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SYNTHESIS OF SILICA XEROGELES BASED ON TEOS AND APTES PRECURSORS AS SORBENTS FOR BIOLOGICALLY ACTIVE SUBSTANCES

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Co-polycondensation products (xerogels) of 3-aminopropyltriethoxysilane (APTES) and 3-aminopropyl-tris(2-hydroxypropoxy)silane (APT-PGL) with tetraethoxysilane (TEOS) were obtained by sol-gel method in aqueous medium, in which APTES and APT-PGL play dual role both as co-monomers and catalysts for hydrolysis and co-condensation reactions. APT-PGL was synthesized by interaction of APTES and propylene glycol at their molar ratio of 1 to 3. The properties of the resulting xerogels were compared with TEOS xerogels synthesized by the known Stöber method using water ammonia as a catalyst. X-ray diffraction phase analysis has shown presence in the synthesized xerogels amorphous halos characterizing different degrees of short-range order in the samples. The SEM data also showed a difference in the morphology of the resulting xerogels. Sodium diclofenac was deposited on xerogels from ethanol solution. The cumulative percentage of the drug desorption from the composite xerogels depends on their morphology.

Ref. 16, tabl. 1, fig. 6.

Key words: xerogels, tetraethoxysilane, 3-aminopropyltriethoxysilane, catalysts, co-condensation.

1.Introduction

In the last two decades researches on synthesis and biomedical application of silicon-based particles (nano-, mesoparticles, mesoporous silica nanoparticles) were greatly increased, that can be explained by their fundamental characteristics such as size, high surface area, low density, adsorption capacity, capacity for encapsulation, biocompatibility and low toxicity.

In particular, their use for drug delivery allows overcoming the shortcomings of already known drug delivery systems, since the particles can be used as carriers of various drugs (anti-inflammatory, antitumor, antibiotics) in oral and transdermal application. In addition, they are able to prolong drug therapeutic action, increase the solubility of poorly soluble hydrophobic compounds, amorphize crystalline drugs and, thus, regulating their release profile [1-5].

A classical sol-gel method for obtaining spherical and monodisperse silica particles widely uses the Stöber method [6], in which silica xerogels are obtained from tetraethoxysilane (TEOS) or its homologue series by alkaline hydrolysis in alcohol-water medium and water ammonia as a catalyst. This method was the basis for obtaining particles of various sizes and shapes, in particular, synthesis of silica-based ordered mesoporous particles MCM41 [7] was developed based on TEOS in the presence of a surfactant (cetyltrimethylammonium bromide) in an alkaline medium. These mesoporous materials form a unique, homogeneous pore morphology with hexagonal and cubic pores, and are one-dimensional pore system. The use of another surfactant (poly(alkylene oxide) triblock copolymer) led to the synthesis of silica nanoparticles with hexagonal pores SPA15 [8].

Since the discovery of these particles, the methods for obtaining particles have been intensively studied and developed, allowing varying the size, porosity, shape of particles and pores, modifying them with various functional groups, and the fields of their application have been specified and expanded. An amine derivative of TEOS - 3-aminopropyltriethoxysilane (APTES) is widely used for modifying silica particles of Stöber types, series MCM41 and SPA15 [9–12].

In one of the first studies on the morphology and properties of particles obtained from TEOS and APTES [13], the synthesis was carried out under the conditions of the Stöber reaction. Two options for introducing APTES into particles were taken into consideration: a) joint hydrolysis and further condensation of TEOS and APTES mixture, b) first, complete TEOS hydrolysis, then APTES was added to the reaction mixture for coating colloidal silica particles. The issues of polymer yield and APTES percentage incorporation into particles were studied. Organo-silica spheres synthesized with APTES and TEOS equal amounts were found to contain as much as 37%

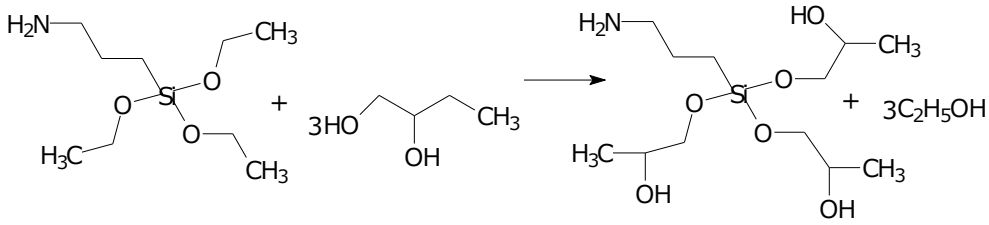
of the total APTES amount. APTES was used both as a catalyst and a co-monomer in the reaction with vinyl, allyl derivatives of TEOS in an aqueous medium in presence of a surfactant [14]. At the content of 72 *mol%* APTES in the reaction mixture, only 10 *mol%* was determined in the particles. The most detailed self-catalyzed synthesis of TEOS and APTES was studied in [15], where the reaction is carried out in a water-alcohol mixture at a wide TEOS/APTES molar ratio (0.1, 1, and 2). The authors explain the low yield of particles (maximum up to 24.5% at a ratio of 1/1, reaction time: 24 hours by the fact that very small particles are not separated during centrifugation and a larger fraction of the Si-containing species remained in the particle suspensions.

