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High-capacity $CaCO_3$ containers: the effect of size on drug loading and interaction with cells

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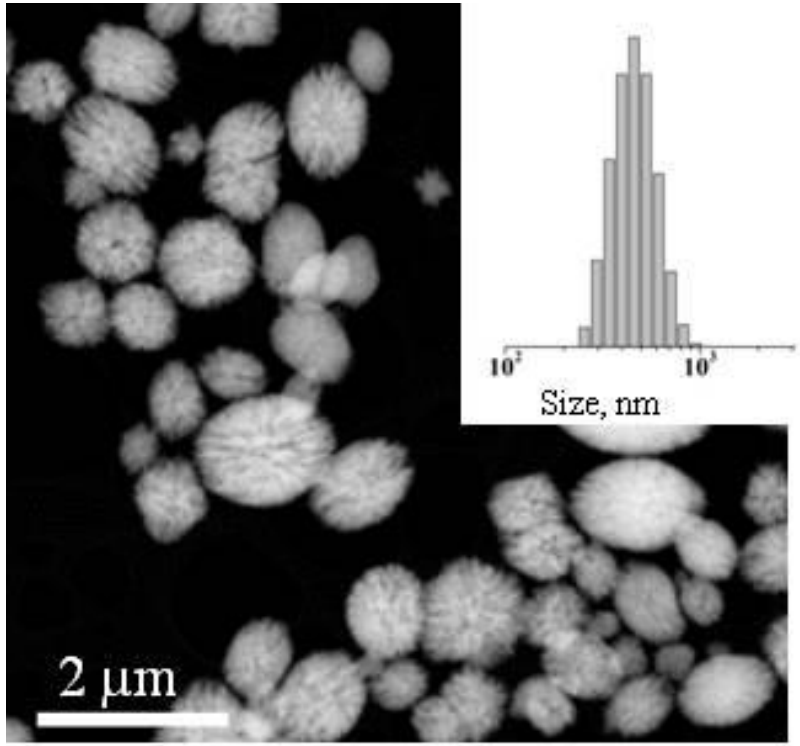
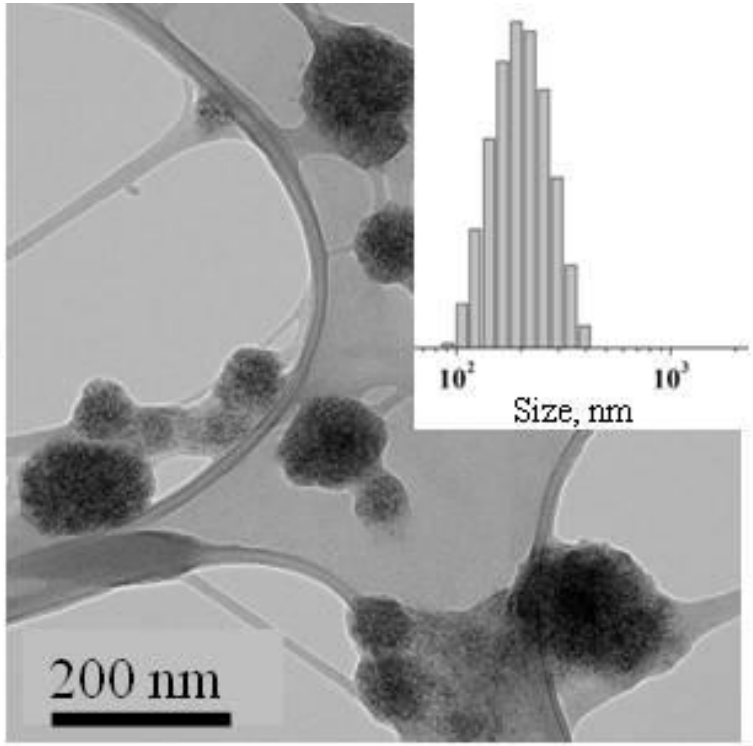
- Series of calcium carbonate particles with sizes of 500 ± 80 nm and 200±90 were obtained by the mass crystallization in aqueous salt solutions by varying the reaction conditions and adding glycerol [1] or combination of polyethylene glycol, polysorbat-80 and cell cultural medium to the reaction volume [2]. $CaCO_3$:Si:Fe nanoparticles of 50±30 nm in diameter were synthesized within the pores of mesoporous silica particles with a subsequent etching out of the template material [3].
- **The crystal structure and polymorphism of the obtained particles were studied, and the influence of the particle size and structure on the efficiency of their loading with an anticancer compound, as well as its release under model conditions at different pH, was determined.**

