

PUBLICATIONS

BIODEGRADABLE POLYLACTIDE NANOPARTICLES WITH ENCAPSULATED BORON AND LITHIUM COMPOUNDS FOR NEUTRON CAPTURE THERAPY OF CANCER

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Neutron capture therapy (NCT) is a binary method for the treatment of malignant tumours. The clinically used ^{10}B agent boronophenylalanine carries one boron atom per molecule (about 5 wt.%), so that high doses are required. Lithium-6 is also considered as an NCT nuclide: the cross-section of the $^6\text{Li}(\text{n},\alpha)^3\text{H}$ reaction is about four times lower than that of $^{10}\text{B}(\text{n},\alpha)^7\text{Li}$ (940 b against 3837 b), but the reaction releases roughly twice the energy (4.78 MeV against 2.79 MeV) and all of its products are high-LET charged particles, so that the whole of it is deposited within the cell. In both cases the limiting problem is the carrier: uptake through the EPR effect requires particles below 100 nm, which is hard to reach with high-molecular-weight polylactide (PLA).

PLA nanoparticles were obtained by nanoprecipitation, with the solvent, the molecular weight and concentration of the polymer and the nature of the surfactant varied. Acetonitrile gave the smallest particles. For PLA of 330 kDa, Tween 80 yielded 79 ± 12 nm against 180 ± 20 nm for sodium dodecyl sulfate, and decreasing the concentration of 150 kDa PLA from 1 to 0.0625 wt.% reduced the mean diameter from 115 ± 11 to 58 ± 4 nm. The organosoluble borohydride $(\text{NBu}_4)_2[\text{B}_{12}\text{H}_{12}]$, carrying twelve boron atoms per molecule, was encapsulated by the same route; ICP-AES gave a maximum loading of 10.5%, falling at higher borohydride-to-polymer ratios.

Water-soluble lithium compounds cannot be encapsulated in this way, and a double water-in-oil-in-water emulsion technique was therefore developed. Replacing magnetic stirring by ultrasonic dispersion reduced the particle size by three orders of magnitude, from 0.9–61 μm to 32–69 nm. Methylene blue, used as a coloured model compound, was localised inside particles of about 50 nm. LiCl was encapsulated under the same conditions in PLA particles down to 30 nm at a content of about 1 wt.%, the optimum ratio of water-soluble compound to polymer being 0.2:1.

The lower lithium loading is caused by the limited compatibility of the polar salt with the hydrophobic PLA matrix, part of the LiCl diffusing out of the particles during solidification; amphiphilic PLA-PEG copolymers and lithium-coordinating additives are being examined to improve it. Taken together, the two routes provide biodegradable carriers of adjustable size below 100 nm for both boron- and lithium-based NCT agents.

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References:

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