BABEŞ-BOLYAI UNIVERSITY PHYSICS FACULTY

Magnetic resonance study on biomedical systems

-PhD Thesis Summary-

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Introduction

Sol-gel processes have been intensively developed since they were found to be suitable for preparing materials and designed devices with specific properties. A large variety of advanced materials including glasses, polycrystalline and composite ceramics were obtained by sol-gel methods.

The sol-gel method allows preparing high purity and homogeneity materials at relative low temperatures. The possibility of obtaining non-crystalline materials with controlled composition and structures makes the sol-gel processing a potential technique for the encapsulation of isotopes for therapeutic applications. The high porosity and surface area associated with the typical structure of the xerogel produced by sol-gel allow obtaining materials with different degradation rate [9-11]. By spray-drying of sol-gels derived microspheres with desired size can be obtained [12-13].

Spray drying is a very important tool used for numerous industrial applications such as waste treatment, production of inorganic salts, pharmaceuticals and food stuffs. In spray drying, a solution or suspension is fed to an atomizer and the droplets formed are mixed with a hot gas. Spray drying is a promising method for preparation of sol-gel derived silica microparticles for controlled release of drug. The largest application for microspheres in medicine is drug delivery. The medical uses of particulate drug delivery systems cover all areas of medicine such as cardiology, endocrinology, gynecology, immunology, pain management and oncology. Most of the advanced drug delivery systems utilize microspheres or microcapsules for the encapsulation of drugs and proteins. The drugloaded microspheres can be applied locally or delivered to the target area after intravenous injection by either passive means (e.g., trapping by size) or active means (e.g., magnetic targeting) [14]. From a manufacturing point of view, spray drying offers the advantage of being single-step process of synthesis nanocrystalline particles, which can be readily scaled up [15, 16]. Additionally, yttrium containing systems, in the form of microspheres or seeds, have received attention in treatment of primary hepatocellular carcinoma, irradiation of diseased synovial membrane for the treatment of rheumatoid arthritis, and treatment of prostate tumors [17]. For these applications, the materials should be biocompatible, non-toxic and chemically insoluble up to all drugs are released or their radioactivity decrease under a certain level.

In spray drying, a solution or suspension is fed to an atomizer and the droplets formed are mixed with a hot gas. This causes the solvent of the droplets to evaporate, leaving a dry powder product [18-22].

During the spray-drying of well-dispersed sols, a gel layer initially forms at the surface of the drops due to rapid evaporation of water from the drop's surface. This gel layer is semi-permeable to water/vapour flow and reduces the rate of evaporation of the solvent. The calculations for the net interaction potential between the colloidal aggregates indicate that the barrier-to-aggregation in this sol is relatively high. Hence, gelation occurs by a reaction-limited process, producing a relatively dense microporous gel layer with correspondingly low permeability. The reduced evaporation rate through

the gel layer results in a temperature increase, which at a high inlet temperature leads to "ballooning". At a low inlet temperature, the well-dispersed colloids in the drops remain relatively mobile as water evaporates through the gel layer at the surface of the drop, producing a diffusion gradient towards the surface. As liquid flows to the drop surface, with accompanying solids, a gradual growth of the solid shell occurs, leaving a void in the centre of the particle [23, 24].

The largest application for microspheres in medicine is drug delivery but they can be used also as radiation carrier for internal radiotherapy. Yttrium-90 is a beta-emitter with suitable nuclear properties for radio therapeutic purposes and can be quite easily incorporated in oxide microspheres in order to develop a biodegradable system able to carry the radiation inside the cancer site and provide a high and localized dose of beta radiation. [14, 25-26]. The structural role of ions in aluminosilicate glasses is determined by their size, which controls their coordination number and by their charge,which controls the strength of the bonds formed to the neighboring oxigens [27, 28-30]. The rare earth ions, due to their size, are able to occupy octahedral sites in the glass structure, instead of tetrahedral one, in which the bonds between rare earth ions and surrounding oxygens are the weakest links in the glass structure compared to Al–O or Si–O bonds. The stronger the rare earth–oxygen bonds, the higher the glass transformation temperature, suggesting that rare earth ions act similarly to aluminum ions in these glasses [27].

To understand many of the key properties of these materials it demands examination of the atomic level structure. NMR has been shown to be a powerful probe of the local structure and provides complementary information to standard characterization techniques such as diffraction (DRX) and electron microscopy (SEM şi TEM).

It has been demonstrated that the ²⁹Si NMR spectra of aluminosilicates are sensitive to the chemical nature of the atoms directly attached to oxygens of the silicate tetrahedra, also described as the second coordination sphere of silicon [5-8].

The correlation between information obtained by NMR spectroscopy, X-ray diffraction and electron microscopy are necessary to a good structural characterization and most realistic physical and chemical survey for this type of materials.

I. The local structure study of silica, aluminosilicate and yttrium aluminosilicate microspheres

1. Microspheres preparation

Silica (Si) and aluminosilicate (AlSi), with molar ratio Al₂O₃/SiO₂=20/80, microspheres of less than 20 μ m in diameter were prepared by the sol-gel and spray drying methods. The sols were obtained by the hydrolysis and polycondensation of tetraethoxysilane (TEOS 98%, Aldrich) for both Si and AlSi samples. For the AlSi sample, aluminum nitrate nanohydrate 99,99 % Aldrich (Al(NO₃)_{3*}9H₂O) was also used as precursor. The nitrate was dissolved in water and hydrochloric acid (0.002M) was added as a catalyst. Microspheres were obtained by spraying the sols with a Buchi-290 Mini Spray-dryer with the two-fluid nozzle with the 1.4 mm nozzle tip. The flow type is co-current with mixing of air and liquid at the nozzle head. The nitrogen spray flow rate was varied between 475 and 600 l/h and the aspirator rate were kept constant at 95%. The inlet temperature was controlled at 150°C for both samples. The outlet temperature was determined by the inlet temperature and relative factors such as nitrogen and liquid flow rates, varying between 68 and 75°C.

The spray drying parameters are listed in table I.