- [1] Trushina, D. B.; Bukreeva, T. V.; Antipina, M. N. Size-Controlled Synthesis of Vaterite Calcium Carbonate by the Mixing Method: Aiming for Nanosized Particles. *Cryst. Growth Des.* **2016**, *16* (3), 1311–1319.
- [2] Popova, V.; Poletaeva, Y.; Pyshnaya, I.; Pyshnyi, D.; Dmitrienko, E. Designing PH-Dependent Systems Based on Nanoscale Calcium Carbonate for the Delivery of an Antitumor Drug. *Nanomaterials* **2021**, *11* (11).
- [3] Eurov, D. A.; Kurdyukov, D. A.; Boitsov, V. M.; Kirilenko, D. A.; Shmakov, S. V.; Shvidchenko, A. V.; Smirnov, A. N.; Tomkovich, M. V.; Yagovkina, M. A.; Golubev, V. G. Biocompatible Acid-Degradable Micro-Mesoporous CaCO3:Si:Fe Nanoparticles Potential for Drug Delivery. *Microporous Mesoporous Mater.* **2022**, *333* (January), 111762.

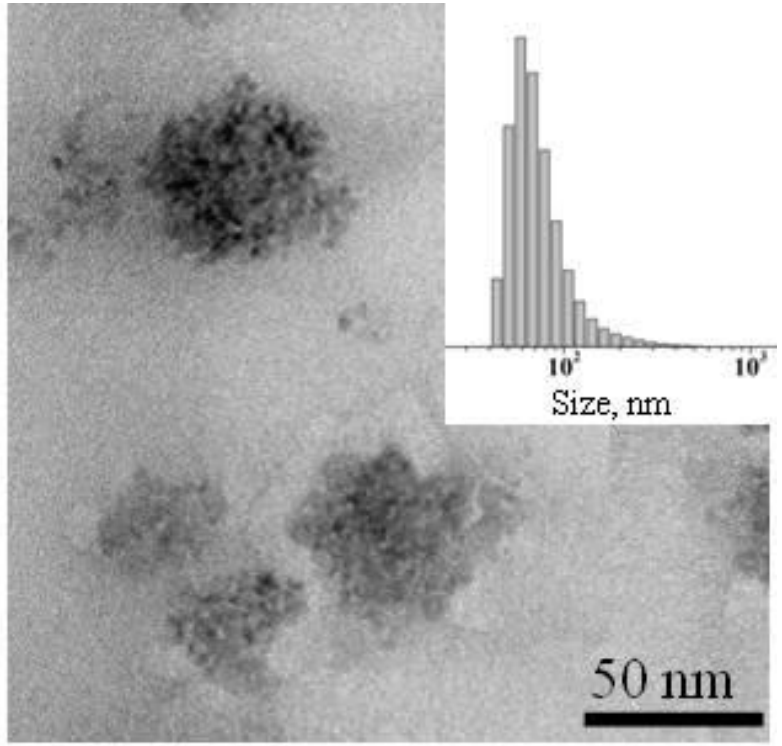
A complete characterization of the particles was carried out using scanning and transmission electron microscopy, X-ray powder diffraction, dynamic and electrophoretic light scattering