Despite a significant number of papers concerning modification of silica particles with APTES, the use of APTES as both the catalyst and co-monomer has not been widely studied. There is still no single platform which can predict the dependence of the final composition on the initial recipe of TEOS-APTES ratios, since so many factors affect the process.

We have synthesized and studied silica xerogels based on TEOS-APTES and TEOS-APT-PGL precursors at the same molar ratio in hydrolysis and co-condensation reactions (APT-T-H and APT-PGL-T-H, respectively), where both reactions are catalyzed by APTES or APT-PGL amine groups. We also synthesized and studied the TEOS-based silica xerogel according to Stöber method (TEOS-H), and the APTES hydrolysate in the form of a powder (ARTES-H).

2.Results and discussions

APT-PGL (3-aminopropyl-tris(2-hydroxypropoxy)silane) was synthesized from APTES by replacing the ethoxy groups ($-OCH_2CH_3$) with 2-hydroxypropoxy groups ($-OCH_2CH(OH)CH_3$).



With complete replacement of ethoxy groups in APTES by 2-hydroxypropoxy groups, the main changes in the FTIR spectrum occurs concerning the absorption bands of ethoxy groups (Fig.1).

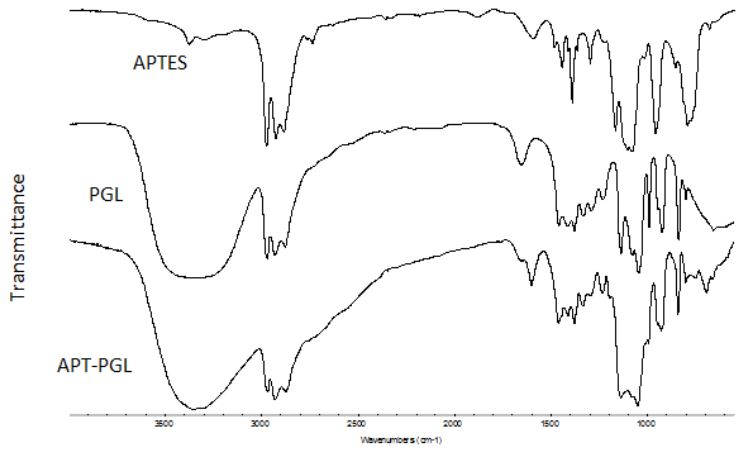


Fig. 1. FTIR spectra of APTES, PGL and APT-PGL

FTIR spectrum of APTES coincide with known one [16] and exhibits the characteristic bands (ν, δ cm^{-1}): 3375 νas and 3295 νs (N–H), 2974, 2927 νas CH (CH_3) and CH (CH_2); 2885 νs CH (CH_3), 1593 ν vibration (NH_2), 1410 δ (Si-CH_2), 1390 δ (CH_3), 1366 and 1296 δ (CH_2), 958 (CH_3 rocking) and 793 νas (Si-O_4).

In APT-PGL spectrum (Fig.1) a wide band 3000-3700 cm^{-1} appears in the ν (OH) region, and all absorption bands characterizing the ethoxy group (1390, 1167, 959, and 793) all together disappear. The 991 cm^{-1} band of PGL, which is attributed to C–O in -CH_2OH, is missing, since this group changes into -CH_2-O-Si- group.

^{1}H and ^{13}C NMR spectra also confirm the structure of the synthesized APT-PGL.

^{1}H NMR spectrum, δ, ppm (Hz): 0.59-0.79 m (2H, CH_2); 1.19 (d1 9H, J 6.5, 3CH_3); 1.61-1.8 (m 2H, CH_2); 2.7-2.9 (m 2H, CH_2); 3.48 (3H, dd, J = 11.6 and 6.8 CH_2); 3.58 (3H, dd, J = 11.6 and 4.1 CH_2); 3.92 (3H, dkd, J = 6.8, 6.5 and 4.1 (CH); ^{13}C NMR spectrum, δ, ppm: 7.4 (SiCH_2), 13.9 (CH_2), 15.1 (CH_3), 20.5 (NCH_2), 63.7 (OCH_2), 65.0 (CH).