Table 1. The spray drying parameters

Parameters		Spray parameters							
	Pump	Pump Asp Flow T _{in} / T _{ou}							
Sample	(%)	(%)	(l/h)	(°C)					
Si	16	95	473	135 / 68					
20Al·80Si	16	95	600	150 / 75					
30Al·70Si	16	95	600	150 / 75					
20Al 70Si10Y	16	95	600	150 / 75					

In order to check the stability of the amorphous samples and to develop the crystalline phases, different heat treatments have been applied on samples at: $300 \ ^{0}C$ (30 min.); $1200 \ ^{0}C$ (30 min.); $1400 \ ^{0}C$ (0 and 10 or 30 min.). In all procedures the samples have been heated up to selected temperatures from room temperature and keep at that temperature the indicated time.

2. Silica and aluminiosilicate microspheres

2.1. Differential Thermal Analysis results

Differential Thermal Analysis (DTA) and Thermogravimetric Analysis (TGA) for all prepared samples, have been obtained with DTG-60H Shimadzu, which simultaneously record the DTA and TGA signals, in the temperature range of 25 –1430 $^{\circ}$ C , 10 $^{\circ}$ C / min. heating rate. The reference substance was alumina which is chemical inertness. Structural and phase changes induced by temperature rising in as-prepared microspheres are investigated by thermal analyses (Fig. 1)

The thermal behavior of all samples shows an endothermic peak below 100°C with loss of mass assigned to the loss of adsorbed water. The small exothermic peaks at around 140°C and 220°C, also accompanied by a small loss of mass, can be related to hydrolysis or condensation processes and to the decomposing of the remaining organic phase, respectively. The thermal behavior of as-prepared microspheres is very similar with sol-gel derived aluminosilicates [58].

The thermogram for Si sample (Fig.1.a) present at around 1200°C a wide endothermic peak without any loss of mass, which can be assigned to a structural relaxation process, followed by a raise of the DTA signal, also without loss of mass, indicating the beginning of the crystallization process. This is sustained by XRD patterns (fig.2) that are showing that up to 1200°C the microspheres remain amorphous. The wide endothermic peak from AlSi sample thermogram, without any loss of mass, beginning around 800 $^{\circ}$ C can be assigned to a similar structural relaxation phenomenon that precede the crystallization process.



a)



b)

Fig.1. DTA and TGA curves of a) Si and c) SiAl_{0.2} samples

2.2. Crystallinity morphology analysis 2.2.1. X-ray difraction

Cristallinity morphology was recorded with LabX XRD-6000, Shimadzu diffractometer, Ni filter, CuK α radiation ($\lambda = 1.5418$ Å) and quartz powder for standard calibration. All diffractorams were recorded at scanning range 10° la 80°.

The X-ray diffraction pattern of Si and AlSi samples, obtained after such heat treatments, are presented in figure 2.

The appearance of some nanocrystals was evidenced only after a heat treatment at 1400 $^{\circ}$ C, initially mainly developed on the microspheres surfaces (Fig.5 and 6 After a longer heat treatment at 1400 $^{\circ}$ C (30 min.) the Si sample became crystalline (Fig.4a), the identified crystalline phase being crystobalite [59], while the microspheres are broken (Fig.5a right).

For the AlSi heat treated samples the first developed crystalline phase is mullite $(Al_6Si_2O_{13})$ (1400, 0 min). The second developed phase is crystobalite (Fig.2b) [60, 61]. Amorphous phase preponderantly containing silica was also evidenced, which could be concluded from a broad characteristic diffraction peak between 20° and 30° in XRD pattern (Fig. 2b).



Fig.2. X-ray diffraction pattern of Si a) and AlSi_{0.2} b) samples as prepared and after different heat treatments

2.2.2. Electron Microscopy

The size distribution and the surface morphology of the silica microspheres were determined by Scanning Electron Microscopy (SEM) with a Jeol JSM 5510LV microscope, Transmission Electron Microscopy (TEM) with a Jeol JEM 1010 microscope with MegaViewIII CCD Camera and Atomic Force Microscopy (AFM) with a NTEGRA Vita system.



Fig.3. SEM/TEM micrographs of the a) Si and b) SiAl_{0,2} as prepared samples

SEM/TEM micrographs (Fig.3) and AFM images (Fig.4) of the as-prepared samples show welldefined particles of spherical shape with a mean diameter between 0.1 and 20 μ m and no visible pores on surfaces. Such particles are hollow so the distortion/deformation of the microspheres walls, more evident for aluminosilicates (Fig. 4b); can be due to the thickness of the microspheres walls and/or because of the particles collision in the spray cylinder.



a) b) Fig.4. AFM images of a) Si and b) SiAl_{0.2} as prepared samples



Fig. 5. TEM images of nanocrystals for Si sample heat treated at 1400 ^{0}Ca) 0 minutes and b) 30 minutes

The TEM images of heat treated AlSi samples (Fig.6b) show that the nanocrystals are mainly developed on microspheres surfaces, like for silica microspheres.



Fig.6. TEM images of nanocrystals for $AlSi_{0.2}$ sample heat treated at 1400 ${}^{0}Ca$) 0 minutes and b) 10 minutes

2.3. Nuclear Magnetic Resonance results

The local structure of silica and aluminosilicate microspheres was investigated by ²⁹Si and ²⁷Al MAS-NMR with an Avance 400 Bruker Spectrometer at 9.4 Tesla external magnetic field, using a 4 mm BBI Bruker probe. The spinning side bands free spectra for central transitions were obtained by spinning the samples at the frequency of minimum 7 kHz for ²⁹Si MAS-NMR and 14 kHz for ²⁷Al MAS-NMR spectra. The ²⁹Si and ²⁷Al MAS-NMR chemical shifts are expressed in ppm relative to 1% Si(CH₃)₄/CDCl₃ and Al(NO₃)₃ water solution, respectively. The experimental spectra have been deconvoluted by using Dmfit program [62].

The ²⁹Si MAS NMR spectra of Si and AlSi, as prepared and heat treated, samples are presented in Fig. 7 and Fig. 8, respectively. The Figure 9 presents the deconvolution of ²⁹Si MAS NMR spectrum of asprepared Si sample.