$CaCO_3$-500nm



$CaCO_3$-200nm



$CaCO_3$:Si:Fe-50nm

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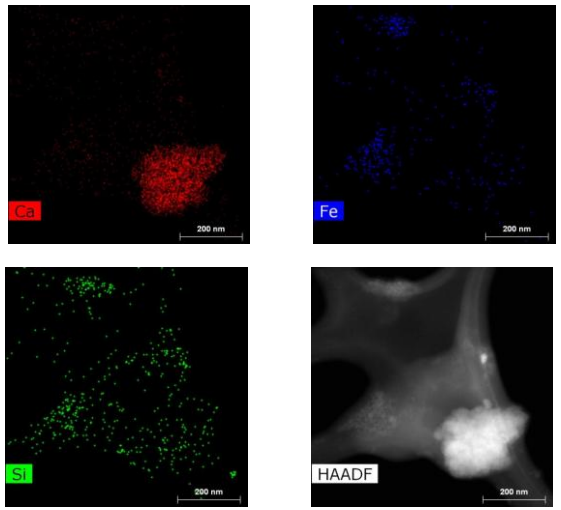
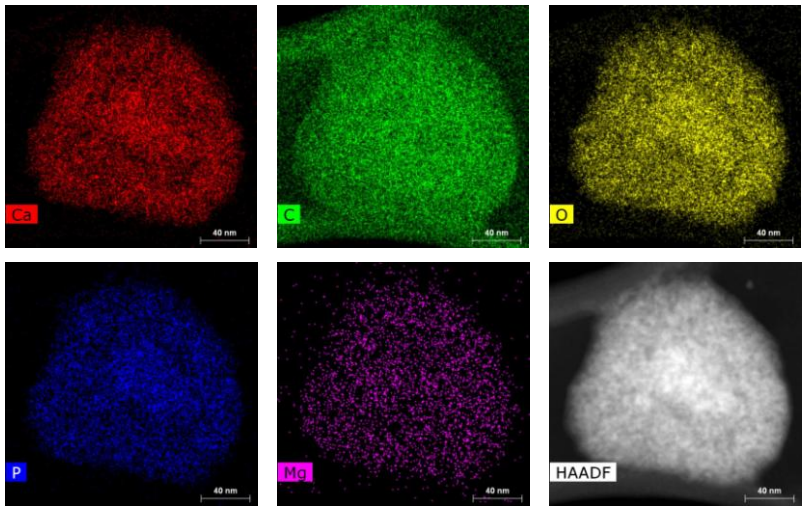
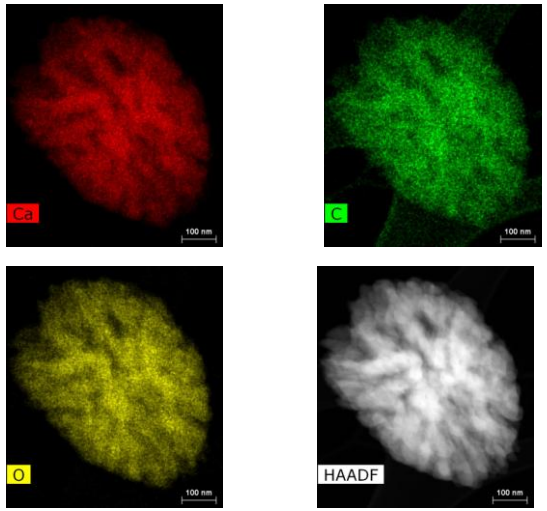
TEM+Mapping