Fig. 2 shows the reaction scheme of hydrolysis, condensation and co-condensation of TEOS and APTES precursors:

The FTIR spectra of APT-T-H and APT-PGL-T-H silica xerogels are almost identical have broad bands of OH groups at 3200-3600 cm^{-1} region, two peaks of NH in the region 1551 and 1638 cm^{-1}, the latter one attributes to adsorbed water, and all vibration bands at 900-1200 cm^{-1} refer to the complete hydrolysis of these co-monomers (920 and 1113 cm^{-1}).

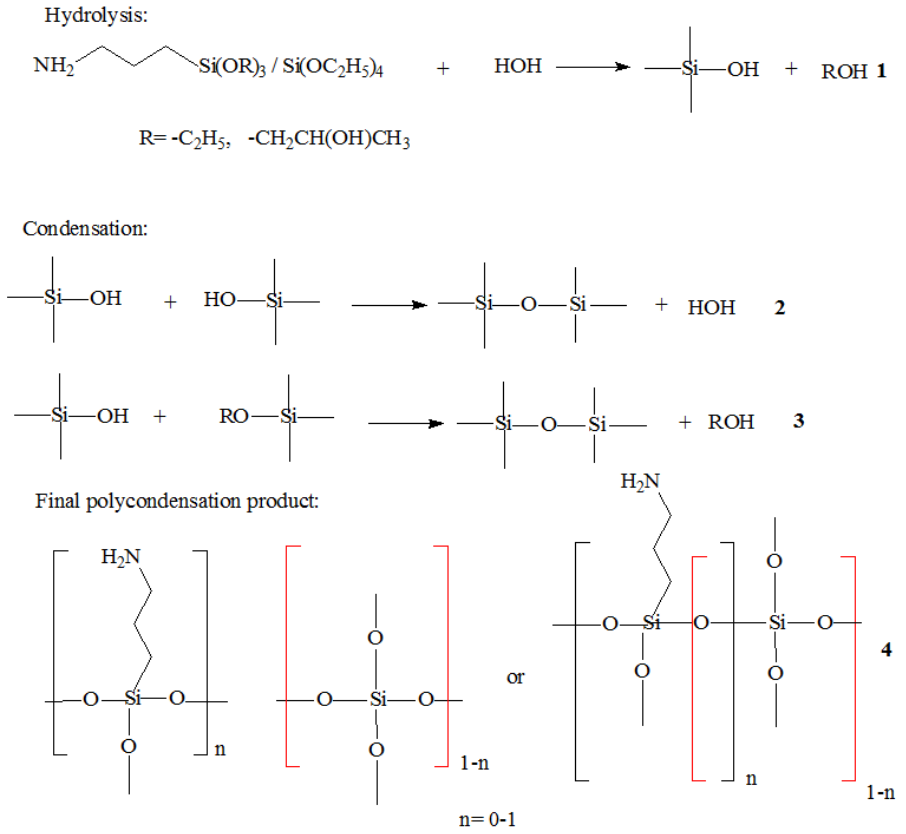


Fig. 2. Reaction scheme of hydrolysis and condensation of TEOS and APTES precursors.

Fig. 3 shows X-ray diffraction patterns of the synthesized silica xerogels and the composite xerogels with deposited DCF. For comparison in all figures the X-ray diffraction pattern of the DCF crystal structure are presented. ARTES-H is presented as a double-hump compound with amorphous halos peaking at 2θ=8.0° and 2θ=22.3°. The amorphous halo of this shape may be due to the presence of two short-range order regions in the sample, due to the location of -Si-O-Si- structures, as well as the close location of amine and hydroxyl groups.

The 2θ =22.3° region of the -Si-O-Si- structures closely coincides with the sample (TEOS-H), the diffraction pattern of which is an amorphous structure with a wide halo, with a maximum at 2θ =23.2°.

On the diffraction patterns of samples APT-T-H and APT- PGL- T-H the amorphous halos of APTES -H are broadened however in the latter sample to a lesser extent, since traces of the second maximum from ARTES -H (2θ=8.0°) are more distinct here.

In all samples the presence of DCF did not change the appearance of the diffractograms, i.e. DCF is incorporated into the structures.