The four oxygen atoms of a $[SiO_4]$ structural unit can be bound or not forward to other silicon atoms, being nominated as bonded and non-bonded oxygen, respectively. Each of these possible $[SiO_4]$ units with none, one, two, three or four bounded oxygens, oxygens interconnecting two such units, are noted using Qⁿ terminology (n being the number of bounded oxygens) which is the main way of silicon units characterization [5-7].



Fig.7²⁹Si MAS NMR spectra of Si, as prepared and heat treated samples



Fig.8. ²⁹Si MAS NMR spectrum of AlSi as prepared and heat treated samples



Fig.9. ²⁹Si MAS NMR spectrum of Si as-prepared sample and its deconvolution

Isotropic chemical shift, which allow us to identify the Q^n unit type, the corresponding signals intensities and their line width, which reflect the chemical shift distribution, are presented in table II for Si samples and in table III for AlSi samples, respectively. The ²⁹Si MAS NMR spectrum of as prepared silica microspheres, present broad and asymmetric resonance lines characteristic for amorphous phases involving the contribution of three such resonance lines associated to Q^2 , Q^3 and Q^4 units [7].

Si samples	Units	δ (ppm)	FWHM (ppm)	Intensity %
As prepared	Q^2	-92.5	7.5	10.3
	Q^3	-101	6.8	46.6
	Q^4	-110.4	9.1	43.1
300 °C (30 min.)	Q^2	-97.6	9.2	7.8
	Q^3	-103.4	8.3	25.6
	Q^4	-111.7	11.8	66.6
1400 °C (0 min.)	Q ³	-101.2	11.7	17.3
	Q^4	-110.2	12.6	82.7
1400 °C (30 min.)	Q^4	-109.1	2.8	100

Table II. The NMR parameters of simulated Q^n lines from ²⁹Si MAS NMR spectra of Si samples

As can be seen in Table 1 the preponderant are the Q^3 and Q^4 units with corresponding lines at around -100 ppm and -110 ppm, respectively. The presence of Q^2 and Q^3 units is due to the presence of some water molecules or OH groups around silicon, as is supported also by thermal analysis data.

In the ²⁹Si MAS NMR spectrum of Si sample heat treated at 300°C for 30 minutes (Fig.7) the intensity of the line corresponding to Q^4 units increase and in the same time that belonging to Q^3 units decrease (Table II) due to the process which involves dehydration and cross-linking between SiO₄ units during that thermal treatment.

For the Si sample heat treated up to 1400° C and taken out from the heater immediately this temperature is rising (Fig.7), there are no Q² units, showing that no low-condensed silicate species are present in the sample structure after such thermal treatment. In these samples the fraction of Q⁴ units increases and in the same time the fraction of Q³ units decrease.

The remaining Q^3 units after such high temperature treatment can be taken as an indication that in resulting samples there is oxygen vacancy as structural defects. After a longer (30 min.) heat treatment at the same temperature (Table II) only Q^4 units are present in the resulting sample structure, in accord with the presence of the crystobalite crystalline phase identified by XRD (Fig.2a), in the totally broken microspheres (Fig. 5a right).

In ²⁹Si MAS NMR spectrum of AlSi as prepared sample (Fig.8) the fraction of Q^3 units decrease comparatively with Si sample, and surprisingly the weight of Q^4 units increase (Tables II and III). This effect can be explained by accepting that rich aluminum phase, the precursor of mullite phase, is separated in the as prepared sample. By 30 minutes heat treatment at 300°C, when accordingly to the thermal analysis data in the AlSi sample remain mainly only oxygens as anions, the silicon atoms are involving in Q^3 and Q^4 units.

After heat treatment at 1400°C in AlSi sample the main crystalline phase identified is mullite but in the sample there are also crystobalite and amorphous phase, as can be observe from XRD patterns (Fig. 2). From the ²⁹Si MAS NMR spectra of these samples (Fig.8) where the lines are broad even after 10 minutes heat treatment at 1400°C, we can conclude that the silicon environment is quite distorted in identified crystalline phases.

AlSi samples	Linita	δ	FWHM	Intensity
	Units	(ppm)	(ppm)	%
As prepared	Q^2	-95.1	10.3	14.1
	Q^3	-100.7	5.9	14.4
	Q^4	-107.5	12.3	71.5
300 °C (30 min.)	Q^3	-101.2	14	32.3
	Q^4	-107.8	15	67.7
1400 °C (0 min.)	Q^2	-87	4.2	4.8
	Q^3	-100	29	54.1
	Q^4	-109.6	11.6	41.1
1400 °C (10 min.)	Q^2	-88	8.3	15.7
	Q^3	-103	30.9	41.3
	Q^4	-110.5	12.3	43

Table III. The NMR parameters of simulated Q^n lines from ²⁹Si MAS NMR spectra of AlSi samples

The fraction of Q^3 units increase and new Q^2 units appear (Table III) in the structure of such partially crystalline samples. These structural units can be assigning to SiO₄ tetrahedra that enter in mullite structure [59]. The -88 ppm line is assigned to an environment with two aluminum oxygen tetrahedra as next nearest neighbors of the silicon oxygen tetrahedra [64, 65] while the -100 ppm line is assigned to silicon oxygen tetrahedra surrounded by one aluminum oxygen polyhedra and three silicon oxygen tetrahedra [66], but such units are quite distorted, as is reflected by the extremely large width of the

corresponding line. In the same time the Q^4 units can be related to the crystobalite and amorphous phase that still remains in sample after heat treatment at 1400°C.

Usually in noncrystalline and polycrystalline oxides materials the aluminum is 4-, 5- and 6-fold coordinated by oxygens and named with Al_{4c} , Al_{5c} and Al_{6c} respectively [67, 68]. Important information on the local structure distortion around aluminum is provided by chemical shift, line width and quadrupolar parameters.

The ²⁷Al MAS NMR spectra of $AlSi_{0,2}$ samples (Fig.10) were analyzed with the same Dmfit program [62]. The Figure 11 presents, as an example, the deconvolution of ²⁷Al MAS NMR spectrum of AlSi 1400°C (0 minutes) heat treated sample. The NMR parameters of AlSi as prepared and heat treated samples are summarized in Table IV.