$CaCO_3$-500nm

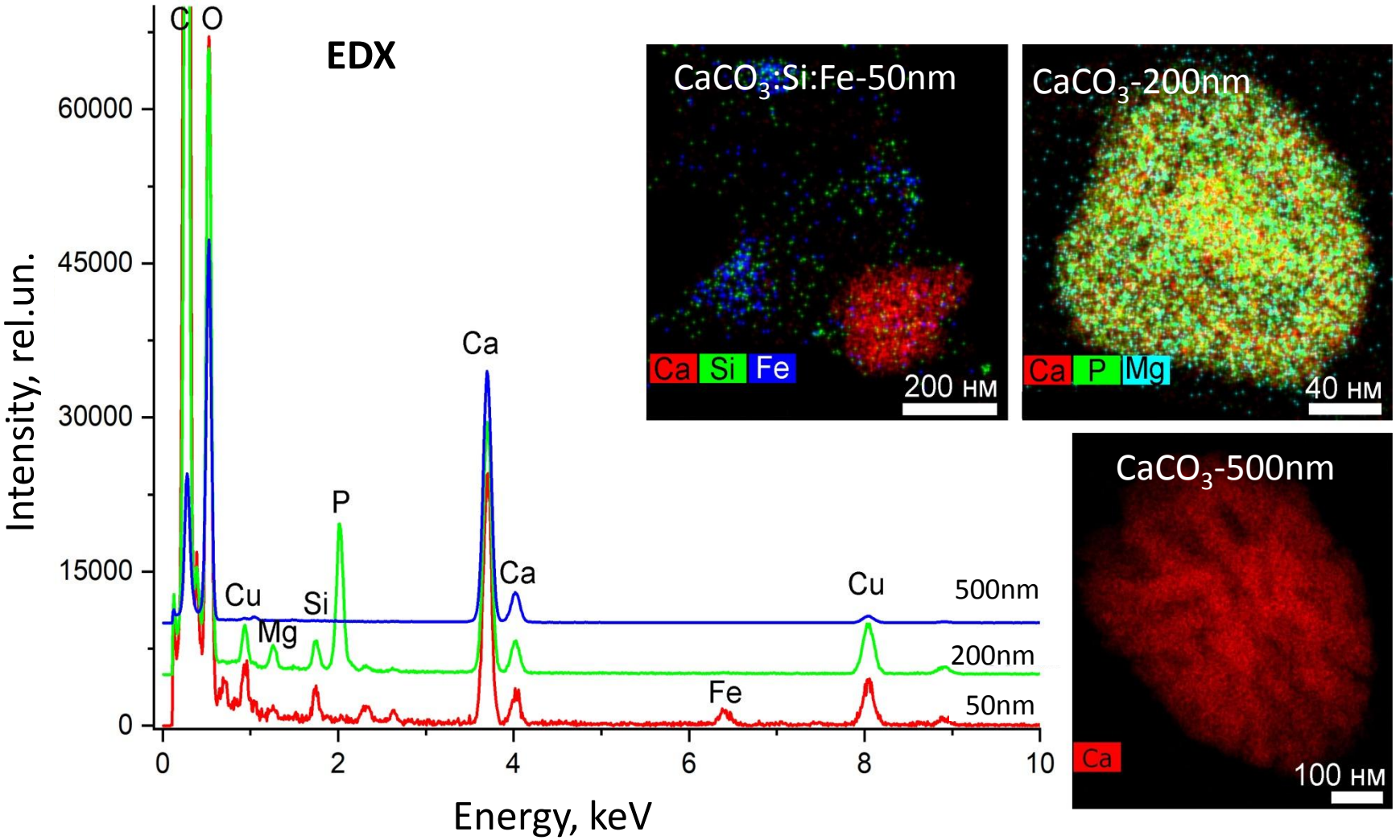


$CaCO_3$-200nm



$CaCO_3$:Si:Fe-50nm

A complete characterization of the particles was carried out using scanning and transmission electron microscopy, X-ray powder diffraction, dynamic and electrophoretic light scattering