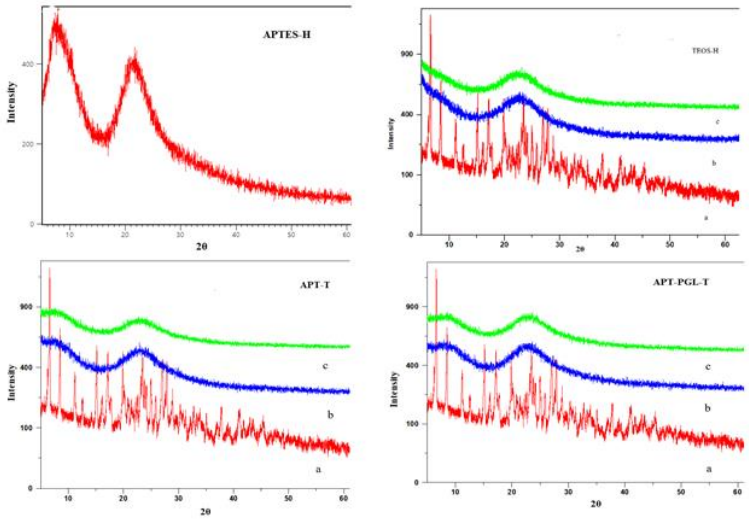


Fig. 3. XRD patterns of APTES-H, TEOS-H, APT-T-H and APT-PGL-T-H:
a) - DCF, b) samples; c) samples +DCF

It is known that in truly amorphous materials no peaks are present in the diffraction patterns. Amorphous halo can be observed if some degree of local orders or defined repeating motif is present within the structure. The absence of DCF reflections on the diffraction patterns of the samples may be due to the fact that either its amount is insufficient to obtain a visible crystal reflection on the diffraction patterns, or at a concentration of the drug in these composites (about 3%) the adsorbed drug undergoes amorphizing.

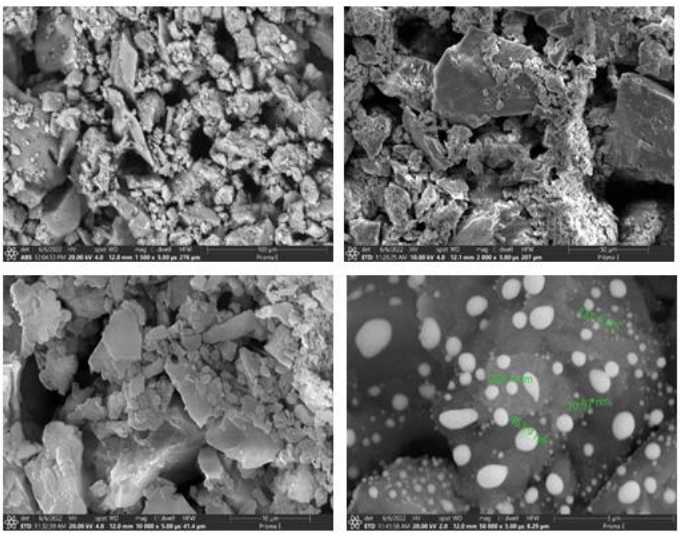


Fig 4. SEM images of the APT-T-H sample

In the sample APT-T-H (Fig. 4) is present a set of large 15-50μ particles, and a larger number of 1-5μ particles, which are connected into conglomerates. There is a small fraction of particles with 20–500 *nm* sizes.

In APT-PGL-T-H SEM image (Fig. 5) also is present a set of large 5-50μ particles, and a greater number of small particles from 50 *nm* size and above, which are combined into associate conglomerates.

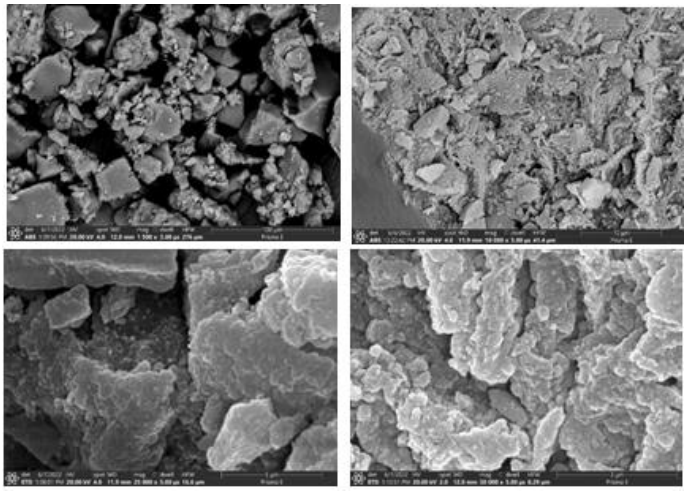


Fig 5. SEM images of the APT-PGL-T-H sample

SEM elemental analysis data showed little differences in silica xerogels composition (Table).

