Spray-dried hybrid material of the diruthenium(II,III)-ibuprofen anticancer metallodrug loaded into chitosan

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A novel class of Ru_2(II,III) paddlewheel structured metallodrugs with the multiply bonded dimetallic core carrying four bioactive ligands per dimetal unit has been subject of our research. The lead-complex bearing the chloride axial ligand, $[Ru_2(Ibp)_4Cl]$ or RuIbpCl, Ibp = carboxylate anion from the non-steroidal anti-inflammatory drug ibuprofen, was shown to exhibit anticancer activity against glioma brain cancer [1,2]. Chitosan (CT) plays relevant role in the pharmaceutical and biomedical fields, and is capable of overcoming biological barriers and acting as brain-targeting drug delivery system. The present work reports studies on the interaction of the RuIbpCl complex with this biopolymer. Chitosan solutions of variable concentrations of RuIbpCl were spray-dried (SD) to give novel CT-metallodrug hybrid materials having different metal contents. Determination of Ru was performed by EDXRT analysis. The CTRuIbpSD loaded materials were characterized by comparison with the corresponding non-loaded CTSD. The shift of the visible electronic band to higher energy (444 nm) in the CTRuIbpSD hybrid materials, in relation to RuIbpCl (484 nm), suggests that the complex may interact with the CT through the axial positions. The FTIR ν_a(COO) and ν_s(COO) stretching bands of the Ibp bridging ligands were found at 1464 and 1412 cm^{-1}, respectively. Significant spectral changes at the regions 4000-3000 and 1600-1500 cm^{-1}, in relation to the CTSD, suggest possible participation of the CT amino groups in the interaction with the complex. The XRD pattern reveals low crystallinity and indicates that the encapsulation may be favored by increasing the metallodrug amount. TG/DSC/MS analysis shows that the thermal behavior of the loaded systems is distinct from that of the non-loaded materials and, additionally, it may be affected by the metallodrug content. Despite the distinct events of mass loss, in all the cases the initial step could be assigned to weakly interacting and/or surface adsorbed water molecules, while exothermic events above 200 ^oC were mainly associated to the release of the Ibp drug ligands accompanied by thermal degradation of the biopolymer chains. SEM microscopy analysis reveals that the hybrid materials are formed by non-aggregated spherical shape particles, for which the morphology achieves higher uniformity and smoother surface as the metallodrug concentration increases. The findings showed that the spray-drying process is useful to promote the incorporation of the diruthenium-ibuprofen complex into the chitosan biopolymer. Moreover, the new hybrid materials have potential to be explored for release of the anticancer metallodrug since the paddlewheel structure is maintained after encapsulation.

[1] de Oliveira Silva, D.; *Anti-cancer Agents Med. Chem.* **2010**, *10*, 312-323.
[2] de Oliveira Silva, D. In *Frontiers in Anti-Cancer Drug Discovery*; Atta-ur-Rahman, M.I. Choudhary, eds.; Bentham Science Publishers: Sharjah, U.A.E., 2014, vol. 4, ch. 3.

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