The spectrum of as-prepared AlSi sample presents two resonance lines, characteristic to 4- and 6-fold coordinated aluminum. The very narrow line at around 0.8 ppm is assigned to hexacoordinated aluminum with NO₃ groups from the remaining $Al(NO_3)_3$ precursor. The other much larger lines at around 11 ppm, 6.6 ppm, -2,3 ppm and 56,8 ppm are assigned to aluminum coordinated with six and four oxygens species integrated in consolidated network.

The ²⁷Al MAS NMR spectrum of 300°C heat treated SiAl sample, present three resonance lines, characteristic to 4-, 5- and 6-fold coordinated aluminum (Fig.11) and their distribution is typically for noncrystalline oxide materials [68]. The corresponding line widths are reflecting quite distorted environments for aluminum in the obtained xerogel microspheres. After heat treatment at 1400°C the spectra show two main resonances; one, in the tetrahedral Al-O region, that is split into two closely overlapping peaks, at about 61 and 40 ppm assigned to the regular tetrahedral Al sites and another one in the range for 6-fold coordinated aluminum that is also split into two overlapping peaks.



Fig. 10. ²⁷Al MAS NMR spectra of AlSi_{0,2} as prepared and heat treated samples



Fig.11. ²⁷*Al MAS NMR spectrum of AlSi 1400°C* (0 min.) heat treated sample and its deconvolution

SiAl samples	Units	δ	Cqcc	FWHM	Intensity
		(ppm)	(MHz)	(ppm)	(%)
As prepared	Al $_{4c}$	56.8	2.7	11.7	6.6
	Al_{6c}^{1}	11.2	2.6	15.8	12.7
	Al_{6c}^{2}	6.6	5	27.4	48.7
	Al_{6c}^{3}	0.8	0.8	2.1	17.8
	Al_{6c}^{4}	-2.3	1.2	8.42	14.2
300 °C (30 min.)	Al $_{4c}$	52.3	6.3	54.6	33.4
	Al _{5c}	30.8	4.9	28.4	16.3
	Al _{6c}	1.8	3.7	18	50.3
1400 °C (0 min.)	Al_{4c}^{1}	61.1	4.5	26.5	23.7
	$\mathrm{Al_{4c}}^2$	40.1	2.5	18.8	11.5
	Al_{6c}^{1}	9.3	3.5	15.6	28
	Al_{6c}^{2}	-6.3	5.4	41.2	36.8
1400 °C (10 min.)	Al $_{4c}^{1}$	63.2	4.7	34.4	54.8
	Al_{4c}^{2}	45.9	3.8	24.7	17
	Al_{6c}^{1}	7.2	1	11.4	8.8
	Al_{6c}^{2}	-0.9	3.9	17.22	19.4

Table IV. The NMR parameters of simulated Al polyhedra lines from ²⁷Al MAS NMR spectra of AlSi_{0,2} samples.

The resonance peak arises at around -6 ppm and those two at around 61 and 40 ppm, can be assign to aluminum oxygen polyhedra that enter in mullite structure [60, 64, 65]. The other one at ~9 ppm can be related to Al sites in the remaining noncrystalline phase, its intensity decreasing in accord with the decrease of the fraction of this phase.

Conclusions

Silica and aluminosilicate samples prepared by sol-gel and spray drying methods are non crystalline, well-defined particles, with spherical shape and a diameter of less than 20 µm with no visible pores on surfaces. The aluminum effect on silica network polymerization as well to the phase separation in the silica matrices, as a precursor of mullite phase, is supported by the ²⁹Si and ²⁷Al MAS NMR data. The high temperature heat treatments of silica microspheres lead to the development of crystobalite nanocrystals, initially on their surfaces. In the case of aluminosilicate microspheres the crystobalite nanocrystals development is preceded by the appearance of the mullite crystals. The studied microspheres are stable from morphological point of view, as far they remain noncrystalline or contain small amounts of nanocrystals, but are broken when they became highly crystalline. The results have been included in the paper *Local structure of silica and alumino-silicate spray-dried microspheres* [85].

3. Yttrium aluminosilicate microspheres

Aluminosilicate microspheres with and without yttrium, of less than 20 μ m in diameter, have been prepared by a combined the sol-gel and spray drying method. The prepared samples are of the following composition 70% SiO₂ and 30% Al₂O₃ (SiAl) and 70% SiO₂, 20% Al₂O₃ and 10% Y₂O₃ (SiAlY). The sols were obtained by the hydrolysis and polycondensation of tetraethoxysilane (TEOS 98%, Aldrich). Aluminum nitrate nonahydrate 99,99 % Aldrich (Al(NO₃)₃·9H₂O) and Yttrium nitrate

hexahydrate 99,8 % Aldrich (Y(NO₃)₃· $6H_2O$) were also used as precursors. The aim of the study was to analysis the structural stability and modification induced by the partial substitution of aluminium oxide with yttrium oxide.

3.1. Crystallinity morphology analysis 3.1.1. Electron Microscopy

Aluminosilicate microspheres with and without yttrium, of less than 20 μ m in diameter, have been prepared by a combined the sol-gel and spray drying method. The prepared samples are of the following composition 70% SiO₂ and 30% Al₂O₃ (SiAl) and 70% SiO₂, 20% Al₂O₃ and 10% Y₂O₃ (SiAlY). The sols were obtained by the hydrolysis and polycondensation of tetraethoxysilane (TEOS 98%, Aldrich). Aluminum nitrate nonahydrate 99,99 % Aldrich (Al(NO₃)₃·9H₂O) and Yttrium nitrate hexahydrate 99,8 % Aldrich (Y(NO₃)₃·6H₂O) were also used as precursors.



a) b) Fig.12. SEM(a)/TEM(b) images of SiAl_{0.2} Y_{0.1} microspheres surface

3.2. X-ray diffraction

The X-ray diffraction patterns do not exhibit crystalline peaks, they show an amorphous structure, which could be concluded from a broad characteristic diffraction peak between 20 and 30 degree (Fig. 13).