Table Elemental analysis data obtained by SEM

Element	Atomic %		Weight %	
	APT-T-H	APT-PGL-T-H	APT-T-H	APT-PGL-T-H
C	20.8	24.5	14.0	16.7
N	6.1	7.3	4.8/4.9*	5.8/5.9*
O	49.8	45.3	44.6	41.1
Si	23.4	22.9	36.7	36.4

* Determined by Dumas-Pregle microanalysis method

The calculation of the yield of the copolymer, assuming complete hydrolysis of both comonomers and their condensation, showed that the yield is 66-67%, and the content of aminopropyl units can be calculated by elemental microanalysis of nitrogen content in the samples of co-polymers. In sample

with 5.9 *wt.% N*, aminopropyl units in the copolymer make up 56.57 *wt %* or 42.15 *mol %*, that is n~0.42, 1-n~0.58.

The difference in the morphology of xerogels obviously affects the release of adsorbed DCF from powders (Fig 6).

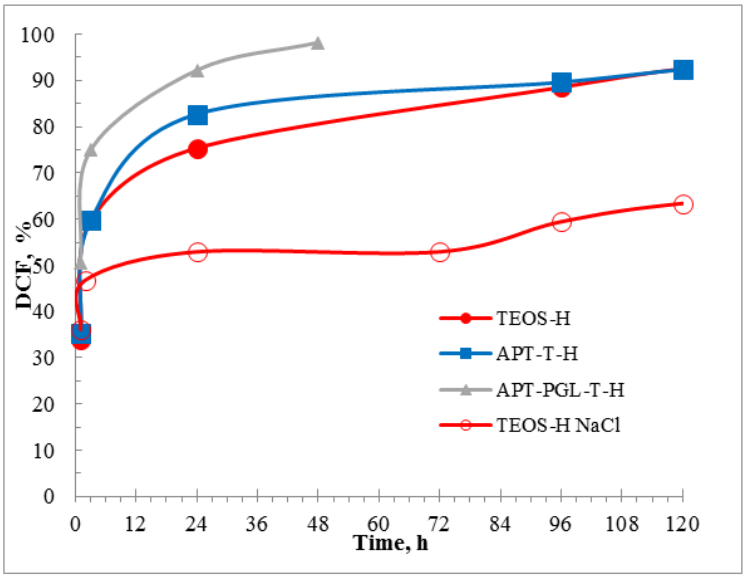


Fig 6. Cumulative release of DCF from composite xerogels

From the powder with adsorbed PGL the drug desorbs in a larger amount in the first hours, which is a manifestation of the difference in morphology, however, the difference between TEOS and TEOS-APTES based samples is not so significant. The data obtained show prolong action of DCF release from the compositions which can be proposed as drug for oral administration, since xerogels as carriers of the drug are not toxic. We are now expanding the range of biologically active substances and drugs for depositing them in the synthesized silica xerogels and studying the kinetics of their release.

Conclusions

The difference in the morphology of silica xerogels obtained using APTES or APT-PGL precursors is probably due to the presence of ethanol or propylene glycol in the reaction system, which are released as a result of the hydrolysis of APTES and APT-PGL, respectively. Since ethanol can be easily removed from the system throughout the process, however, PGL remains in the system and can have an impact on the structure of the aqueous system in a certain way. In turn, APTES and APT-PGL can also be structured in an aqueous solution, and this structuring is stable, which is confirmed by the APTES diffraction pattern of the hydrolyzate (powder). Amorphous halos in the diffraction pattern may be due to the fact that when water is removed from the APTES hydrolyzate

(xerogel), the structured regions don't break down and remain in the dry xerogel. This is quite consistent with the concept of the formation of five-six-membered APTES cycles in an aqueous solution and the preservation of such cycles on different surfaces [15, 16].

The yield of xerogels is only up to 65% may be the result of the loss of fine particles during the washing and centrifugation of APT-T-H and APT-PGL-T-H powders, as well as that 24 hours are not sufficient for proceeding a complete hydrolysis-condensation cycle.

A comparison of the kinetics of DCF release from xerogels shows a significant effect of morphology on the cumulative release, which, of course, is associated with the characteristics of the samples - porosity, pore size, location of amine groups (on the particle surface or in pores), and, accordingly, the mechanism of the drug binding to xerogel particles. This is the subject of further research.

