyethylene glycol hydrogels.

It has been determined that TTP$_{EG}$ synthesized without PEG excess forms turbid colloidal gels. It was found that TTP$_{EG}$·10PEG·40H$_2$O and STP$_{EG}$·H$_2$O hydrogels are polymeric and formed via a three-dimensional polycondensation mechanism, as well as silicon–glycerol hydrogels.

The network structures of polymeric silicon– and titanium–polyethylene glycol hydrogels are formed by cross-linked sub-chains with considerable molar weights of 4×10^4 (STP$_{EG}$·2H$_2$O gel) and 4×10^5 g mol^{-1} (TTP$_{EG}$·10PEG·40H$_2$O gel).

Acknowledgements

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