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Short communication

Effects of formulation and sol-gel synthesis conditions on physical stability and chemical structure of organomodified silica nanoparticles: a screening study

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Introduction

Nanoparticles (NPs) have drawn increasing interest from every branch of medicine as potential carriers for targeted drug delivery in the optimum dosage range providing increased therapeutic efficiency, and at the same time minimizing the side effects. This is especially important in cancer chemotherapy, where patients experience severe side effects that seriously affect the quality of life. However, many factors (i.e. particle size, zeta potential, drug loading, stability, interactions with the biological milieu) influence the overall efficacy of the nanoparticulated drug carriers. Therefore, an in-depth approach is needed to design such formulation, evaluate and understand its biological behavior and predict its possible toxicity and therapeutical effects.

The aim of our study was to screen the effects of preparation procedure and formulation factors (pH, silica precursors ratio) on the physical stability (particle size, polydispersity index, zeta potential) in different relevant media, and the chemical structure of silica and organomodified silica nanoparticles.

Materials and Methods

Materials

Tetraethoxysilane (TEOS) and 3-aminopropyl triethoxysilane (APTES) were purchased from Sigma Aldrich (Germany); Ethanol (96%), Sodium hydroxide and Acetic acid were purchased from Alkaloid AD (N. Macedonia). All other reagents and chemicals used were of analytical grade.

Methods

Previously described sol-gel method was used for the preparation of the silicate nanoparticles (Djurdjic et al., 2018). The process involves hydrolysis and condensation of metal alkoxides ($Si(OR)_4$) such as TEOS, APTES in the presence of mineral acid (e.g., HCl) or base (e.g., NH_3) as a catalyst. Pure TEOS and TEOS/APTES NPs in the ratio of 99:1 were prepared. The physical stability of formulations was tested by diluting the corresponding sample volume of 300 μg NPs with

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an appropriate medium (0.1M HCl, phosphate buffer 4.5 and 7.4) of up to 3 mL and incubating at 37 °C. Appropriate volume (100 μL) was taken 1, 3, 5 and 7 hours after the start of incubation. Particle size (PS), polydispersity index (PDI) and zeta potential (ZP) analysis were performed by dynamic light scattering using the Malvern Zetasizer Nano ZS90 (Malvern Panalytical, UK). Fourier transform infrared spectra were acquired on freeze-dried samples using Nicolet iS10 (Thermo Scientific, USA). Multivariate analysis (SIMCA 14, Umetrics, Sweden) was employed to investigate the possible effects of the formulation and process variables upon the NP chemical structure (FTIR spectra) and in vitro stability of their PS, PDI and ZP.

Results and Discussion

Categorical PCA X&Y models were employed to identify the effects of the independent variables (pH during the sol-gel synthesis of NP, silica precursors TEOS/TEOS-APTES) upon the NP's PS, PDI, ZP stability trends and FTIR spectra. Each model contained two main components explaining (R^2X) 90.8, 98.3, 99.4 and 98.8% of the variations in PS, PDI, ZP and FTIR spectra, respectively. The predictivity coefficient (Q^2) was within satisfactory limits (0.825 – 0.986) for all models. The results revealed that the hydrodynamic diameter of the particles and their stability in pH 7.4 was mainly governed by the silica precursors (TEOS/TEOS-APTES) employed in the formulations, while no significant variations among the formulations in PS stability were observed in pH 1 and 4.5. The PDI of the formulations in all tested media was affected by both the preparation procedure and silica precursors. The stability of ZP at pH 1 was mainly influenced by the silica precursors, while the pH of the preparation procedure mainly affected the ZP stability at pH 7.4. All observed effects were probably due to the surface-oriented amino groups that govern the surface potential of the particles affecting particle growth during synthesis and stability during incubation, and the pH of the sol-gel synthesis process which also affects the silica hydrolysis rate and condensation behavior, thus resulting in noticeable effects on the PS, PDI and ZP (Wu et al., 2013). The SNV derived FTIR data revealed that the position and intensity of the bands at 1549, 1410, 1090, 902 and 770 cm^{-1} were most affected by the silica precursors used in the synthesis procedure, while the pH of the sol-gel synthesis procedure didn't demonstrate any significant effect on the FTIR spectra. The bands at 1090 and 770 cm^{-1} correspond to the antisymmetric and symmetric stretching of the Si-O-Si species from the silica NP matrix and were blue-shifted in the pure SiO_2 matrices. The bands at 1549 and 1410 cm^{-1} originate from the deformation CH2 and NH2 vibrations of the alkylamino chain, which appeared only in the APTES based formulations, while the band at 902 cm^{-1} is associated with the Si-OH and Si-O-R stretching modes (Brinker and Scherer, 2013).

Conclusion

Silica nanoparticles can be prepared by the hydrolysis reaction of TEOS and APTES in ethanol using mineral acid or base as a catalyst using the sol-gel method. In this screening study, using multivariate analysis, we have observed the effects of the silica precursors ratio and pH of the sol-gel synthesis procedure upon the stability patterns of the formulations (PS, PDI and ZP) in different biorelevant media and their surface chemical structure. The generated data pool could be used as a platform for further development and optimization of drug-loaded silica-based nanoparticles.

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