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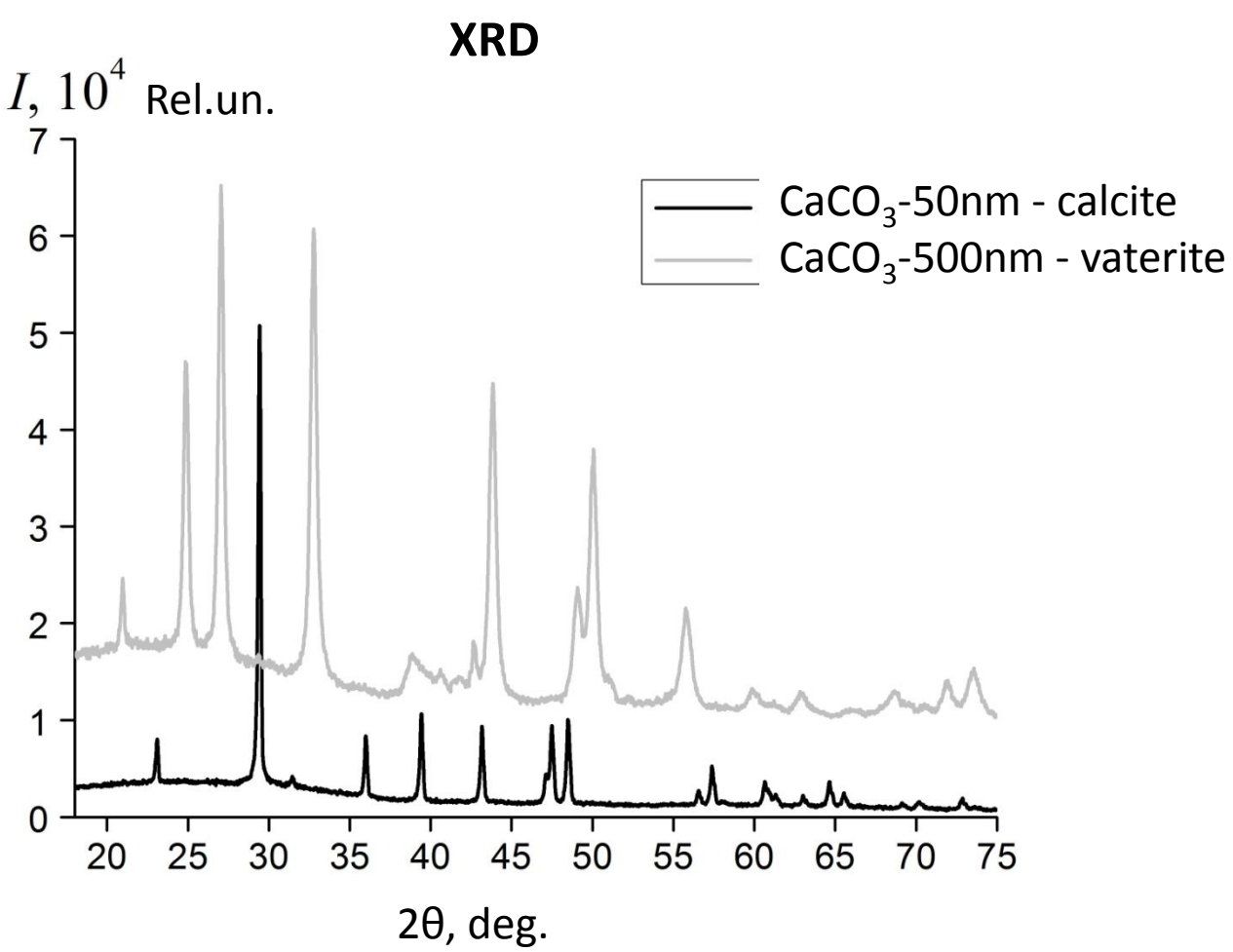
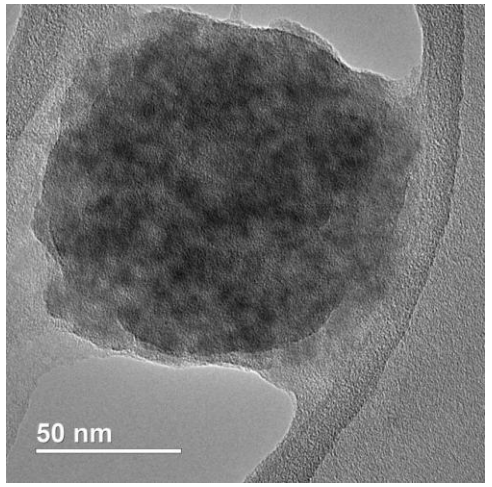
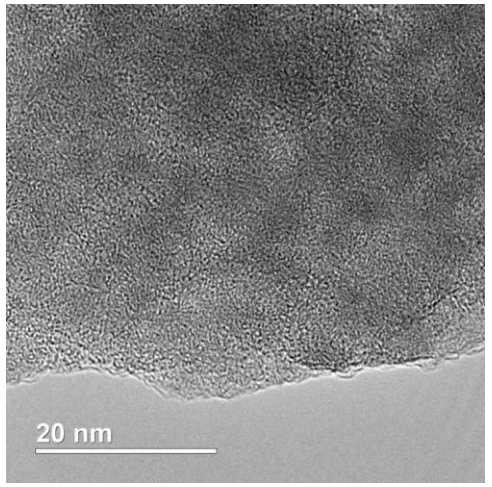
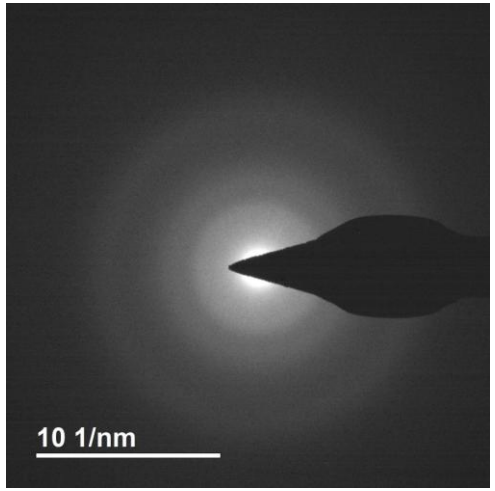






