Scientific Research Abstracts
Vol. 7, p. 241, 2017
ISSN 2464-9147 (Online)
XVI International Clay Conference | ICC 2017 | Granada, Spain

POLYMER-MODIFIED BIOCOMPATIBLE HALLOYSITE NANOTUBES-DOPED COMPOSITES FOR DRUG DELIVERY AND TISSUE ENGINEERING APPLICATIONS

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Halloysite clay nanotubes have become a promising and very popular material in fabrication of biomedical materials [1]. Here we report our recent results on fabrication, nanoscale characterisation and practical in vitro and in vivo applications of halloysite nanotubes for drug delivery and tissue engineering applications. First, we evaluated the toxicity of halloysite nanotubes in vivo using *Paramecium caudatum* protists [2] and *Caenorhabditis elegans* nematodes [3]. Our results indicate that halloysite nanotubes are biocompatible and non-toxic material. We have also perfumed detailed characterisation of pure and polymer-modified halloysite nanotubes using a selection of characterisation techniques.

Next, we demonstrate the selective prototype anticancer drug delivery into selected human cell lines using polymer-modified 50-nm diameter halloysite nanotube delivery vehicles [4]. We have produced versatile dextrin end stoppers to secure the intracellular release of several anticancer preparations (brilliant green, paclitaxel). We found that drug-loaded halloysite nanotubes penetrate through the cellular membranes and reside in cytoplasm. The uptake efficiency for halloysite nanotubes depends on the cells growth rate, for example, faster proliferating cells internalise larger amounts of nanotubes. We also found that the intracellular glycosyl hydrolases-mediated decomposition of the dextrin stoppers stimulates the release of the lumen-loaded brilliant green. This resulted in the preferable elimination of human lung carcinoma cells (A549), in comparison with hepatoma cells (Hep3b). The enzyme-activated intracellular delivery of loaded drugs using dextrin-coated halloysite nanotubes is a promising platform for anticancer treatment, which we elaborated into the more complex systems.

We also produced porous biopolymer cross-linkers free hydrogels doped at 3-6wt % with halloysite nanotubes using the freeze-drying method [5]. Our results confirm the enhancement of mechanical strength (doubled pick load), better water uptake and improved thermal properties in chitosan-gelatine-agarose composite hydrogels doped with halloysite nanotubes. Electron and atomic force microscopies have shown the even and uniform distribution of halloysite nanotubes within the tissue engineering scaffolds. We also utilised for the first time enhanced dark-field microscopy to visualise the distribution of halloysite nanotubes in implantation area in vivo (in rats). Our results confirm the increased in vitro cell adhesion and proliferation of cells on the nanocomposites. Importantly, no changes in viability and cytoskeleton formation were detected. Biocompatibility and biodegradability of implanted scaffolds (in rats) has confirmed that the scaffolds promote the growth of novel blood vessels around the implantation areas. The implanted scaffolds were fully resorbed within six weeks after subcutaneous implantation. Our results indicate that the halloysite-doped scaffolds are biocompatible as demonstrated both in vitro and in vivo and may find applications as promising candidates for tissue engineering applications [6].

Acknowledgments: the work is performed according to the Russian Government Program of Competitive Growth of Kazan Federal University. This work was funded by the subsidy allocated to Kazan Federal University for the state assignment in the sphere of scientific activities.

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