Fig.13. X-ray diffraction patterns of SiAl_{0,3} and SiAl_{0,2} Y_{0,1} samples



Fig.14. DTA and TGA curves of SiAl_{0.2}Y_{0.1} sample

The two other large peaks around 15 and 45 degree [69], for the yttrium containing sample, can be due to small nanocrystals that are developed, probably at the microsphere surface.

On the other hand, the differential thermal analysis (DTA) and thermogravimetric analysis showed that the nitrates precursors decompose completely only around 500 °C (Fig.14).

3.3. Nuclear Magnetic Resonance results

The local structure before and after aluminum substitution with yttrium are characterized by MAS-NMR on the ²⁹Si and ²⁷Al nucleus. The addition of yttrium to samples is expected to induce changes in their local structure and thus has an influence on their dissolution properties.

The ²⁹Si MAS-NMR spectra of the as-prepared microspheres (Fig. 15) show a large and slightly asymmetric peak, characteristic to the amorphous samples.



Fig.15. The ²⁹Si MAS NMR (continuous lines) and ¹H-²⁹Si CP MAS NMR (dotted lines) spectra of microsphere samples

The widths of the asymmetric peaks for both samples cover the range of Q^2 , Q^3 and Q^4 species, so it is assumed that these resonance lines are present.

In this sort of materials, synthesized at low temperature, it is expected many remaining hydroxyl groups. In this approach, the presence of Q^2 and Q^3 units is mainly due to the presence of some water molecules or OH groups around silicon, as is supported also by ¹H-²⁹Si CP MAS NMR experiments (Fig. 15). The Q^2 units could be consider like O₂Si-(OH) ₂ groups and the chemical shifts typical of highly condensed species Q^3 and Q^4 may be assigned to O₃Si-OH (or O₃Si-O-Y³⁺) and O₄Si, respectively.

The SiAl sample presents a small line around -79 ppm, which corresponds to Q^0 units type involving four nonbridging oxygen atoms. The signals corresponding to $[SiO_4]$ groups in Q^0 environments, could be due to the silicon atoms surrounded by aluminum and/or OH groups : $Si(OAI)_n(OH)_{4-n}$ [70-72] as is shown in ¹H-²⁹Si CP MAS NMR spectra of this sample. The detection of these species indicated that a part of the silicons are not incorporated into the polymerized silica matrix.

Isotropic chemical shift, which allow identifying the Q^n unit type, signals intensities and the corresponding line width, which reflect the chemical shift distribution, obtained by the deconvolution procedure, are summarized in Table 1 for both of as-prepared samples. The figure 16 presents the deconvolution of ²⁹Si MAS NMR spectrum of SiAl_{0.2}Y_{0.1} sample.

As can be observed in ²⁹Si MAS NMR spectra of as-prepared samples the fraction of Q^4 units decreases, in the sample with yttrium, Q^3 units fraction increases and the Q^0 type units practically disappear (Tables V).

The slightly decrease of Q^4 units fraction and the increase of Q^3 units fraction suggest that a part of the yttrium atoms are localized near silicon tetrahedra and Si-O-Si network depolymerisation take place supporting the Si-O-Y clusters formation accordingly with corresponding X-ray diffraction pattern (Fig.13).

As prepared	Units	δ	FWHM	Ι
samples		(ppm)	(ppm)	(%)
SiAl	Q ⁰	-78.7	2.9	1.7
	Q ²	-93	8.3	11.7
	Q ³	-100.5	6.3	23.3
	Q^4	-106.9	12.4	63.3
	Q^2	-92.2	8.8	8.9
SiAlY	Q^3	-101.2	7.7	34.6
	Q^4	-109.4	10	56.5

Table V. The NMR parameters of simulated Q^n lines from ²⁹Si MAS NMR spectra



Fig.16. The ²⁹Si MAS NMR spectrum of $SiAl_{0,2}Y_{0,1}$ sample and its deconvolution

Interestingly, the fwhm values for the Q^2 and Q^3 signals become broad, suggesting an increase in structural inhomogeneity. All these results give information on the molecular scale about the interface between the Si-Y-O clusters and the aluminosilicate microspheres matrices.

In fact, the broad bands related to the Q^2 and Q^3 groups, found for $SiAl_{0,2}Y_{0,1}$ sample, can be attributed to the spreading out of the chemical shift due to the chemical and structural diversity of the environments caused by the yttrium centres. In this connection, the Si–O–H bonds present in the Q^2 and Q^3 groups may be partially substituted by Si–O–Y bonds.

In noncrystalline and polycrystalline oxide systems the aluminum is 4-, 5- and 6-fold coordinated by oxygens [67, 68]. Important information on the structure distortion is provided by chemical shift, line width and quadrupolar parameters.

The ²⁷Al MAS NMR spectra (Fig.17) were analyzed with the same Dmfit program [62] the quadrupolar parameters being extracted for both samples. The figure 18 presents the deconvolution of ²⁷Al MAS NMR spectrum of $SiAl_{0,2}Y_{0,1}$ sample. The MAS NMR parameters are summarized in Table VII.



Fig.17. The ²⁷Al MAS NMR (continuous lines) and ¹H-²⁷Al CP MAS NMR (dotted lines) spectra of microsphere samples SiAl_{0,3} and SiAl_{0,2} Y_{0,1}



*Fig.18.*²⁷*Al MAS NMR spectrum of SiAl*_{0,2} *Y*_{0,1} *sample and its deconvolution*

The sharp line at around 0,8 ppm seem to be due to Al in Al(NO₃)₃ that has not been completely consumed during the synthesis. In this region the other lines are broadened, containing at least three asymmetric lines, accordingly with its deconvolution (Fig.18), assign to AlO₆ units. There are small differences between the spectra (Fig.17) only around 0 ppm, so just these Al structural units seem to be affected with aluminum substitution by yttrium. The parameters of ²⁷Al MAS NMR spectra (Table VI) show that the aluminum ions are mainly hexacoordinated like in disordered *phyllosilicates* [73, 74] proofing that the formed material is essentially siliceous and that aluminum is only partially integrated in the structure like AlO₄ units.