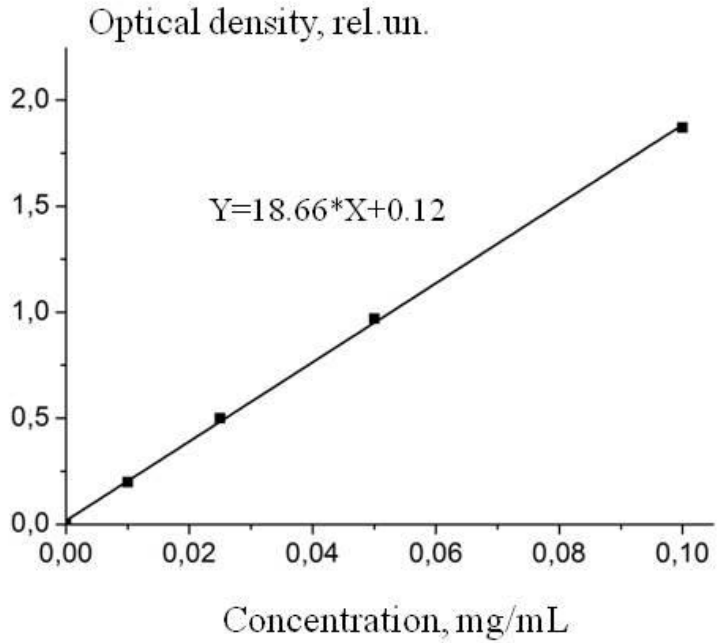
$CaCO_3$-200nm
amorphous

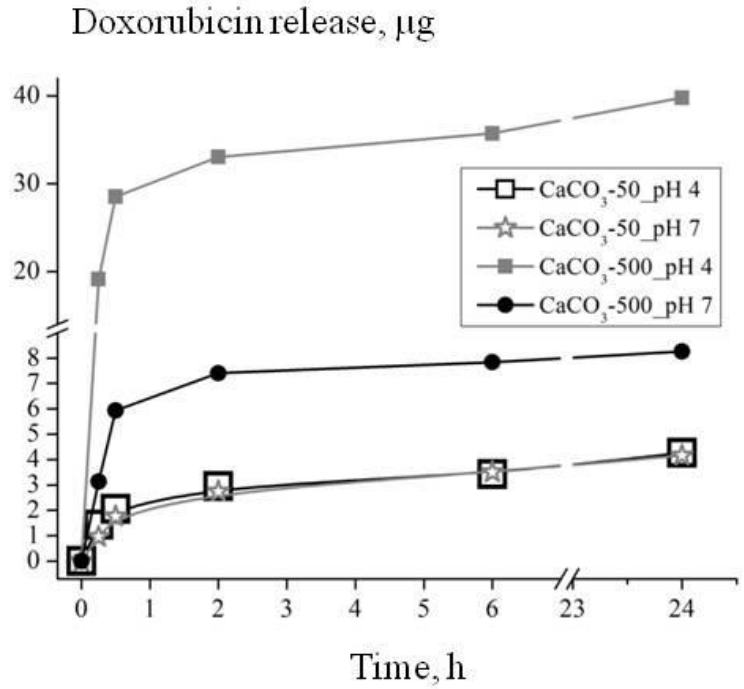


CaCO3 particles were loaded with anticancer drugs, porphyrazine and doxorubicin, with an encapsulation efficiency of 2-5 and 4-11 wt.%, respectively.

