were obtained by means of the film lipid hydration method. This conventional method is poorly efficient, and involves considerable processing time since several extrusion steps must be performed to yield appropriated particle size and polydispersity. Microfluidic-assisted synthesis of liposomes has recently emerged as a powerful technique to overcome these shortcomings, featuring exquisite micromixing conditions (due to the laminar regime in which these systems usually operate) and enabling the efficient and reproducible production of monodisperse populations without postprocessing. Another key advantage of the microfluidic technology is that it enables the control of the vesicle size by easily modifying the fluidic parameters.
Recently, we have designed, fabricated, and characterized different poly methylmethacrylate (PMMA) microfluidic chips for the insertion of the amphyphilic boron compound Lactosyl-carborane in liposome bilayers. Different flow rate ratios (FRR) between the organic phase and the aqueous phase were evaluated in order to optimize particle size.

Results
Microfluidic technology allowed to obtain monodisperse liposomes with a mean diameter of 89.58 ± 0.94 nm (PI = 0.176 ± 0.011) together with a boron encapsulation efficiency approximately 50% higher than those obtained with the traditional method. In addition, processing time using the microfluidic method was significantly lower.

Conclusion
The microfluidic technology is a field growing very rapidly, with a wide range of applications in other areas relevant to drug delivery using nanovehicles such as chemotherapy and genetic therapy. Besides BNCT applications, our group is also currently working in the microfluidic-assisted synthesis of oxaliplatin-loaded liposomes and siRNA/PEI nanocomplexes respectively.
In this work, we present the results of both methods for the synthesis of liposomes for BNCT together with the microfluidic system capability of our group for other applications.

Keyword: liposomes, lactosyl-carborane, microfluidics

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Hybrid gold and boron nanoparticles for treatment and boron dose estimation in boron neutron capture therapy for malignant glioma

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Introduction

Boron neutron capture therapy (BNCT) exploits the release of alpha-particles inside tumor tissues that provide the main effect but direct measurement of this absorbed dose is impossible. For this reason, neutron activation of golden foils placed in proximity to the irradiated samples is typically used as a proxy. With this method, accumulation of radioactive 198Au isotope and measurement of the released 411 keV gamma-rays within the 2.7-day half-life provides neutron capture data. We therefore propose a novel approach of using both boron and gold in the form of composite nanoparticles for direct, in situ absorbed dose evaluation in tumor tissues. Our objective was to develop an in-sample, absorbed dose estimation method using gold and boron compounds accumulated in glioma cells and to design and develop hybrid nanoparticles for direct dose estimation.

Materials and Methods

Human glioma T98G cells were incubated with gold nanoparticles (GNPs, 50 ppm) and boron-phenylalanine (BPA) at boron concentrations of 0, 10, 20, 40 ppm over 24 hours. The control group contained boron without gold. Cells were irradiated in vials with 1 ml of initial boron and/or gold-containing medium in a rotating acryl glass phantom under the neutron producing target of the accelerator-based neutron source at the Budker Institute of Nuclear Physics. Epithermal neutron irradiation lasted 2-3 hours with 2.0 MeV proton energy and 2-3 mA proton current to achieve 6 mAh of overall irradiation. Sam-

ples with GNPs were analyzed by gamma spectrometer. Colony-forming assays (CF-assays) were done two weeks post-irradiation and colonies of ≥50 cells were counted.
A novel method of cascade ultrasonic dispersion / destruction of micron particles was applied to obtain composite boron nanoparticles using water as a dispersion medium. Degradation of large boron crystallites with ultrasound and formation of <100 nm nanoparticles were studied using X-ray crystallography, dynamic light scattering (DLS) and transmission electron microscopy (TEM). Gold and boron concentrations in compounds and cells were measured by inductively-coupled plasma atomic emission spectroscopy (ICP-AES).

Results
At the initial stage of experiments, accelerator-based neutron source efficacy in producing nuclear capture reactions was proven by exponential decrease in colony formation as boron concentrations increased. These results were in line with those previously obtained at the nuclear reactor in Tokai village. Presence of GNPs did not significantly influence the neutron irradiation effect on BPA-enriched cells. Sample activation resulted in radioactive 198Au isotope generation which was utilized for absorbed dose calculations at each boron concentration. We propose the following formula for absorbed dose calculation: D=(k*N*n)/m, where D is the boron dose in GyE, N in the number of activated gold atoms, n is the boron concentration in ppm, m is the mass of gold in grams, and k is the coefficient, calculated depending on the depth (cm) to the sample in the acryl phantom. According to this methodology, cells with 129.8±7.3 μg of gold could obtain 12.98 GyE of radiation. We have also designed and refined composite boron-gold nanoparticles with a novel production method and analyzed their properties in irradiation experiments.

Conclusion
We are the first to develop an in-sample, absorbed dose estimation method using gold and boron compounds accumulated in glioma cells. We also introduced hybrid gold and boron nanoparticles and showed their role in both tumor ablation and direct irradiation dose measurement. We believe such nanoparticles can be further applied to visualize composite boron compound distribution in tumor tissues via isotope scanning or single photon emission spectroscopy (SPECT) to provide data on absorbed neutron dose during BNCT.

Keyword: glioma, nanoparticles, gold activation, absorbed dose calculation, accelerator-based neutron source