As prepared	Units	ð	Cqcc	FWHM	1
samples		(ppm)	(MHz)	(ppm)	(%)
SiAl	Al _{4c}	56.5	2.4	8.2	2.6
	Al _{6c} ¹	11.8	2.8	11.4	13.2
	Al _{6c} ²	1.2	4.6	18.8	49.2
	Al _{6c} ³	0.8	0.9	1.2	6.8
	Al _{6c} ⁴	-2.7	1.7	7.3	28.2
C! A INZ	Al _{4c}	56.7	2.3	9.2	5.7
SIALY	Al _{6c} ¹	11.2	2.5	12	8.9
	Al _{6c} ²	2	4.2	28.7	58.7
	Al _{6c} ³	1	1	2.1	15.7
	Al _{6c} ⁴	-2	1.9	5.6	11

Table VI. The NMR parameters of simulated Al_{nc} lines from ²⁷Al MAS NMR spectra

The distribution of aluminum sites is not to much affected by the yttrium presence in the sample suggesting that yttrium it is integrated in the structure of as prepared microspheres like aluminum.

Conclusions

Aluminosilicate samples with and without yttrium, prepared by a combined sol-gel and spray drying method, are well-defined particles with spherical shape and a diameter of less than 20 μ m with no visible pores on surfaces.

The X-ray diffraction patterns show an amorphous structure of both as-prepared samples but some features for yttrium containing samples support the small yttrium silicate nuclei development.

The presence of Q^0 species in aluminum silicate indicate that a part of the silicons are not incorporated into the polymerized silica matrix. The aluminum ions are mainly hexacoordinated in both samples like in disordered phylosilicates.

After substitution with yttrium partially Si-O-Si depolymerisations take place because a fraction of these atoms are localized near silicon tetrahedra. Yttrium presence does not affect to much the distribution of aluminum sites indicating that yttrium it is integrated in the structure of formed

phyllosilicates phases and its dissolution will be comparable with that coresponding to this type of layered silicates. The results have been included in the paper *Structural properties of yttrium aluminosilicates microspheres* [86].

4. The SBF influence on the structure of some aluminosilicate microspheres

To observe the structural changes which can be ocure at the contact between samples and human body fluids, a lot of samples were immersed in SBF (Kokubo solution, pH 7,4) at 37°C for 48 hours, solution which are similar with human blood plasma (Tabel VII) [75-78].

Ion	Concentratio	utration (mmol/dm ³)				
	SBF	Human blood plasma				
Na⁺	142,0	142,0				
CI.	147,8	103,0				
K ⁺	5,0	5,0				
HCO ₃ ⁻	4,2	27,0				
Ca ²⁺	2,5	2,5				
Mg ²⁺	1,5	1,5				
HPO ₄ ²⁻	1,0	1,0				
SO ₄ ²⁻	0,5	0,5				

Table VII. Ions concentration in SBF and human blood plasma

Three types of aluminum silicate samples were prepared: 80% SiO₂ şi 20% Al₂O₃ (SiAl_{0,2}), 70% SiO₂ şi 30% Al₂O₃ (SiAl_{0,3}) şi 70% SiO₂, 20% Al₂O₃ şi 10% Y₂O₃ (SiAl_{0,2}Y_{0,1}), by the sol-gel and spray drying methods, as was describe in "Microspheres preparation". The aim was to investigate the structural changes induced in aluminosilicate microspheres with 20 % mol Al₂O₃ by partial silicon substitution with aluminum and yttrium and also to characterize the degradation of the samples and the local structure changes occurred in the microspheres network during the immersion in simulated body fluid (SBF).

4.1. Crystallinity morphology analysis

The AFM (Fig.19a) and TEM (Fig.20a) results show the obtained particles are hollow and have a spherical shape with a diameter between 0.2 μ m and 20 μ m. The distortion/deformation of the microspheres walls can be due to the thickness of the microspheres walls and also because of the particles collision in the spray cylinder.

AFM image (Fig.19b) and TEM micrographs (Fig.20b) of the samples show nanostructured layers on microspheres surfaces due to the immersion in SBF.



Fig.19. AFM image of microspheres before a) and after immersion b) in SBF



b) Fig.20. TEM images of microspheres surface a) before immersion and b) after immersion in SBF

a)

The X-ray diffraction patterns show an amorphous structure even after SBF immersion of the samples, which could be concluded from a broad characteristic diffraction peak between 20° and 30° (Fig.21).



Fig.21. X-ray diffraction patterns of as-prepared samples and after immersion in SBF

The composition and distribution of aluminum among tetrahedral and octahedral sites determine the surface charge, the bonding behavior of active sites and thus, they significantly affect many properties, including reactivity with aqueous solutions [79].

4.2. **Nuclear Magnetic Resonance results**

The structure of noncrystalline aluminosilicates is realised by interconected $[SiO_4]$ and $[AIO_n]$ units [79, 80]. The four oxygen atoms of a structural $[SiO_4]$ unit can be bound or not forward to other silicon atoms. Each of these possible [SiO₄] units with none, one, two, three or four bounded oxygens are noted using Qⁿ terminology (n being the number of bounded oxygens) which is the main way of silicon unit characterization. The ²⁹Si MAS-NMR spectra of the as-prepared microspheres show a large and slightly asymmetric line, characteristic to the amorphous samples (Fig. 22). The widths of the lines for all the samples cover the range corresponding to three $[SiO_4]$ species, so it is assumed that three resonance lines corresponding to Q², Q³ and Q⁴ species are present, but that they are not resolved [5, 81]. The amount of Q⁴ units decreases when the silicon is substituted by aluminum and then by aluminum and yttrium. In this approach, aluminum act as a network forming cation when is tetracoordinated and at the same time hexacoordinated aluminum or yttrium change the degree of silica matrix polymerization playing a role of network modifiers.

After 48 h of SBF immersion the ²⁹Si MAS-NMR spectra of the microspheres show the important changes that occurred in the silica network, as result of dissolution and structural reconstruction that took place during immersion (Fig. 22).