3. Experimental

3.1 Materials.

Tetraethoxysilane (TEOS,) 3-aminopropyltriethoxysilane (APTES), 1,2 propylene glycol (PGL), sodium diclofenac (DCF) were purchased from Aldrich and used as received.

3.2. Equipment

FTIR spectra were recorded on FTIR Avatar Nicolet spectrometer. ^{1}H and ^{13}C NMR spectra were recorded: on Varian Mercury-, ^{1}H 300.088, ^{13}C 75.466 MHz, Temp=30.0, solvent D_2O.

SEM images of the powders were obtained using Prisma E SEM (ThermoFisher). X-ray diffraction patterns were recorded by a EMPYREAN, Panalytical Company (45kV,40 *mA*) diffractometer using Cu-Kα radiation.

In vitro drug release was determined by UV spectrophotometry (Cary 100 UV-Vis Spectrophotometer) at wavelength λ_{max} 275 *nm*. Three samples of 0.03-0.04 *g* of each powder were placed in Eppendorf tubes and filled with 2 ml of saline (0.9% NaCl) or phosphate buffer solution with pH-6.86 ($Na^+/K^+/H_2PO_4$). After appropriate time intervals, the liquid was withdrawn for DCF determination, and a fresh portion of the solutions was added into the test tubes. The percentage of released DCF was calculated as an average of 3 measurements, relative to the amount of DCF in the sample.

3.3. Samples preparation

Synthesis of APT-PGL: 3-aminopropyl-tris(2-hydroxypropoxy)silane, $C_{12}H_{29}NO_6Si$, MM 311.4 .

40g (0.526 *mol*) PGL is added to 38.8 *g* (0.176 *mol*) APTES in a three neck flask equipped with Liebig condenser, the mixture is heated under constant stirring at 110-115 ^{0}C, and after 30 minutes the formed ethanol starts distilled. After an hour and a half from the beginning of the process, small

particles appear in the flask, and after cooling - the whole mass solidified.

APT-PGL is a slightly moist powder that in air and light transforms into liquid. To understand whether this is a property of the product itself (its physical state) or its hydrolysis occurs due to air moisture, the IR spectra of the initial powder, the powder partially in liquid and completely liquid were taken (after 30 and 60 minutes of staying in air, respectively).

Changes in spectra were revealed only in completely liquid form – an appearance of the absorbance band at 1649 cm^{-1} that can be attributed to adsorbed water (usually in region 1635-1650 cm^{-1}) [20-22]. The powder is stored in a dark tightly closed container in a cool place and is used as is.

Synthesis of APTES-H: To 9.5 g (0.043 *mol*) of APTES 7 ml (0.39 *mol*) water is added in a beaker, stirred on a magnetic stirrer, and after 2-3 minutes the pH of the solution measured is 10-11. After 1 hour of stirring, particles appear, after 2 hours from the start of the process, the mixture is heated to 60 ^0C for 30 minutes. A gel-like mass immediately forms, which broke down upon stirring. After 5 hours, the pH dropped to 8. The entire mass containing gel-like particles in the liquid is left in air to evaporate water, and then the wet mass is dried in a vacuum oven (temperature of 40-45 °*C*, drying pressures 90-100 *mm* Hg). The resulting product is a white powder, with melting point above 300 ^0C, easily soluble in water. Product yield made up 4.46g.

Synthesis of TEOS-H: Samples with TEOS were obtained by aqueous hydrolysis in the presence of a catalyst (water ammonia) without using alcohol (Stöber reaction).

28 *ml* (26.6 *g*, 0.13 *mol*) TEOS is mixed with 22.8 *g* (1.26) water about 5 minutes under magnetic stirring and then 7.2 *ml* of 10 % NH_4OH solution is added, the mixture is stirred for 3 hours, and then left for 24 hours at room temperature. After 24 hours - the whole mass transformed into a soft gel, which, when stirred, broke down into small pieces. The sample is dried at 100 ^0C until reaching constant weight. The resulting product is a white powder with melting point above 300 ^0C. Yield of the powder- 9.0 *g*.

Synthesis of APT-T-H: 2.8 *g* (0.0135 *mol*) APTES is mixed with 10 *ml* water within 1-2 minutes (pH of the mixture is 12), then 9.8 *g* TEOS (0.047 *mol*) and 10 *ml* water is added. The reaction mixture turned white and after 35 minutes the viscosity increases, small particles form, and after another 15 minutes the whole mass solidified (pH is 10). After leaving the mixture for 24 hours the wet powder is rinsed twice with water, and dried in a vacuum oven (40-45 °*C*, 90-100 *mm Hg*). The resulting product is a white powder, with melting point above 300 ^0C. Yield of the powder- 4.02 *g*.

