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Design, synthesis and morphology of the organosiloxane hybrid particles based on L-aspartic acid derivatives

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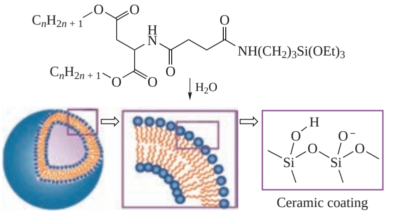
Dialkyl esters of siloxane derivatives of L-aspartic acid with various length of alkyl groups were synthesized. Subjected to sol–gel process, these derivatives form particles, whose stability, size and morphology were revealed.

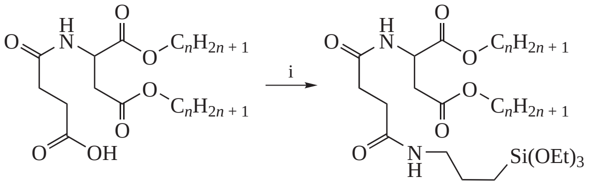


Development of transport systems possessing required physico-chemical and biological properties aimed at the targeted delivery of biologically active compounds remains among important problems of the medicine.[1–4] However, there is a number of drawbacks among existing drug delivery systems, such as toxicity of the particles based on inorganic complexes and low stability of the organic-based carriers.[5] Vesicular drug delivery systems based on silicon-containing dialkylamines have been proposed to solve these problems due to their ability to form bilayer vesicles coated with a polymeric siloxane chain called 'cerasome' in an aqueous medium.[6–9]

The synthesis of dialkyl *N*-(1,4-dioxo-8-triethoxysilyl-5-aza-octyl)-L-asparates with alkyl groups of various length as new cerasome-forming lipo amino acids (CFLA) and investigation of physico-chemical properties of these compounds and aqueous dispersions thereof were the purposes of this study. Introduction of the amino acid fragments into the amphiphilic structure increases the stability of the molecule due to additional amide bonds and reduces the possible cytotoxic effect.

The target compounds were prepared from diesters of L-aspartic acid containing succinic acid moiety **1a–d**.[10] Reactants **1** were treated with *N*-hydroxysuccinimide in the presence of DCC, followed by addition of (3-aminopropyl)triethoxysilane (Scheme 1).[†] ^{1}H NMR spectra of products **2a–d** contain signals for the residue of (3-aminopropyl)triethoxysilane and those for the alkyl groups.

To form the CFLA-based cerasomes, compounds **2a–d** were treated with 10% hydrochloric acid in EtOH. The mixture was evaporated on a rotary evaporator, then the film obtained was hydrated with phosphate buffer and sonicated.[‡] To create the polymer network on particle surface, the siloxane groups were exposed to hydrolysis in the presence of acid (sol–gel process). The polymerization of siloxane groups and charge occurrence on bilayer surface followed by spontaneous formation of cerasomes (as the target compounds obtained are amphiphiles with triethoxy-silane in polar head) were the main processes in this method.[11]



1a–d **2a–d**

a $n = 10$ **c** $n = 14$
b $n = 12$ **d** $n = 16$

Scheme 1 *Reagents*: i, DCC, *N*-hydroxysuccinimide, then $H_2N(CH_2)_3$-$Si(OEt_3)$.

Using dynamic light scattering (DLS), the particle size (hydrodynamic diameter) of formed dispersions was defined (Table 1).

Decyl derivative **2a** and dodecyl one **2b** give smaller particle size than the tetradecyl derivative **2c** and hexadecyl one **2d**. As the diameter of particles of **2a**,**b** fits permissible ranges for means of drug delivery to organs and tissues and the volume of

Table 1 Particle size according to DLS.

Compound	Particle diameter/nm	Total monodispersity (%)
2a	140	99
2b	170	96
2c	980	98
2d	1010	97

[†] *Didecyl* N-*(1,4-dioxo-8-triethoxysilyl-5-azaoctyl)-L-asparate* **2a**. Compound **1a** (3.86 g, 7.7 mmol) and *N*-hydroxysuccinimide (0.97 g, 8.5 mmol) in chloroform (100 ml) were stirred for 15 min at room temperature, then DCC (1.75 g, 8.5 mmol) was added. The mixture was stirred for 1 h and filtered. (3-Aminopropyl)triethoxysilane (2.05 g, 9.3 mmol) was added to the filtrate, and the mixture was stirred for 24 h. The solvent was removed *in vacuo*, the residue was washed with hexane. Yield 4.72 g (83%), R_f 0.33 ($CHCl_3$–MeOH, 1:1). ^{1}H NMR, δ: 0.61 (t, 2H, $SiCH_2$), 0.9 (m, 6H, Me), 1.27 (m, 28H, CH_2), 1.30 (m, 9H, Me), 1.63 (m, 4H, $COOCH_2CH_2$), 2.57 [m, 2H, CH_2CH_2COOH (Suc)], 2.94 [m, 6H, CH_2COO (Asp)], 3.28 (m, 2H, CH_2NH), 3.88 (m, 6H, OCH_2), 4.15 (m, 2H, $COOCH_2$). MS (MALDI), *m*/*z*: 716.50 [M$^+$].

Compounds **2b–d** were synthesized similarly.

[‡] *Formation of cerasomes*. To a sample of CFLA (20 mg), 3 ml 10% HCl solution in ethanol was added, the mixture was stirred at 35 °C for 1 h. The solvent was evaporated to form a thin film which was dried for 6 h. The film was hydrated in phosphate buffer pH 7.4. The obtained dispersion was sonicated for 30 min at 45 °C.

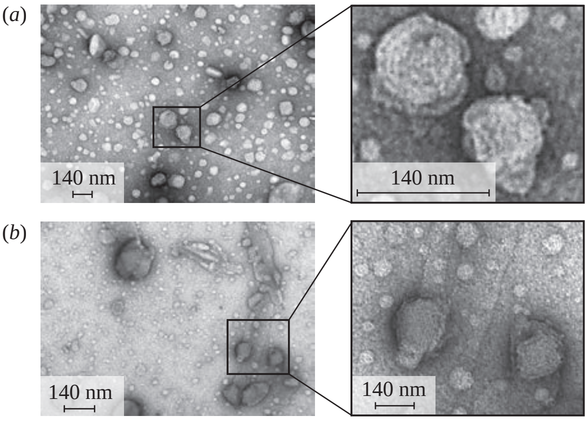


Figure 1 TEM images of cerasomal dispersions based on compounds (*a*) **2a** and (*b*) **2b**.

particles is big enough for large macromolecules encapsulation, therefore, compounds **2a** and **2b** seem to be the more suitable form for perspective drug delivery.

The morphology of the aggregates based on compounds **2a**,**b** was studied by transmission electron microscopy (TEM). Photomicrographs showed the presence of vesicles of spherical shape with a diameter of 50–200 nm (Figure 1). The data correspond to the results of DLS.

To estimate the stability of the cerasomal dispersions, the optical density change was investigated and particle size was determined. The optical density of the dispersion and particle size during storage did not significantly change within 120 days. This indicates a high stability based on the formation of a solid polysiloxane network aggregate surface, which prevents the adhesion and fusion of the particles.

In conclusion, size and stability of the particles formed in a sol–gel process of derivatives of L-aspartic acid esters were defined, the images of spherical cerasomes were obtained by electron microscopy.

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