The effect of samples immersion on silicon environment, such as developments of new Q^n units, can be observed by comparing the intensity of each unit before and after immersion (table VIII).



Fig.22. The ²⁹Si NMR spectra of microsphere samples, before and after SBF immersion

The deconvoluted spectra for all the samples indicate the conversion of some Q^4 species into Q^3 and Q^2 species due to the reactions that occurred at the microsphere-SBF solution interface. The structure at the microspheres surface is fragmentized by replacing oxygen bond with OH terminals, so the fraction of Q^3 units is increasing on the expense of Q^4 units. The partial dissolution of the particles

produced depolymerized silicon species that could interact with Ca and P ions from SBF. The line around -78.82 ppm could be assigned to Q^0 species sourounded by Al ions from microspheres surfaces and Ca or P ions from SBF. The detection of these species indicated that a part of the dissolved silica had been incorporated into the nanostructured layers which are formed on the surface of microspheres after SBF immersion (fig. 19b).

P	arameters es	$\underset{\delta(ppm)}{Q^{0}}$	I (%)	FWHM (ppm)	$\underset{\delta(ppm)}{Q^2}$	I (%)	FWHM (ppm)	$\underset{\delta(ppm)}{Q^3}$	I (%)	FWHM (ppm)	$\underset{\delta(ppm)}{Q^4}$	I (%)	FWHM (ppm)
) IAI	As prep.	-	-	-	-95.09	14.13	10.32	-100.67	14.37	5.93	-107.54	71.51	12.28
80Si2	SBF 48h	-82.78	5.92	8.13	-93.92	29.64	13.23	-103	57.05	12.52	-110.5	7.4	14.59
90AI	As prep.	-78.7	1.7	2.9	-93	11.7	8.3	-100.5	23.3	6.3	-106.9	63.3	12.4
70Si3	SBF 48h	-79.20	3.82	4.89	-85.26	17.78	9.29	-95.97	56.26	16.15	-104.43	22.15	13.44
)Al10	As prep.	-	-	-	-92.2	8.9	8.8	-101.2	34.6	7.7	-109.4	56.5	10
70Si2(SBF 48h	-78.90	0.67	1.97	-93.49	57.20	25.28	-102.78	42.13	14.25	-	-	-

Usually in noncrystalline and polycrystalline systems the aluminum could be 4-, 5- and 6-fold coordinated by oxygens forming AlO_n units. The coordination number of the AlO_n polyhedra can be determinated unambiguously, even from relatively broad lines and uncorrected chemical shift data, but the identification of different aluminum environments with the same coordination number is more difficult because the ²⁷Al chemical shifts are not very sensitive to the chemical environment.



Fig.23. The ²⁷Al MAS/NMR spectra of microsphere samples, before and after SBF immersion

The position, linewidth and integrated areas of each signal obtained by the deconvolution (Fig.23) procedure are summarized in Table IX and X, for as-prepared and after SBF immersion samples, respectively.

After 48h of immersion the ²⁷Al MAS-NMR spectra show completely different comparing with those obtained for the as prepared samples. This could lead to the conclusion that aluminum units are present mostly at the microspheres surfaces in regions incorporating Ca and P ions from SBF with a structure like disordered phyllosilicates phases containing phosphorus ions [73, 74, 82, 83]. Taking into account the clay interstratified structure, the four-coordinated aluminum could be a constituent of the tetrahedral sheet of the silicate substituting silicon atoms and the six-coordinated aluminum can be a constituent of the octahedral sheet, surrounded by four oxygens and two hydroxyl groups.

As prepared samples	Units	δ	I	Cqcc	FWHM
I I I I I I I I		(ppm)	(%)	(MHz)	(ppm)
80Si20Al	Al _{4c}	56.8	6.6	2.7	11.7
	Al_{6c}^{1}	11.2	12.7	2.6	15.8
	$\mathrm{Al_{6c}}^2$	6.6	48.7	5	27.4
	Al_{6c}^{3}	0.8	17.8	0.8	2.1
	Al_{6c}^{4}	-2.3	14.2	1.2	8.42
70Si30Al	Al _{4c}	56.5	2.6	2.4	8.2
	Al_{6c}^{1}	11.8	13.2	2.8	11.4
	Al_{6c}^{2}	1.2	49.2	4.6	18.8
	Al_{6c}^{3}	0.8	6.8	0.9	1.2
	Al_{6c}^{4}	-2.7	28.2	1.7	7.3
70Si20Al10Y	Al _{4c}	56.7	5.7	2.3	9.2
	Al_{6c}^{1}	11.2	8.9	2.5	12
	$\mathrm{Al_{6c}}^2$	2	58.7	4.2	28.7
	Al_{6c}^{3}	1	15.7	1	2.1
	Al_{6c}^{4}	-2	11	1.9	5.6

Tabel IX

Tabel X

48 h	Units	δ	I	Cqcc	FWHM
SBF samples		(ppm)	(%)	(MHz)	(ppm)
80Si20Al	Al _{4c}	60.5	48.8	2.9	14
	Al _{6c} ¹	7.8	51.2	5	25.3
70Si30Al	Al _{4c} ¹	64.5	7.4	2.5	9.5
	Al _{4c} ²	59.4	24.6	3.9	14.6
	Al _{6c} ¹	7.74	57.9	4	17.4
	Al _{6c} ²	-12.87	10.1	5.1	31.28
70Si20Al10Y	Al _{4c}	60.5	48	3.1	15.2
	Al _{6c} ¹	8.1	40	3.7	15.2
	Al _{6c} ²	-14.2	12	2.4	36.21

In the same time aluminum can be located in the interlayer space compensating for the net negative charge of the layer. These aluminum atoms are octahedrally coordinated to water molecules [82, 83].

After SBF immersion the amount of tetracoordinated aluminum increase for all the samples and this fact might indicate diffusion of aluminum from the octahedral to the tetrahedral sheet of the phyllosilicate as a consequence of the hydration during SBF immersion and also due to the presence of Ca and P ions. The positions and intensity of the ²⁷Al MAS NMR peaks for SiAl_{0,2}Y_{0,1} and SiAl_{0,2} samples after SBF immersion, show little variation between the spectra indicating similarities between the mean atomic environments. For these samples, in ²⁷Al MAS NMR spectra the amount of tetracoordinated aluminum is higher then that of hexacoordinated.