The release of doxorubicin occurs in two stages. The initial stage is characterized by a sharp increase in the concentration of the drug in solution, then there is a gradual release of doxorubicin remaining in the particles. This circumstance indicates that, at the initial stage, the release of the compound from the surface and from the pores of the particles was observed due to the desorption process, as well as due to the primary dissolution of the carbonate matrix in the surface layers, in comparison with the bulk of the particle. The subsequent slowdown of this process may be due to the gradual dissolution of the carbonate matrix at acidic pH values.

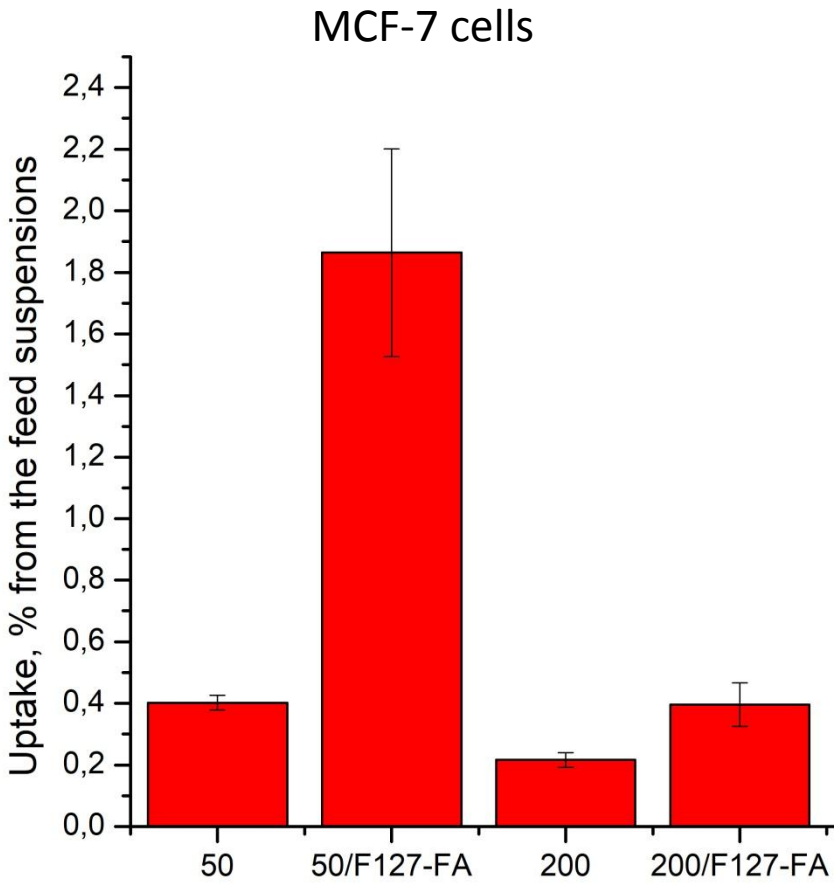
The spontaneous release at pH 7 reached 15%, and when the particles are dissolved at pH 4, the release was about 45% of the substance during the day, regardless of the encapsulated substance





Functionalization of the surface of calcium carbonate particles with a biocompatible Pluronic-folic acid conjugate (F127-FA) did not affect the particle size distribution and aggregative stability for all three samples.

The effect of coatings on the rate of internalization and accumulation of particles by cells expressing folic acid receptors was established. It was also shown that the internalization of 50 ± 30 nm particles was more active than other samples.



Acknowledgment
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