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Production, Characterization and In vitro Evaluation of [223Ra]RaCl2 Nanomicelles for Targeted Alpha Therapy of Osteosarcoma

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Abstract : Radium-^{223} dichloride ($[^{223}Ra]RaCl_2$) is an alpha particle-emitting radiopharmaceutical currently approved for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease. $[^{223}Ra]RaCl_2$ is bone-seeking calcium mimetic that bonds into the newly formed bone stroma, especially osteoblastic or sclerotic metastases, killing the tumor cells by inducing DNA breaks in a potent and localized manner. Nonetheless, the successful therapy of osteosarcoma as primary bone tumors is still a challenge. Nanomicelles are colloidal nanosystems widely used in drug development to improve blood circulation time, bioavailability, and specificity of therapeutic agents, among other applications. In addition, the enhanced permeability and retention effect of the nanosystems, and the renal excretion of the nanomicelles reported in most cases so far, are very attractive to achieve selective and increased accumulation in tumor site as well as to increase the safety of $[^{223}Ra]RaCl_2$ in the clinical routine. In the present work, $[^{223}Ra]RaCl_2$ nanomicelles were produced, characterized, in vitro evaluated, and compared with pure $[^{223}Ra]RaCl2$ solution using SAOS2 osteosarcoma cells. The $[^{223}Ra]RaCl_2$ nanomicelles were prepared using the amphiphilic copolymer Pluronic F127. The dynamic light scattering analysis of freshly produced $[^{223}Ra]RaCl_2$ nanomicelles demonstrated a mean size of 129.4 nm with a polydispersity index (PDI) of 0.303. After one week stored in the refrigerator, the mean size of the $[^{223}Ra]RaCl_2$ nanomicelles increased to 169.4 with a PDI of 0.381. Atomic force microscopy analysis of $[223Ra]RaCl_2$ nanomicelles exhibited spherical structures whose heights reach 1 µm, suggesting the filling of 127-Pluronic nanomicelles with $[^{223}Ra]RaCl_2$. The viability assay with $[^{223}Ra]RaCl_2$ nanomicelles displayed a dose-dependent response as it was observed using pure $[^{223}Ra]RaCl2$. However, at the same dose, $[^{223}Ra]RaCl_2$ nanomicelles were 20% higher efficient in killing SAOS2 cells when compared with pure $[^{223}Ra]RaCl_2$. These findings demonstrated the effectiveness of the nanosystem validating the application of nanotechnology in targeted alpha therapy with $[^{223}Ra]RaCl_2$. In addition, the $[^{223}Ra]RaCl_2$nanomicelles may be decorated and incorporated with a great variety of agents and compounds (e.g., monoclonal antibodies, aptamers, peptides) to overcome the limited use of $[^{223}Ra]RaCl_2$.

Keywords : nanomicelles, osteosarcoma, radium dichloride, targeted alpha therapy
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