Knowing that usually at the biomaterial surfaces after immersion in SBF, nanostructured layers of hydroxyapatite type on developed by incorporating P and Ca ions from SBF, MAS-NMR spectroscopy on the ³¹P nuclei was also used for structural characterization of the samples after immersion in SBF in order to characterize the incorporation of phosphorus ions from SBF in developed microspheres shells.

The phosphorus tetrahedra can be linked together into chains and/or rings. Structural order in the phosphate systems can be described using the same Q^n terminology, where n is the number of bridging oxygens per P atom. Unlike silicon, which can occur in five different units, the [PO₄] tetrahedra present a double bounding P=O [75], so only four phosphorus units can exist in oxide systems. The ³¹P MAS-NMR spectra of the immersed samples are presented in figure 24. The ³¹P MAS-NMR spectra of all samples immersed in SBF show broad and slightly asymmetrical resonance lines.



Fig.24. The ³¹P MAS NMR spectra of microsphere samples after 48h SBF immersion

The slight asymmetry of the peaks indicates the presence of two resonance lines, Q^1 and Q^2 type, which could be due to the different environment around the P atoms for all the samples. The line broadness is caused by distortion of the network around phosphorus atoms reflecting less crystallinity of developed layers. The position, linewidth and integrated areas of each signal obtained by the deconvolution procedure are summarized in Table XI.

According to the literature, the resonance lines centered at negative chemical shift could be mainly assigned to phosphorus in the orthophosphate ions $(PO_4)^{3-}$ in the hydroxyapatite type phase developed on the particles surfaces [84].

						Tabe	el XI						
Parai Samples	neters	Q ¹ 1 δ(ppm)	I (%)	FWHM (ppm)	Q ¹ 2 δ(ppm)	I (%)	FWHM (ppm)	Q ² 1 δ(ppm)	I (%)	FWHM (ppm)	Q ² 2 δ(ppm)	I (%)	FWHM (ppm)
80Si20Al	SBF 48h	-5.9	21.2	5.9	-10.4	76.2	14.3	-10.7	2.6	3.3	-	-	-
70Si30Al	SBF 48h	-6.5	2.3	4	-8.9	30.5	10.6	-12.2	64.7	17.2	-15.5	2.5	7.5
70Si20Al10Y	SBF 48h	-3.9	4.3	2.9	-9.7	51	5.9	-15	40.3	16.4	-16.1	4.4	3.5

Tabel XI

The results of the deconvolution of the spectra show an increase in the number of orthophosphate units on the surface of the microspheres during 48h, due to the formation of the reaction layer rich in phosphorus. The structural changes appeared after SBF immersion of the microspheres, are due to the chemical reactions with SBF and also to the deposition on the microspheres surface of ions like calcium and phosphorus, from the SBF, and form a hydroxyapatite like phase. This nanostructurated layer, which can be seen in TEM images (Fig. 20b) and can not be detected by X-ray diffraction due to the nanocrystalls size, it is not developed uniform on the microspheres surface.

Conclusions

Aluminosilicate samples prepared by sol-gel and spray drying methods are well-defined particles with spherical shape with a diameter of less than 20 µm with no visible pores on surfaces.

After immersion in SBF the silica network of all samples is much depolymerized as results of oxygen bonded replacement by OH terminal groups.

The environment of aluminum is complete changed by immersion in SBF, the same two types of aluminum tetra- and hexacoordinated are present like in as prepared samples but now their environments are quite distorted. The amount of tetracoordinated aluminum increase for all the samples and this fact might indicate integretion of aluminum in developed nanocrystalline layers on the microspheres surface as a consequence of the hydration during SBF immersion and also due to the presence of Ca and P ions. The results have been included in the paper *The SBF influence on structural properties of aluminosilicates microspferes* [87].

Final conclusions

Silica and aluminosilicate samples prepared by sol-gel and spray drying methods are non crystalline, well-defined particles, with spherical shape and a diameter of less than 20 µm with no visible pores on surfaces. The X-ray diffraction patterns show an amorphous structure for as prepared samples. The aluminum effect on silica network polymerization as well to the phase separation in the silica matrices, as a precursor of mullite phase, is supported by the ²⁹Si and ²⁷Al MAS NMR data. The high temperature heat treatments of silica microspheres lead to the development of crystobalite nanocrystals, initially on their surfaces. In the case of aluminosilicate microspheres the crystobalite nanocrystals development is preceded by the appearance of the mullite crystals. The studied microspheres are stable from morphological point of view, as far they remain noncrystalline or contain small amounts of nanocrystals, but are broken when they became highly crystalline.

Aluminosilicate samples with yttrium, prepared by a combined sol-gel and spray drying method, are well-defined particles with spherical shape and a diameter of less than 20 μ m with no visible pores on surfaces. The X-ray diffraction patterns show an amorphous structure but some

features for yttrium containing samples support the small yttrium silicate nuclei development. The presence of Q^0 species in aluminum silicate indicate that a part of the silicons are not incorporated into the polymerized silica matrix. The aluminum ions are mainly hexacoordinated in both samples like in disordered phylosilicates. After substitution with yttrium partially Si-O-Si depolymerisations take place because a fraction of these atoms are localized near silicon tetrahedra. Yttrium presence does not affect to much the distribution of aluminum sites indicating that yttrium it is integrated in the structure of formed phylosilicates phases and its dissolution will be comparable with that coresponding to this type of layered silicates.

After immersion in SBF the silica network of all samples is much depolymerized as results of oxygen bonded replacement by OH terminal groups. The environment of aluminum is complete changed by immersion in SBF, the same two types of aluminum tetra- and hexacoordinated are present like in as prepared samples but now their environments are quite distorted. The amount of tetracoordinated aluminum increase for all the samples and this fact might indicate integretion of aluminum in developed nanocrystalline layers on the microspheres surface as a consequence of the hydration during SBF immersion and also due to the presence of Ca and P ions and aluminum.

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