Synthesis of APT-PGL-T-H: 4.2g (0.0135 *mol*) APT-PGL is mixed with 10 *ml* of water (pH of the mixture is 12), then 9.8 *g* of TEOS (0.047 *mol*) and 10 *ml* of water is added. The reaction mixture became cloudy, after 30 minutes the viscosity increased (pH -12), and after 1.5 hours the whole mass

transformed into a soft gel. After leaving the mixture for 24 hours the wet powder is rinsed twice with water, and dried in a vacuum oven (40-45 °*C,* 90-100 *mm Hg*). The resulting product is a white powder, with melting point above 300 ^{0}C. Yield of the powder- 4.04 *g*.

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TEOS-Ի և *APTES*-Ի ՊՐԵԿՈՒՐՍՈՐՆԵՐԻ ՀԻՄԱՆ ՎՐԱ ՍԻԼԻՑԻՈՒՄԻ ՔՍԵՐՈԳԵԼՆԵՐԻ ՍԻՆԹԵԶԸ ՈՐՊԵՍ ԿԵՆՍԱԲԱՆՈՐԵՆ ԱԿՏԻՎ ՆՅՈՒԹԵՐԻ ՍՈՐԲԵՆՏՆԵՐ

Զ. Մ. ՖԱՐՄԱԶՅԱՆ, Մ. Լ. ԱԹԱԲԵԿՅԱՆ, Է. Հ. ՀԱԿՈԲՅԱՆ, Ա.Գ. ՇԱՀԽԱԹՈՒՆԻ, Է. Ռ. ԱՌԱԿԵԼՈՎԱ, Ս. Լ. ԳՐԻԳՈՐՅԱՆ, Ս. Գ. ԳՐԻԳՈՐՅԱՆ, Վ. Օ. ԹՈՓՈՒԶՅԱՆ

Զոլ-գել մեթոդով ջրային միջավայրում սինթեզվել են քսերոգելներ տետրաէթօքսիսիլանի հետ (TEOS) 3-ամինոպրոպիլտրիէթօքսիսիլանի (APTES) և 3-ամինոպրոպիլ-տրիս(2-հիդրօքսիպրոպօքսի)սիլանի (APT-PGL) փոխացդեցու-թյամբ, վերջիններս կատարում են երկակի ֆունկցիա և՛ որպես համամոնոմեր, և՛ որպես հիդրոլիզի և համապոլիկոնդենսացիայի ռեակցիաների կատալիզատորներ: APT-PGL-ը ստացվել է APTES-ի և պրոպիլեն գլիկոլի փոխազդեցությամբ՝ նրանց 1/3 մոլային հարաբերակցությամբ: Ուսումնասիրվել են ստացված քսերոգելների հատկությունները դրանք համեմատելով տետրաէթօք-սիսիլանի (TEOS) քսերոգելների հետ, որոնք սինթեզվել են հայտնի Stöber-ի մեթոդով, օգտագործելով ամոնիակաջուրը որպես կատալիզատոր:

Ռենտգենյան ֆազային անալիզը ցույց է տվել սինթեզված քսերոգելներում ամորֆ հալոների առկայությունը, որոնք բնութագրում են նմուշների կարճ հեռահարության տարբեր աստիճաններ: ՍԷՄ-ի տվյալները ցույց են տվել ստացված քսերոգելների մորֆոլոգիայի տարբերությունը:

Դիկլոֆենակ նատրիումը (DCF) նստեցվել է քսերոգելների վրա էթանոլային լուծույթից: Դեղի անջատման կուտակային տոկոսը կախված է քսերոգելների մորֆոլոգիայից:

СИНТЕЗ КСЕРОГЕЛЕЙ НА ОСНОВЕ ПРЕКУРСОРОВ ТЭОС И АПТЭС В КАЧЕСТВЕ СОРБЕНТОВ БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ

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Синтезированы продукты со-поликонденсации (ксерогели) 3-аминопропилтриэтоксисилана (APTES) и 3-аминопропил-трис-(2-гидроксипропокси)силана (APT-PGL) с TEOS золь-гель методом в водной среде, где APTES и APT-PGL являются и со-мономерами, и катализаторами реакций гидролиза и со-конденсации. APT-PGL получали взаимодействием APTES и пропиленгликоля при их мольном соотношении 1 к 3. Исследованы свойства полученных ксерогелей в сравнении с ксерогелями тетраэтоксисилана (TEOS), синтезированными по известному методу Штёбера с использованием аммиачной воды в качестве катализатора. Рентгенофазовый анализ показал наличие в синтезированных ксерогелях аморфных гало, характеризующих

разную степень ближнего порядка в образцах. Данные СЭМ также показали различие в морфологии образцов.

