Novel strategies for cancer treatment: drug delivery combining graphene oxide quantum dots and core-filled lipid vesicles

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Cancer remains a global health problem and according to the International Agency for Research on Cancer, the incidence of all cancer cases will raise from 12.7 million new cases in 2008 to 21.2 million by 2030. [1] Doxorubicin (DOX) is a wide-spectrum “first-line” anticancer drug. However, its clinical application is limited as it is often associated with serious and generalized toxicity, development of drug resistance and low therapeutic efficiency. [2] Therefore, our research focuses in obtaining a smart nanosystem to delivery DOX to cancer cells more efficiently and with less toxicity. In view of this, we developed an *all-for-one* strategy, consisting on two different nanocarriers loaded with DOX: dioctadecyldimethylammonium bromide and monoolein, DODAB:MO (1:2) formulations and graphene oxide quantum dots (GO-Dots) that we aim to combine in a hybrid smart nanosystem for cancer therapy.

Formulations composed by DODAB:MO (1:2) are non-toxic, biodegradable lipid vesicles filled with honeycomb like lipid non lamellar structures [3,4] with high drug encapsulation capacity (85% DOX encapsulation) that ensure stability both in storage (stability for 3 months) and in the body circulation and provide a pH dependent release of DOX. Fluorescence anisotropy and UV-Vis spectrophotometry were combined to study DOX distribution in the lipid formulation (Log P=3,45±0,119) and DOX effect in the formulation microviscosity. Fluorescence lifetime imaging microscopy (FLIM) and confocal microscopy were also used to confirm cellular uptake in breast carcinoma cell lines.

In the proposed work, the optical properties of GO-Dots and the advantages of these emerging luminescent nanomaterials were also explored, namely their abundant surface carboxylic groups that enable the conjugation with a large diversity of functional groups. Further advantages comprise excellent biocompatibility, high surface-to-volume ratio and its inherent fluorescent property that allows monitoring the cellular uptake of systems. [5] GO-Dots were synthesized by acidic chemical oxidation of carbon black according to a reported method. [6] GO-Dots pH dependence (due to ionization of its surface groups) was characterized by fluorescence and electrophoretic light scattering. After establishing the GO-Dots behavior according to the surface ionization groups, conjugates of DOX and GO-Dots were prepared at different pH values. *In silico* predictions indicated that, at the physiological pH of blood circulation and healthy tissues, drug and dots possess opposite charges being able to establish electrostatic interactions while at acidic pH values characteristic of cancer tissues, a trigger effect will cause the release of the drug, since GO-Dots are protonated and uncharged. The conjugates formed between DOX and GO-Dots were studied by fluorescence and UV-Vis absorbance spectroscopy, confocal Raman scattering and ATR-FTIR. Finally the encapsulation of GO-Dots in liposomes was verified by fluorescence quenching of *n*-(9-anthroyloxy)-stearic acid probes (*n* = 3 or 12).

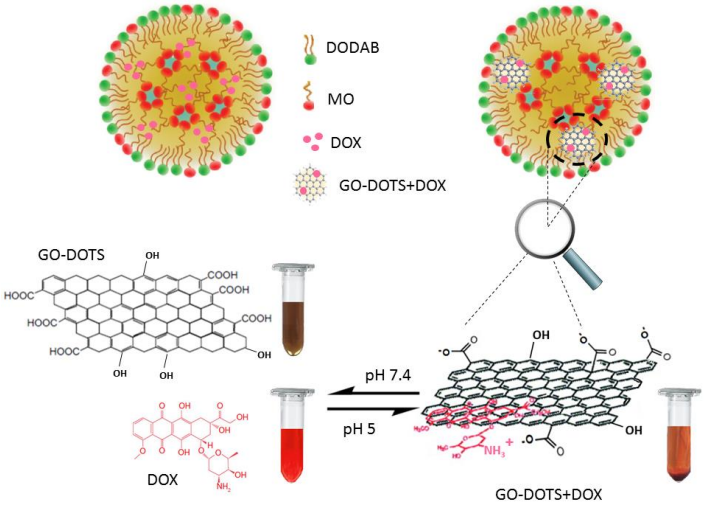

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Figure 1 –Top: Schematic representation of DODAB:MO (1:2) containing DOX or GO-DOTS+DOX. Bottom: Representation of pH dependence of conjugation of G-DOTS with DOX as well as photography of aqueous solution of GO-DOTS, DOX and conjugates taken under visible light.