Диклофенак натрия (DCF) осаждали на ксерогели из этанольного раствора. Кинетика десорбции и кумулятивный процент выхода препарата зависят от морфологии ксерогелей.

REFERENCES

[1] *Hoffmann F., Cornelius M., Morell J., Froba M.*- Silica-based mesoporous organic–inorganic hybrid materials // Angew. Chem. Int. Ed., 2006, v. 45(20), p.p. 3216 – 3251.

[2] *Simovic S., Ghouchi-Eskandar N., Moom Sinn A., Losic D., Prestidge C.* - Silica Materials in Drug Delivery Applications // Curr.ent Drug Discov. Technol., 2011, 8, 250-268

[3] *Mamaeva, V., Sahlgren C., Lindén M.* - Mesoporous silica nanoparticles in medicine—Recent advances // Adv. Drug Delivery Rev., 2013, v. 65(5), p.p. 689-702.

[4] *Şen Karaman D., Kettiger H.* Silica-based nanoparticles as drug delivery systems, in book Inorganic Frameworks as Smart Nanomedicines/ editor A.M. Grumezescu, Elsevier, 2018, p.p. 1–40.

[5] *Li T., Geng T., Md A., Banerjee P., Wang B.*- Novel scheme for rapid synthesis of hollow mesoporous silica nanoparticles (HMSNs) and their application as an efficient delivery carrier for oral bioavailability improvement of poorly water-soluble BCS type II drugs //Colloids Surf. B, 2019, v.176 p.p.185-193.

[6] *Stöber W., Fink A., Bohn E.* - Controlled growth of monodisperse silica spheres in the micron size range //J. of Colloid Interface Sci., 1968, v.26(1), p.p. 62–69.

[7] *Beck J. S., Vartuli J. C., Roth W. J., Leonowicz M. E., Kresge C. T., Schmitt K. D., Schlenker J. L.* - A new family of mesoporous molecular sieves prepared with liquid crystal templates //J. Am. Chem. Soc., 1992, v. 114(27), p.p. 10834–10843.

[8] *Zhao D.* - Triblock copolymer syntheses of mesoporous silica with periodic 50 to 300 Angstrom pores //Science, 1998, v.279(5350), p.p. 548–552.

[9] *Qian K. K., Bogner R. H.* - Application of mesoporous silicon dioxide and silicate in oral amorphous drug delivery systems //J.Pharm. Sci., 2012, v.101(2), p.p. 444–463.

[10] *Maleki A., Kettiger H., Schoubben A., Rosenholm J. M., Ambrogi V., Hamidi M.* - Mesoporous silica materials: From physico-chemical properties to enhanced dissolution of poorly water-soluble drugs //J.Control.Release, 2017, v.262, p.p. 329–347.

[11] *Dadej A, Woźniak-Braszak A, Bilski P, Piotrowska-Kempisty H, Józkowiak M, Geszke-Moritz M, Moritz M, Dadej D, Jelińska A.* - Modification of the release of poorly soluble sulindac with the APTES-modified SBA-15 mesoporous silica //Pharmaceutics, 2021 Oct 15; 13(10): p.p. 1693.

[12] *Szegedi A., Popova M., Goshev I., Klébert S., Mihály J.* - Controlled drug release on amine functionalized spherical MCM-41 //J.Solid State Chem., 2012, v.194, p.p.257–263.

[13] *Van Blaaderen A., Vrij A.* - Synthesis and characterization of monodisperse colloidal organo-silica spheres //J. Colloid Interface Sci., 1993, v.156(1), p.p.1–18.

[14] *Raphael M. Ottenbrite and Jason S. Wall.* - Self-catalyzed synthesis of organo-silica nanoparticles // J. Am. Ceram. Soc., 2000, v.83(12), p.p.3214–15.

[15] *Chen S., Hayakawa S., Shirosaki Y., Fuji, E., Kawabata K., Tsuru K., Osaka, A.* - Sol-gel synthesis and microstructure analysis of amino-modified hybrid silica nanoparticles from aminopropyltriethoxysilane and tetraethoxysilane // J. Am.Ceram. Soc., 2009, v.92(9), p.p. 2074–2082.

[16] *Ishida H., Chiang C., Koenig J.L.* - The structure of aminofunctional silane coupling agents: 1. γ-Aminopropyltriethoxysilane and its analogues // Polymer, 1982, v.23(2), p.p.251–257.